All Ages Lead Model (AALM) Peer Review Charge Questions Compilation of Preliminary Responses

Dr. Hugh Barton, Preliminary Responses to AALM Charge Questions

1. Are the features of the AALM adequately described in the "Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations?"

Adequately can be interpreted to mean several things including: providing a sufficient scientific justification for the equations, parameters, and parameter values in the model, providing a clear description that the varied stakeholders concerned about lead can use to understand the model, and an absence of editorial mistakes in the document.

While much of the document is well written, its organization is somewhat difficult to follow, and it is very technical reflecting the complexity of the model. This makes the document difficult to absorb and likely of more limited help to those who are not modelers and lead experts.

An example of the need to improve the presentation of materials is the beginning of Chapter 3. It dives into history of the development of alternative versions of the model without providing the reader any indication what the goal is (p 53) or how the text addresses the subheading 3.1 "Introduction and Goals of this Analysis". This is just one example of how the document does not well guide the reader. On p53 line 35, it indicates that this chapter describes comparisons between two implementations of the Leggett model, but it's not clear how that is relevant to the Fortran model version that this document is describing overall.

Change CLS to CSL throughout the document when referring to the acsl model (e.g., p1 multiple lines).

There is a lot of repetition of text between Chapter 3 and 4, with Chapter 3 addressing the AALM.FOR version itself. On the other hand, important information on optimization of parameters (using AALM.CSL) is either clearer or only described in Chapter 4. This makes it difficult for the reader.

Starting tissue values are discussed on p 16 lines 18-21, but it is not clear what would be done.

Integration step size is discussed on p 17, is confusing. The last line recommends not changing step size during a simulation, but this follows a lot of discussion about changing the step size.

Editorial issues not noted in responses to individual charge questions have been added to the end, so as not to interrupt the flow of responses to charge questions.

2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?

In general, the model is based upon research findings particularly as it is based upon the earlier models of Leggett and O'Flaherty. Those two models use somewhat different approaches to modeling the biology and using the data, which was explored in the comparisons reported in Chapter 4.

It is unclear what the statement on p 62 lines 23-24 about parameters being placeholders means. This seems to suggest these are not well based upon data or reasonable extrapolations.

3. In general, is the theoretical basis for the model adequately described in Chapter 2 (Theoretical Framework, Parameters, and Equations)?

It's not clear what "theoretical basis" refers to here. As noted above, the document is challenging to read and absorb due to the complexity of what it is attempting to convey. Additionally, given the history of the development of the model code, the document describes things in several places (e.g., Chapters 2 and 4) with somewhat, though important, information in each place.

Are the following specifics regarding AALM, also adequately described?

3a. Values specified for the intake rates as a function of age for different media.

AIR: The text on p 10 appears to be misleading about the specification of air intakes and sources of exposure (indicated to be three source). It states in lines 2-3 that ventilation rates can reflect activity levels. Since the rates are specified for age ranges, it would appear to require calculating the ventilation rate to reflect weighted averages of activity levels. Also, the activity levels would be the same for all sources of exposures because the source concentrations are used to created weighted average concentrations. One perhaps could use the fraction from the source to adjust for different activity levels, but such an approach did not appear to be described anywhere. Finally, lines 25-26 indicates discrete and pulse exposures can be combined, but it isn't clear how easy it is to do this, and the User Guide only describes discrete and pulse exposures separately using water intake as an example.

Further, p 10 lines 8 – 15 describe calculation of a weighted average Pb exposure concentration, but this appears to assume that the activity levels of the individual in these different locations is the same. If correct, this important assumption is not stated.

SOIL: It isn't clear how the recommended values (p281) were obtained from the Exposure Factors Handbook values (p280), given the different age categories used, though the values have many similarities.

The statement about using the soil pathway rather than the other pathway (p11 bottom and p12 top) seems important, but too vague to be meaningful or clear for someone unfamiliar with the model.

WATER: The recommended values are said to be based upon two previous tables of values, without specific explanation. P 281 line 10 needs "ventilation rates" corrected to water intake. Such minor edits are needed throughout the document to improve the adequacy of the description.

b. Uptake/absorption parameters and parameters requiring modification for specific routes of exposure.

On the RBA tab of the EXCEL spreadsheet, the GI absorption fraction is called "F1" in the boxes and "AF1" in the heading on column D where values would be entered. Terminology should be consistent in sheet and with documentation.

c. Biokinetic parameters describing lead distribution and elimination.

The kinetics for binding to plasma proteins (P 26 lines 29-31) seem very slow, though perhaps all that matters is the equilibrium ratio.

Additionally, please comment on any strengths or weaknesses in the justification provided for model assumptions (data inputs, methodology, etc.) and the quantitative impact of those assumptions on the model and its results.

4.What are the Panel's views of Chapter 3 (Evaluation and Development of AALM.FOR) with regard to the:

a. Predictive accuracy and reliability of the AALM based on comparisons to available data sets.

Chapter 3 uses the term "prediction" to mean simulation output (e.g., p54 lines 2-6). This leads to confusion because the chapter does not distinguish between predictions based upon an established model and parameter values and simulations that were used to optimize parameters and thus would be expected to show strong similarity between model output and data. While optimization may have been done using the ACSL version of the model, rather than the Fortran version, these two models should be considered similar enough that using the Fortran version to simulate the data should not be considered a de novo prediction. What this charge question means by "predictive accuracy and reliability" is also unclear.

The description of the modeling of the Hattis data appears to have an error (p 56 line 37) indicating 20 years + the duration of the strike, that presumably is 20 year + duration of prestrike employment.

Several simulations, whether pure predictions or fits by adjusting parameters, are quite good.

The results for infants in Sherlock and Quinn 1986 (Fig 3-15; note y-axis incorrectly labeled "intake" when it is "concentration") is mediocre. In the simulations of Ryu et al 1983 (Fig 3-14), the model shows a much more rapid increase following the change in formula as compared to the data.

b. Extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms.

It is shown in graphs and indicated in the document that the acsl and Fortran versions of the model gave very similar results. This appears to be a valuable test due to the broad range of situations simulated with both versions.

c. Availability of other datasets that may be useful for further model evaluation.

None known to this reviewer.

5. Is the "AALM Fortran Users Guide" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved?

The users guide and the EXCEL spreadsheet indicated that the visual basic editor would be found using the Alt+F11 keys. However, using Office 365 this did not appear to work (or perhaps it was specific to this Lenovo laptop), so it was necessary to find instructions on the web for an alternative way to access it. This was not a "user friendly" beginning.

The Users Guide tells people how to use the EXCEL spreadsheet and shows examples of water exposures, but it doesn't explain how to do the other exposure media nor try to explain to a stakeholder how they would use the model to address an issue. The Technical Support Document describes how the model was established and values for various parameters obtained, but also doesn't explain how to make decisions to address issues the model could be used to address.

6.How could specific features of the AALM be further refined to improve its predictive accuracy?

While it would only impact matching fecal data (and calculating mass balance), it would seem that correcting for the RBA (p8 lines 2-4) would not be difficult. The exposure model currently passes the RBA adjusted intake to the biokinetic model, so presumably the remainder (1-RBA adjusted intake) would be added to fecal excretion (and the mass balance) to obtain the output.

7.How could specific features of the AALM be further refined to make it more user friendly?

Exposure: Although the user guide gives an example for water intake, this doesn't necessarily help with other media that have their own complexities, e.g., soil and dust intake, diet. Worked examples might help.

The naming of parameters in the EXCEL spreadsheet was not completely consistent within the spreadsheet nor with the documentation as noted above for Q3B. This needs to be evaluated carefully throughout the spreadsheet and documentation as there may be other such examples.

8.Is the AALM consistent with the Agency's Regulatory Environmental Model Guidance found at URL:http://cfpub.epa.gov/crem/?

No comment.

9.What additional information (if any) about AALM might be useful to users who want to assess a hypothetical or real-world risk assessment problem, in order to facilitate the correct application of the model and to communicate its modeling outcomes correctly and efficiently

As noted above, examples for how to implement all the different exposure media would be helpful.

EDITORIAL COMMENTS

P 9 line 12: change "intakes concentrations" to "intake concentrations"

P9 line 13 and 19: Appendices are at the end of the document, not in this chapter.

P 9 lines 27-30: Needs to be at least two sentences. Fix grammar.

P 13 line 17: Add "at" before "different"

P 18 line 7: For completeness, plasma protein and extravascular to the listing of compartments that lead in diffusible plasma can exchange into.

P 18 lines 22 and 29: Appendices are at the end of the document.

P 23 line 32: BRi is a rate not a fraction

P 27 line 20: Delete "of binding"

P 31 line 35: Change "form" to "from"

P 32 line 12: Delete "up"?

P 32 line 23: Delete "in"

P 53 lines 31-34: long, complex, incomplete sentence

P 57 line 26: make “period” plural

P 59 line 33: make “Figures” singular

P 61 line 13: fix “were parameters were”

P 66 line 20-21: delete one “renovations” from this sentence

P 80 line 5: fix grammar, “experienced”?

P 279 line 8: “TRW” undefined and unreferenced

P 281 line 10: Change “ventilation rates” to water intake

Dr. Harvey Clewell Preliminary Responses to AALM Charge Questions

1. Are the features of the AALM adequately described in the "Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations?"

Yes, the document does an excellent job of documenting the development and evaluation of the AALM. The model parameters and equations in AALM.FOR are clearly defined, and the evaluation of the model is thorough and well-described. The description of the relationships between the various models (IEUBK, ICRPv005.FOR, AALM-LG.CSL, AALM-OF.CSL, and AALM.FOR is also very helpful for reviewing the AALM.

2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?

Yes, the model development made good use of the available data on lead biokinetics for parameter identification and model evaluation.

3. In general, is the theoretical basis for the model adequately described in Chapter 2 (Theoretical Framework, Parameters, and Equations)?

Yes, the description is thorough and convincing.

Are the following specifics regarding AALM, also adequately described?

a. Values specified for the intake rates as a function of age for different media.
b. Uptake/absorption parameters and parameters requiring modification for specific routes of exposure.
c. Biokinetic parameters describing lead distribution and elimination.

Yes, the basis for each of the parameters in the model is well described and the selected values appear to be consistent with previous practice and available data.

Additionally, please comment on any strengths or weaknesses in the justification provided for model assumptions (data inputs, methodology, etc.) and the quantitative impact of those assumptions on the model and its results.

While I found that the justifications for model assumptions were sound, I think it should be a matter of concern that both the Leggett and O'Flaherty models are highly sensitive to two parameters:

- parameters C1 and C2 in the calculation of urinary clearance in AALM-OF.CSL
- parameters TEVF and TORBC in the plasma compartment of AALM-LG.CSL

The sensitivity of the model to these parameters is much greater than 1 in absolute value, indicating significant amplification of error from the input parameter to the model output. (As an

aside, the sensitivity analysis should include the direction of the sensitivity; that is, pos positive for a direct dependence and negative for an inverse dependence.)

4. What are the Panel's views of Chapter 3 (Evaluation and Development of AALM.FOR) with regard to the:

a. Predictive accuracy and reliability of the AALM based on comparisons to available data sets.

In general, the comparisons to available data sets provide a strong basis for confidence in the accuracy and reliability of the AALM. One exception is the comparison of the model predictions to data from 90 day old infants (Figure 3-15). The model appears to systematically underestimate blood Pb concentrations at low Pb intake and overestimate them at high Pb intake. The discussion of this figure on p.60 does not discuss the failure of the model to reproduce the low-intake data point..

b. Extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms.

I am satisfied that the model has been adequately verified and operates as expected. The ability to harmonize the results from the alternative model structures (AALM-LG.CSL and AALM-OF.CSL) definitely provides greater confidence in predictions from AALM.FOR.

c. Availability of other datasets that may be useful for further model evaluation.

I am not aware of any additional datasets that would be useful for model evaluation.

5. Is the "AALM Fortran Users Guide" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved?

The users guide is nicely laid out and easy to follow, but it can not make up for the poor design of the spreadsheet interface. An appendix should be added that provides several examples of typical uses of the AALM and the user entries that would be required.

6. How could specific features of the AALM be further refined to improve its predictive accuracy?

I am troubled by the heuristic approach used for controlling numerical integration error during the model simulations, as described in section 2.3.1. I do not understand why a variable-step predictor-corrector algorithm such as the Adams method or the Gear implicit method isn.t used so that the acceptable error in the simulation can be specified.

7. How could specific features of the AALM be further refined to make it more user friendly?

I did not find the Excel spreadsheet interface to be the least bit user friendly. I would have expected that a resource as likely to receive widespread use as the AALM would be designed with a graphical user interface that provided a sequence of screens where related sets of user information can be entered. BMDS provides such an interface.

Also, the user should not have to be involved in decisions about arcane simulation control issues like step size. A predictor-corrector algorithm should be used.

8. Is the AALM consistent with the Agency's Regulatory Environmental Model Guidance found at URL:http://cfpub.epa.gov/crem/?

(The link above did not work, but I was able to find the document at https://www.epa.gov/sites/production/files/2015-04/documents/cred_guidance_0309.pdf) Overall, I feel the development and evaluation of the AALM was consistent with the EPA Guidance. However, no uncertainty analysis was performed. Given the high sensitivity of the model to some parameters, I think a formal Monte Carlo uncertainty analysis is warranted.

9.What additional information (if any) about AALM might be useful to users who want to assess a hypothetical or real-world risk assessment problem, in order to facilitate the correct application of the model and to communicate its modeling outcomes correctly and efficiently?

I believe that adding examples to the AALM Users Guide that highlight important considerations in using the model would help users to correctly apply it.

Minor corrections:

The extension CLS is mistakenly used in place of CSL in the name of the acslX model, AALM.CSL, in the Table of Contents, List of Figures, List of Tables, Section 1.1, Section 3.1, Table 3.2 (title), Figure 3.6 (title and caption), and throughout Section 4.

The term "deposition fraction" is not an appropriate description of the exchange of free concentration of PB ion between plasma and tissues. It is likely a throwback to radionuclide disposition modeling, but should be replaced with a term like "transport" or "transfer".

Section 3.5.2, p.64, line 39: change "…the model was extensively evaluated Chapter 4. The latter report described…" to "Chapter 4 describes"

Section 3.5.2, p.64, line 41: Need citation for "the latter report".

Figure 3-15, p.89: I believe the ordinate axis label should be Blood Pb Concentration (ug/dL), not Blood Pb Intake (ug/dL).

Dr. Joel M. Cohen Preliminary Responses to AALM Charge Questions

Dr. Deborah Cory-Slechta Preliminary Responses to AALM Charge Questions

Question 2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?

For the most part, the model features are supported by available research findings in published peer-reviewed by literature or by reasonable extrapolation from such data. The one exception seems to be for brain. This is understandable in that brain Pb concentrations are simply not available from which more exact modeling can be undertaken. Consequently, they are not really available for use in risk assessment scenarios. However, it is critical to remember that brain Pb is the basis of the neurodevelopmental toxicity in children, and could contribute to the increasing effects of Pb described in relation to neurodegenerative diseases. For that reason, statements about brain Pb and appropriate references should be included in statements related to brain Pb. For example, p. 31 makes the statement of 'non-uniform distribution of Pb in brain tissues. It is not clear where this assertion comes from. If it was based on studies done in rodents, it is critical to recognize that studies citing greater accumulation of Pb in hippocampus suffer from the fact that concentrations in different regions were based on regional dry weights, which artifactually increases levels in some regions, and when based on wet weights, as appropriate, there is a uniformity of concentrations across regions.

Furthermore, the text then goes on to cite numerous parameters of Pb in relation to e.g., transfer rates and the percent of outflow from plasma into brain with no references provided for any of these statements. No information is included as to potential excretion of Pb from brain once it has entered. This is of potential significance at least based on information for other essential metals, e.g., iron that appear to remain in brain for at least 9 mos in rats, which when extrapolated to humans is on the order of decades. While some studies have cited a half-life of 2 years of Pb in brain (e.g., Garza et al., 2006), citations in support of that statement are not provided.

One other consideration relates to air Pb. The document currently includes 4 different respiratory compartments from air Pb to plasma. What is not considered in the model, and again likely cannot be as no real data is available, is the extent to which nasal olfactory uptake of Pb in ultrafine particles may contribute to the brain Pb compartment. As these particles are taken up via olfactory (or trigeminal or vagal) nerves, they directly enter into brain and bypass the blood brain barrier. While inhalation of Pb and regional brain Pb analyses have not been undertaken, assessments in goat showed significantly higher levels in olfactory epithelium and olfactory bulb, consistent with this route (Stuerwald et al., 2014). Consequently, levels in brain of such metals are not reflected in peripheral (e.g., blood) measures of the metal. While data that could be used to model this is clearly not available, it is probably useful to include this possibility in the document, given the potential for incorporation of such information should it become available and to fully characterize limitations of the model.

Question 3. In general, is the theoretical basis for the model adequately described in *Chapter 2: Theoretical Framework, Parameters, and Equations*?

In general, the theoretical basis of the model, is adequately described, but as noted above in response to question 2, it is useful to include references where they are missing to the parameters and data that were used.

Dr. Philip Goodrum Preliminary Responses to AALM Charge Questions

USEPA ORD All Ages Lead Model (AALM) – Response to Charge Questions to AALM Panel – Preliminary Comments Prepared by Philip Goodrum, Ph.D., DABT

*Original charge questions are in BLUE (emphasis/underscores added) and preliminary responses are in BLACK.

Preliminary responses to questions are given below. Minor editorial comments/observations are included in a separate list at the end.

1. Are the features of the AALM adequately described in the "Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations?"

Yes, the Technical Support (TS) document strikes an appropriate balance between presenting the technical underpinnings of the model and basis for choices for model structure and inputs, without getting bogged down in too much detail. There are specific points where summaries of USEPA and literature are presented along with final inputs selected for AALM – but discrepancies are not fully explained. These are noted below.

The TS document makes judicious use of summary tables in both the main text and appendices to present the model variables, selected parameter values, and equations grouped by "submodels". This was nicely done and very easy to follow.

A fundamental feature of AALM is that provides a single tool to quantitatively evaluate links between exposure and tissues levels of Pb for all ages. AALM applies exposure, uptake, and biokinetic modeling to predict blood, bone, and tissue Pb concentrations from birth (including a fetal module to load tissues at birth) through late adulthood. Importantly, USEPA states (TS p. 113, lines 28-34) that the intent of the AALM is to replace or supplement the current IEUBK and ALM models, while also providing additional assessment capability for older children and adolescent subpopulations. This is a major step forward from both technical and public policy perspectives for conducting human health risk assessments.

In addition, alternative choices for underlying kinetics models have been carefully considered and evaluated over a period of more than a decade. Some descriptions of the differences in model structure, inputs, and performance are provided to assist the Pb risk assessment community in understanding the implications of moving forward with AALM in a regulatory context. The TS would benefit from additional examples of differences in uptake and predicted blood Pb distributions, specifically comparing the current proposed AALM with alternative kinetics model iterations, as well as IEUBK and ALM model applications to the same default scenarios, inclusive of baseline, water, diet, soil & dust ingestion, and inhalation pathways. This would largely be captured in additional appendix materials, but summaries of the key

similarities and differences in model performance could be carried forward in existing chapters of the main text.

While the AALM currently remains a research tool that predicts Pb concentrations in blood over specific ages, it stops short of presenting a fully developed risk characterization module. Each simulation generates a single time series of predicted mean blood Pb concentrations over time, summarized in both an Excel table and graphic. By contrast, the IEUBK and ALM models generate probability distributions of blood Pb concentrations, by applying a lognormal distribution model to the predicted mean concentrations. This utility does not currently exist in AALM, though users could post-process the results on their own. The TS document is silent on this point and should at least discuss this omission along with any anticipated next steps.

Another important advancement of AALM is the ability to simulate one or more "plus trains" of Pb exposure via multiple exposure pathways. The user interface, while functional, is not exactly "friendly", and requires some investment of time and patience to run a simulation for a desired exposure scenario. The TS and notes in the AALM model itself do provide adequate warning and coaching for users to get there, but future builds of AALM could streamline the user interface. Also, more examples, clearly laid out in a menu table with options, would reduce the startup time for most users.

2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?

Yes, the model features are well supported by published peer-reviewed literature and reasonable extrapolations. Comments on specific features of AALM presented to the panel are addressed in response to Charge Question #3 below.

3. In general, is the theoretical basis for the model adequately described in Chapter 2 (Theoretical Framework, Parameters, and Equations)?

Yes, overall, the theoretical basis for the two key submodels - exposure and biokinetics - are adequately described. Figure 2-1 (flow chart) is particularly helpful. The model focuses on predicting central tendency conditions, largely relying on estimates of arithmetic means for key model variables. This greatly reduces the complexity of the model structure and selection of input values, compared with, for example, a fully probabilistic modeling framework. However, omitting the distributions may constrain options for conducting a robust sensitivity analysis, since the currently model framework requires somewhat ad-hoc changes to combinations of model inputs.

The decision to apply a model time step of 1 day (distinct from the numerical integration time step) is an appropriate comprise between computational efficiency (in terms of managing output to the user) and practicality. From a user's perspective, dividing a lifetime into a series of daily exposures, grouped over specific age ranges, is a satisfying logical construct. It makes sense that age-specific changes in an individual's physiology can be reasonably represented with this

construct, and the exposure scenarios (particularly episodic pulse trains) would yield patterns of daily intake rates. Building different exposure scenarios is intuitive, and offers greater flexibility with a one day time step, one compared with IEUBK and ALM.

One critical aspect of the theoretical basis for AALM is the calibration exercise described in Chapter 4. The AALM model performance was compared with that of IEUBK and, for the scenarios evaluated, it was concluded (p. 114, lines 26-28):

> *The optimized AALM discussed in Section 4.7 thus predicts blood Pb concentrations in children that are approximately 2-fold higher than the currently established regulatory IEUBK model based on the same Pb intakes.*

Based on these findings, selected kinetics parameters were adjusted (e.g., RRBC, KBIND). This makes sense given that the scenarios were fixed to yield the same Pb intakes. However, as described below, some of the exposure parameter values that are proposed for AALM appear to also contribute an upward bias in intakes themselves, and should be revisited.

Are the following specifics regarding AALM, also adequately described?

Values specified for the intake rates as a function of age for different media.

- **Food Pb Intake** (pp. 278-280) – a bodyweight-normalized intake rate of 0.14 µg/kg-day is proposed, which corresponds to an absolute intake rate of 10 µg/day for an adult weighing 71.4 kg. The TS document presents age-specific estimates selected by the USEPA TRW, which routinely updated the dietary exposure module of the IEUBK model to reflect national survey data on food consumption rates and Pb residue levels. The decision to simplify the input parameter to a single bodyweight-normalized value makes good sense from both a model implementation perspective (i.e., it is very straightforward to calculate this intake term from age-specific body weight). However, a value of 0.128 or 0.13 µg/kg-day is better supported than 0.14 µg/kg-day. The basis for this statement is as follows:

  1) The AALM model yields estimates of food Pb intake for children that, on average (considering each 1-year age group separately from ages 1 to 7 years, inclusive) differs from the input parameters recommend by the TRW by 9.4%. This takes into account the age- specific body weights for male and female children, as presented in the TS document.

  2) A simple sensitivity analysis was conducted to illustrate how this error/deviation from TRW changes as a function of changes in intake rates ranging from 0.120 to 0.150 µg/kg-day. (see the following page – Exhibit 1).

  3) An error rate of 0% corresponds with a Pb intake rate of 0.128 µg/kg-day, which corresponds with an absolute intake rate of 9.1 µg/day for a 71.4 kg adult. It is unclear why a parameter value rounded to a whole number (e.g., 9 µg/day) would be

> preferable, given the number of significant figures USEPA has historically applied to estimates of food Pb intakes in the IEUBK model. A slightly lower Pb intake rate of 0.126 µg/kg-day corresponds with an absolute intake rate of 9 µg/day for a 71.4 kg adult. While the error/discrepancy is quite low (-1.5% on average for children ages 1-7 years), it implies a slight underestimation may occur during childhood.

It would be helpful to explain that even though an intake rate of 9.1 µg/kg-day (or similar value) reproduces the TRW values quite well on average, there is a systematic discrepancy on a year-by-year basis. Specifically, this approach for AALM will consistently underestimate food Pb intakes (compared with TRW's recommended inputs) during birth to 3 years, and overestimate intakes during 3 to 7 years.

Exhibit 1. AALM Technical Guidance - Food Pb Intake (pp. 278-280)

Adults	10	ug/day	proposed
	0.14	ug/kg-day	calculated
	71.4	kg BW	presumed BW used in calculation

Adult BW	Dietary Pb Intake		Child (1 to 7 years)
kg	ug/kg-day	ug/day	% difference
71.4	0.120	8.6	-6.2%
71.4	0.126	9.0	-1.5%
71.4	0.128	9.1	0.0%
71.4	0.130	9.3	1.6%
71.4	0.140	10.0	9.4%
71.4	0.150	10.7	17.2%

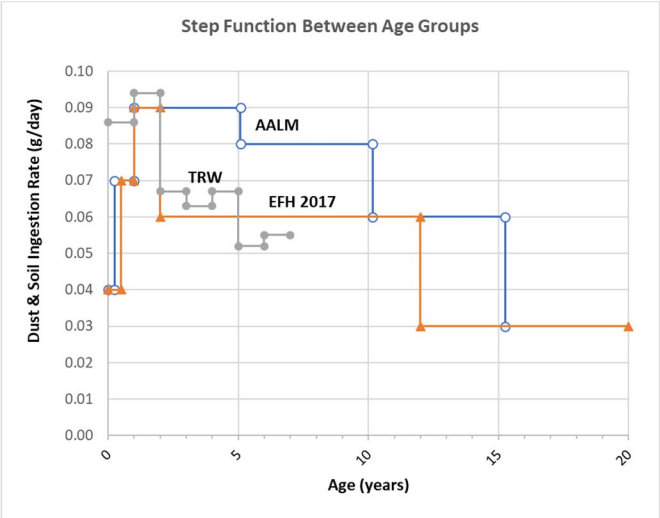
Intake (all ages):	0.128	ug/kg-day
Avg % diff:	0.0%	compared with TRW for child ages 1 to 7 years
Adult (M) BW:	71.4	kg
Adult intake:	9.1	ug/day

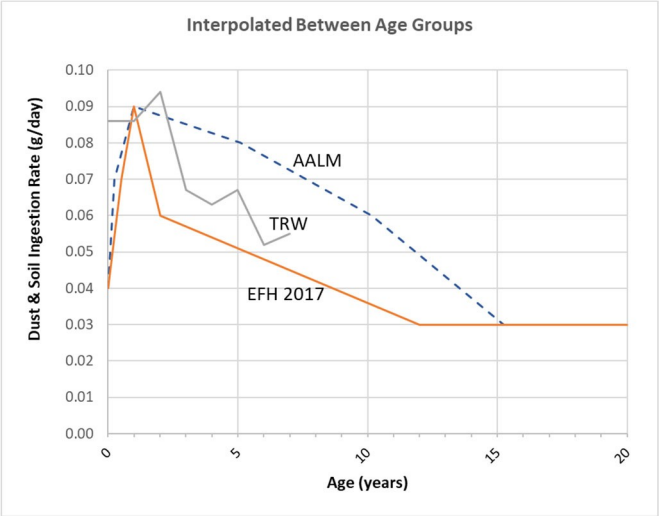
Child	Multiplier	Body weights (kg)		Intake (ug/day)				Difference	
years	ug/kg-day	F	M	F	M	**F/M avg**	**TRW**	[AALM - TRW] (ug/day)	[AALM - TRW]/TRW %
0 to < 1	0.128	8.9	9.4	1.14	1.20	**1.17**	**2.26**	-1.09	-48%
1 to < 2	0.128	12.3	12.9	1.57	1.65	**1.61**	**1.96**	-0.35	-18%
2 to < 3	0.128	14.6	15.3	1.87	1.96	**1.91**	**2.13**	-0.22	-10%
3 to < 4	0.128	16.4	17.2	2.10	2.20	**2.15**	**2.04**	0.11	5%
4 to < 5	0.128	18.0	18.8	2.30	2.41	**2.36**	**1.95**	0.41	21%
5 to < 6	0.128	19.7	20.2	2.52	2.59	**2.55**	**2.05**	0.50	25%
6 to < 7	0.128	21.7	21.8	2.78	2.79	**2.78**	**2.22**	0.56	25%
								average	**0.0%**

Intake (all ages):	0.140	ug/kg-day
Avg % diff:	9.4%	compared with TRW for child ages 1 to 7 years
Adult (M) BW:	71.4	kg
Adult intake:	10.0	ug/day

Child	Multiplier	Body weights (kg)		Intake (ug/day)				Difference	
years	ug/kg-day	F	M	F	M	**F/M avg**	**TRW**	[AALM - TRW] (ug/day)	[AALM - TRW]/TRW %
0 to < 1	0.14	8.9	9.4	1.25	1.32	**1.28**	**2.26**	-0.98	-43%
1 to < 2	0.14	12.3	12.9	1.72	1.81	**1.76**	**1.96**	-0.20	-10%
2 to < 3	0.14	14.6	15.3	2.04	2.14	**2.09**	**2.13**	-0.04	-2%
3 to < 4	0.14	16.4	17.2	2.30	2.41	**2.35**	**2.04**	0.31	15%
4 to < 5	0.14	18.0	18.8	2.52	2.63	**2.58**	**1.95**	0.63	32%
5 to < 6	0.14	19.7	20.2	2.76	2.83	**2.79**	**2.05**	0.74	36%
6 to < 7	0.14	21.7	21.8	3.04	3.05	**3.05**	**2.22**	0.83	37%
								average	**9.4%**

- **Dust and soil ingestion rate** (g/day) (pp. 280-281) – for estimates applied to childhood, two sources of information are presented: 1) USEPA's Exposure Factors Handbook (EFH), recently updated in 2017 for this exposure variable; and 2) USEPA TRW's estimates as intended for use in the IEUBK model. In addition, literature sources are cited, but not summarized or discussed in any manner. The AALM model can be run as both a step function, or as interpolated values between age groups. The graphics below show the proposed AALM inputs side-by-side with the two key sources for both run options. During childhood, after approximately age 2 years, the proposed AALM inputs are systematically higher than the values cited; no explanation is given to explain this discrepancy:





Page 12, line 10, states, "*Values for IRsoil are interpolated between inputted ages*." A similar statement

for water ingestion rate is made on p. 13, lines 9-10. Does this mean that a step-function option is never implemented for these exposure factors? If this is not true, and a step function is in fact one run option, suggest adding this clarification to these sections.

a. Uptake/absorption parameters and parameters requiring modification for specific routes of exposure.

The fact that RBA is applied to *intake* rather than *uptake* is noted in several places (e.g., Section 2.2.3), and it is stated that this simplification may yield an underprediction of excretion and, therefore, a negative mass balance with Intake > body burden + excretion. It also appears that by adopting the same RBA as has been historically used in IEUBK and ALM, the proposed inputs may tend to overpredict *uptake* because the variability in fed/fasted state is not taken into account.

Absorption via inhalation is modeled as a function of [depositional fraction x absorption fraction] for 4 different compartments of the respiratory tract (p. 23, lines 11-20): 1) intrathoracic; 2) bronchiolar; 3) bronchiole; and 4) alveolar. Collectively, the assumption is that, of 40% of the total inhaled Pb is initially deposited in the respiratory tract (the balance of which is exhaled), 4% is translocated to the GI tract through mucociliary clearance (swallowing). These estimates are summarized in a table (copied below) and attributed to data from 5 studies conducted from 1969 through 1980 in which human subjects inhaled submicron Pb-bearing particles:

Compartment	1	2	3	4
Deposition Fraction (R)	0.08	0.14	0.14	0.04
Rate Coefficient (BR, day^{-1})	16.6	5.4	1.66	0.347
$t_{1/2}$ (hour)	1	3	10	40

The table lists the four compartments, but if the numbering sequence corresponds with the order of the regions described above (as presented in the TS document), then the 4% value (i.e., 0.04), presumably for region number 4 in the table, would correspond with the alveolar region, which is not the region associated with translocation to the GI tract. Rather, the balance (i.e., 36%) initially deposited in the thoracic and bronchiolar regions would be more likely to translocate to the GI tract.

In a more recent study by Lach et al. (2014)[1], deposition was estimated from lead aerosol particle size distributions measured in firing ranges. Results showed that 49% of total inhaled Pb would be deposited in the respiratory tract, of which 37% would be translocated to the GI tract. This finding is similar to the tabular summary above.

It's possible that particle size distribution at the firing ranges is different from that of the inhalation studies cited in the TS document and attributed to the original Leggett (1993) model. While the TS document does already include a caveat regarding the sensitivity of the assumption of deposition fractions to the particle size distribution, the discrepancy in the cited literature noted above should be revisited.

b. Biokinetic parameters describing lead distribution and elimination.

c. The integration logic described on pp. 16-18 makes good sense.

Additionally, please comment on any strengths or weaknesses in the justification provided for model assumptions (data inputs, methodology, etc.) and the quantitative impact of those assumptions on the model and its results.

[1] Lach, S., B. Steer, G. Gorbunov, V. Micka, R. Muir. 2014. Evaluation of exposure to airborne heavy metals at gun shooting ranges. *The Annals of Occupational Hygiene*, 59:307-323. https://doi.org/10.1093/annhg/meu097.

Depending on the air Pb concentrations, the AALM results may be sensitive to a change in the assumptions regarding fractions of inhaled particles translocated to the GI tract, where absorption is much lower (e.g., 30% absorption) compared with the pulmonary region of the respiratory tract. That is, increasing the fraction that is translocated to the GI tract would effectively lower the total uptake and absorption via inhalation.

4. What are the Panel's views of Chapter 3 (Evaluation and Development of AALM.FOR) with regard to the:

    a. Predictive accuracy and reliability of the AALM based on comparisons to available data sets.

This question appears to align with the objective #6 stated on p. 95, lines 13-15:

> *(6) an evaluation and optimization of the Leggett and O'Flaherty biokinetics models against a common set of observations that lead to the version of the AALM in acslX (AALM.CLS v.4.2, July 2015).*

The comparison of model predictions to empirical data for tissue levels is helpful. No comments.

    b. Extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms.

The example scenarios used to compare AALM-LG to other platforms are good. Just a few miscellaneous items:

- Figure 4-9 (time series following cessation of exposure) – we is half-life calculate for the bottom graphics (bone) but not the top graphics (blood)?
- A few graphics show results from side-by-side comparisons with IEUBK. What about the same for ALM?

    c. Availability of other datasets that may be useful for further model evaluation. No other data sets were identified by this reviewer.

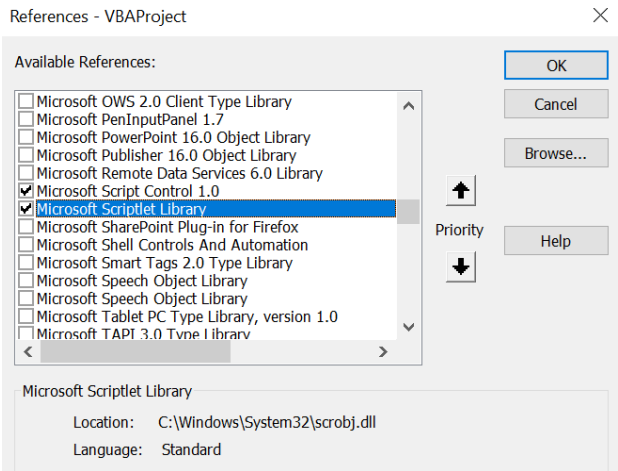
5. Is the "AALM Fortran Users Guide" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved?

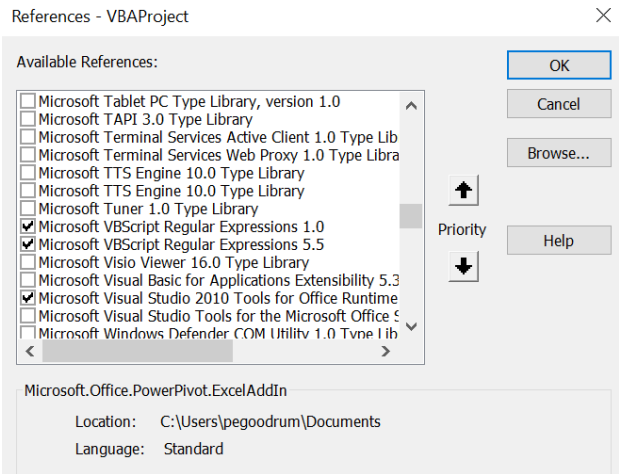
This reviewer implemented the AALM on a DELL laptop operating with Windows 10 Pro with the following device specifications:

Device specifications

Device name	1372-laptop
Processor	Intel(R) Core(TM) i7-8565U CPU @ 1.80GHz 1.99 GHz
Installed RAM	16.0 GB (15.8 GB usable)
Device ID	2A09AEA2-FF37-4EC8-93E9-74410707E5A1
Product ID	00330-52070-83271-AAOEM
System type	64-bit operating system, x64-based processor
Pen and touch	Touch support with 10 touch points

1. Installation experience was relative straightforward. My MS Excel VB scripts were not the same as noted in the installation guide, which required some guessing by the user. My options are copied below:





Upon selecting these VB scripts for installation, the tool functioned without any issues.

2. It was initially unclear to this user that every run simulation required clicking on each of the boxes named “Step 1”, “Step 2” and “Step 3”. This only became obvious after trial and error.

3. Step 2 is not at all intuitive, though logically it makes sense that pulse trains need to be specified for some period of time, with some intervening interval. The Guide would greatly benefit from more examples of screen shots with various entries, followed by a summary table. Choose examples that would be logical entries to run simulations such as:

    a. 2 days on, 5 days off, for a period of 3 months (e.g., part-time worker scenario)

    b. 5 days on, 2 days off, for a period of 9 months (e.g., day care scenario)

    c. Etc.

6. How could specific features of the AALM be further refined to improve its predictive accuracy?

- Revisit certain exposure assumptions – see comments/responses to Charge Question #3 above.

7. How could specific features of the AALM be further refined to make it more user friendly?

- Create a single worksheet in which figures are automatically generated for some of the more comment x-y scatter plots (e.g., time series for blood, plasma, bone, etc; blood vs plasma; intake vs blood Pb; etc.)
- Create a library of input files (or example Excel workbooks) that correspond with example scenarios. Then use those scenarios as part of the Guide to coach new users on various common scenarios, and how to populate the dialogue boxes.
- Create a single worksheet for risk characterization, whereby a lognormal distribution model assumption is applied and a plot is automatically generated. Include a short set of entries at the top of the page that are dynamic (i.e., change the plots when the entries are changed). Incorporate user-specified GSD and age ranges to display. Include a tabular summary of common risk metrics: 1) probability of exceedance of user-specified threshold; 2) predicted blood lead concentration at user-specified percentile.
- As part of the Simulation Control worksheet, include an option (toggle) for the user to enter a constant media concentration for each of the common exposure media (e.g., soil, dust, air, water, etc), as an alternative to populating the age-specific concentrations in each separate worksheet.
- Consider including ALM directly in the current workbook such that entries are automatically populated (linked) to the entries specified by the user when running AALM. As a research tool, this will facilitate the understanding of AALM's application in a risk assessment context, including features that have been enhanced and/or changed.

8. Is the AALM consistent with the Agency's Regulatory Environmental Model Guidance found at URL:http://cfpub.epa.gov/crem/?

Yes, each of the steps summarized in Section 3 of the 2009 Guidance (copied below) appear to have been implemented in the development of the current version of AALM.

Summary of Recommendations for Model Development

- Communication between model developers and model users is crucial during model development.
- Each element of the conceptual model should be clearly described (in words, functional expressions, diagrams, and graphs, as necessary), and the science behind each element should be clearly documented.
- When possible, simple competing conceptual models/hypotheses should be tested.
- Sensitivity analysis should be used early and often.
- The optimal level of model complexity should be determined by making appropriate tradeoffs among competing objectives.
- Where possible, model parameters should be characterized using direct measurements of sample populations.
- All input data should meet data quality acceptance criteria in the QA project plan for modeling.

9. What additional information (if any) about AALM might be useful to users who want to assess a hypothetical or real-world risk assessment problem, in order to facilitate the correct application of the model and to communicate its modeling outcomes correctly and efficiently?

- See responses to Charge Question #7.

Editorial Comments

Technical Support Document

1. Table of Contents
    a. Section 3.1: misspelling of "Objectives"
    b. Section 4.4: make "AALM-of" all CAPS for consistency

2. Text
    a. Change "discreet" to "discrete": p.11, line 10; p.12 line 16; p. 13, line18
    b.

3. Table A-1
    a. Soil submodel, p. 195: typo on subscript "Soil"on RBA term

Exposure	Soil	For each discrete age: $INsoil_{discrete} = Soil_{TWA_{discrete}} * IR_{Soil} * RBA_{Doil}$

    b. Other submodel, p. 197: subscript "1" on Other1

Exposure	Other	For each discrete age: $\text{Other}_{\text{Total}_{\text{discrete}}} = \text{Other1} + \text{Other}_2 + \text{Other}_3$

    c. Submodels for summation of intakes, p. 197: add the word "rate" to header, for consistency with prior headers, (i.e., "Daily lead intake rate from all sources (µg/day)

Daily lead intake from all sources (µg/day)		
Exposure	Inhaled	For input to biokinetics: $\text{BRETH} = \text{INair}_{\text{total}}$
Exposure	Ingested	For combined ingestion pathways: $\text{IN}_{\text{ingestion}_{\text{total}}} = \text{IN}_{\text{water}} + \text{IN}_{\text{dust}} + \text{IN}_{\text{food}} + \text{IN}_{\text{other}}$
Exposure	Ingested	For input to biokinetics: $\text{EAT} = \text{IN}_{\text{ingestion}_{\text{total}}}$

    d. Growth submodel, p. 198, suggest adding one more set of parentheses for exponential term for $\text{BLDHCT}_{\text{HOWOLD>0.01}}$

Biokinetics	Growth	$\text{BLDHCT}_{\text{HOWOLD}\leq 0.01} = 0.52 + \text{HOWOLD} * 14$ $\text{BLDHCT}_{\text{HOWOLD>0.01}} = \text{HCTA} * (1 + (0.66 - \text{HCTA}) * e^{-(\text{HOWOLD}-0.01)*13.9})$

Suggest the following:

$$\text{BLDHCT}_{\text{HOWOLD>0.01}} = \text{HCTA} * (1 + (0.66 - \text{HCTA}) * e^{-((\text{HOWOLD} - .01)*13.9)})$$

INRATE

e. Plasma submodel, p. 214, suggest removing parentheses in ratio of term $\frac{\quad}{\text{OUTRATE}}$ and in numerator of final term (INRATE):

$$\mathrm{YPLS}_0 = \left(\mathrm{YPLS}_0 - \left(\frac{\mathrm{INRATE}}{\mathrm{OUTRATE}}\right)\right) * e^{(-\mathrm{OUTRATE}*\mathrm{DELT})} + \frac{(\mathrm{INRATE})}{\mathrm{OUTRATE}}$$

f. Biokinetics /Bone submodel, p. 254, use plain text for numerator:

Biokinetics	Bone	$\mathrm{BONFRC} = \frac{YSKEL}{\mathrm{TBODY1}}$

g. Biokinetics urine submodel, p. 256, Clearance equation: change numerator "URINE" to "URIN" for consistency with other equations and parameter specification (e.g., p. 269 definition of URIN)

Clearance (day^{-1})		
Biokinetics	Urine	$\mathrm{CLEAR} = \frac{\mathrm{URINE}}{\mathrm{DELT}} * \frac{1}{\mathrm{YPLAS}}$
Biokinetics	Blood	$\mathrm{BCLEAR} = 100 * \frac{\mathrm{URIN}}{\mathrm{DELT}} * \frac{1}{\mathrm{YBLUD}}$

4. Table B-1.
   a. Explanation column for "Sex": change to "Female or male"

Sex	unitless	C	S	Female of male

   b. Explanation for water ingestion rate, "IR_water": change "dust" to "water"

IR_water	L/day	C	F	Dust ingestion rate for water Pb exposures

   c. Confirm that term "indoor soil" is intentional – is it better defined as simply "soil" ?

p. 257

Age_soil_IR	day	A	F	Age for indoor soil ingestion rate

p. 259

Pulse_i_width_soil; i=1,2	day	C	F	Width for pulse train exposure to indoor soil
Pulse_start_soil	day	C	F	Start age for pulse train exposure to indoor soil

5. Appendix C
   a. p. 276, table at Line 4: following the units in the footnote, explain the statistics given in the

table (e.g., mean ± SD; or mean ± SE). Also, missing close parenthesis on header, Floors, sample size.

3 dusts for a statistical sample of U.S. residences. Based on a sample of approximately 2000 homes, the
4 mean Pb loading (µg/ft^2) were as follows:

Floors (n = 3,894	Window Sills (n = 2,302)	Window Troughs (n = 1,607)
13.6±484	195±1683	1991±12,086

Units: µg/ft^2

b. p. 276, line 13: delete the word "of" in the phrase "A value <u>of</u> equal to…"; line 14: add hyphen for "soil-derived"; line 15: comma after "e.g."

13 track in from contaminated soil). A value of equal to the soil Pb concentration (see section on *Soil Lead*
14 *Concentration*) is recommended for *Dust_baseline* for simulating residences where soil derived dust is
15 the major source of indoor dust Pb (e.g. no other significant indoor sources such as paint or hobbies).

Furthermore, modify the sentence to explain how the corresponding soil Pb concentration is 25 µg/g, 50 µg/g, or 250 µg/g depending on proximity to historical emission sources and the age of the housing stock. In total, suggest the following revision:

> "A value equal to the soil Pb concentration (i.e., 25, 50, or 250 µg/g, depending on proximity to historical emission sources and age of housing stock – see section on *Soil Lead Concentration* below) is recommended for *Dust_baseline* for simulating residences where soil-derived dust is the major source of indoor dust Pb (e.g., no other significant indoor sources such as paint or hobbies)."

c. p. 277, table preceding line 1, the footnotes use the word "range" for both the 5th -95th percentiles as well as for what is presumably the min-max. Suggest either changing footnote a to "5th - 95th percentiles" or changing footnote b to "range (minimum, maximum)"

Full Transect (n = 4841)	Statewide Average (n = 48)
25 (8, 44)[a]	30 (14, 68)[b]

Units: µg/g.
Statewide average is the average of state means.
[a]5th-95th percentile range
[b]range

d. p. 277, table following line 7, change footnotes to clarify units apply to GM, mean, and median:

7 soil Pb concentration were estimated (U.S. EPA, 2019):

Housing Stock	GM	GSD	Median	Mean
Pre-1940	113.4	3.58	113.4	246.8
1940-1977	28.6	2.9	28.6	50.0
Pre-1978	26.3	3.8	26.3	64.1

GM, geometric mean, µg/g; GSD, geometric standard deviation

Suggest: units (GM, median, mean): µg/g

GM, geometric mean; GSD, geometric standard deviation

e. p. 278, table following line 17, same comment as (c) above

17 following central estimates for water Pb concentration were estimated (U.S. EPA, 2019):

GM	GSD	Median	Mean
0.69	2.1	0.69	0.89

GM, geometric mean, µg/g; GSD, geometric standard deviation

f. p. 281, line 8, delete extra "e" at end of line

g. p. 281, line 10, change "ventilation rates" to "drinking water ingestion rates"

8 The EPA TRW estimated drinking water intakes rates in children based on and analysis of data from the e
9 1994–1996 and 1998 Continuing Survey of Food Intakes by Individuals (CSFII; USDA, 2000) as
10 reported by Kahn and Stralka (2009). Age category mean ventilation rates were as follows:

h. p. 282, table after line 3 – include a second column for Age that provides equivalent years

Age (days)	Water Intake (L/day)
0	0.20
90	0.30
365	0.35
1825	0.35
3650	0.45
5475	0.55
9125	0.70
≥18250	1.04

Age (days)	Age (years)	Water Intake (L/day)
0	0	0.20
90	0.25	0.30
365	1	0.35
1,825	5	0.35
3,650	10	0.45
5,475	15	0.55
9,125	25	0.70
≥18,250	50	1.04

The same comment applies to the following summary tables:

- p. 281, dust and soil ingestion rates
- p. 284, ventilation rates

i. p. 282, line 10, delete the extra "(" after RT

10 exhausts while they were sedentary. However, regional deposition and clearance in the RT (will depend

j. p. 284, line 15, reword "for from"

15 few exceptions, these have not used IVBA methods for from which RBA can be reliably predicted

k. pp. 284-285, lines RBA for dust and soil. Page 285, lines 3-8 indicate that EPA TRW recommends a value of 60% for ingested soil Pb. As implemented in the IEUBK model, this applies to dust as well. Considering adding this point to discussion of dust on p.284 (which occurs first), with a cross reference to RBA for soil.

l. p. 285, lines 20-23, RB for food – typographical error at end of line 21 and start of line 22, "…ingestion of Pb that has and TBA <1 ..." should be "…ingestion of Pb that has an RBA<1…"

20 ***RBA_food.*** RBA of water-soluble Pb dissolved in food is assumed to be 1. RBA of Pb in foods has not
21 been studied and it is possible that certain exposure settings could result in ingestion of Pb that has and
22 TBA <1 in association with food. For example, adherence of surface dust, soil or sediments to consumed
23 foods.

Soil_baseline	µg/g	C	F	Baseline indoor Soil Pb concentration used in exposure pulse train	Background	25	(U.S. EPA, 2019; Smith et al., 2013)
					Residential (>1940)	50	
					Residential (<1940)	250	

Michael J. Kosnett Preliminary Responses to AALM Charge Questions

The following are pre-meeting, preliminary comments on the Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations (May 2019) external review draft. More comments will be added before the meeting, and further additions/revisions are anticipated following the meeting.

Initial comments on exposure and biokinetics:

A valuable aspect of the AALM is its capacity to combine age and medium specific intakes that are assigned a baseline value, supplemented by pulsed intakes that may take place intermittently - e.g. baseline Pb soil and dust intake at home 7 days a week all year, supplemented by Pb soil and dust intake at work 5 days a week 11 months a year, and Pb soil intake at a park 2 days a week 3 months of the year. In like manner, the model can combine in the same day a given value of air Pb concentrations and ventilation rates at work during part of a day with a different concentration of Pb in air and a different ventilation rate at home. This is remarkable flexibility compared to most models that have heretofore been developed.

With respect to relative bioavailability (RBA) it would be helpful for the developers to explain why 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. For example, in Section 2.2.3.3. (pdf page 22) the narrative states, "The model accepts a single inputted value for RBA which represents soil from all sources, in all exposure settings." The same provision for a single RBA applies to all Pb in indoor dust (Section 2.2.3.2). This seems counter to the model's flexibility in allowing for multiple values of Pb intake in soil or dust at different times of the day (or week). It seems likely that the soil or dust that compared to lead ingested in an occupational environment, lead ingested in a residential setting by may have different solubility, particle size, and chemical composition, and by extension different RBA.

With respect to lead intake in water (section 2.2.3.4; pdf page 24), the narrative states:

$$IN_{WATER} = PB_{WATER} \bullet IR_{WATER} \bullet RBA_{WATER} \qquad \text{Eq. (2.2-18)}$$

where INwater is the intake of Pb in water (µg Pb/day), Pbwater is the Pb concentration in water (µg Pb/L), IRwater is the rate of ingestion of water (L/day) and RBAwater is the relative bioavailability of Pb in water and dust, relative to water-soluble Pb. Values for IRwater are

> interpolated between inputted ages. The model accepts a single inputted value for RBA which represents both water [SIC], in all exposure settings. Lead dissolved in water would, by definition, have RBA = 1; however, the RBA parameter could be used in scenarios in which ingestion exposures include Pb-bearing particulates suspended in water for which the RBA may be <1.

Here again, the intent of the model to account for intervals of ingestion of water containing soluble lead (with an RBA = 1) as well as intervals of ingestion of suspended lead that may have a lower RBA is salutary. Notwithstanding t1hat human data pertaining to different bioavailability of soluble Pb versus suspended fine particulate is sparse, it is conceivable that a receptor could be simultaneously exposed (during the course of a day) to a given mass of soluble and particulate lead. How would the model account for the possibility that these two different types of Pb in the same sample might have quite different RBAs? This scenario is plausible in domestic tap water, where intermittent releases of particulate Pb may greatly exceed baseline soluble lead.

With respect to subsection 2.2.3.5. Food Pb Exposure, the model appears to account for Pb intake in food as a user determined input in units of µg Pb/day. The model allows the user the flexibility to separately input intake for market basket food and home grown produce, and to combine baseline intake with pulsed intake. However in the case of food, as opposed to soil and dust and water, the model appears to not adjust for age specific changes in overall daily food intake across the lifespan.(The narrative states: “The model *does not* calculate food Pb intakes from inputted data on Pb concentrations in food and food consumption rates”). Is it up to the user to estimate and incorporate “pulses” of age-related changes in food intake (e.g. after consulting the EPA Exposure Factors Handbook or other sources)? If so, would it be helpful to include in an appendix to the model documentation suggested values for such age specific intake rates?

The AALM.FOR biokinetic module has adapted the Leggett model paradigm that Pb that enters “nonexchangeable” skeletal lead compartments only returns to the plasma compartment during bone remodeling. As a consequence of this structure, when long term exogenous lead exposure is terminated, the blood Pb concentration declines rapidly. For example, see Figure 3-2 B (pdf page 87), or the Leggett model output in EPA (2013) Integrated Science Assessment for Lead, page 3-81. This output appears to fit well with the empiric data shown in Figure 3-6 for a lead worker whose exposure was interrupted during a strike. However, there is concern, based on other actual observations, that the decline in blood lead is not as rapid as predicted by the Leggett biokinetic assumptions. Manton et al (2000) published data that demonstrated blood lead half-times between 20 to 38 months in young children exposed to lead dust from residential home remodeling. In the case of adults with occupational lead exposure, Hodgkins et al (1991) presented data that demonstrated an impact of past air lead levels on contemporaneous blood lead concentration more than 5 years after large reductions in air lead exposure had been

achieved. Schutz et al (1987) presented data on former lead workers indicating that the decline in blood lead following cessation of exposure followed a two compartment model – a fast compartment with a half-time of 1 to 2 months, and a slow compartment with a median half-time of 5 years. Hryhorczuk et al (1985) observed that for workers with chronic lead intoxication and normal renal function, the median blood lead elimination half-time was 619 days. It can be noted that a biokinetic feature of the O'Flaherty model with respect to bone lead compartments allows for diffusion of lead in *all* bone compartments to plasma at an age-dependent rate. This might predict a slower decline in blood lead concentration following cessation of extended periods of elevated lead exposure. It would be helpful to obtain additional data-sets that document the decline in blood lead concentration following abrupt cessation of longterm elevated lead exposure, so that the accuracy of the AALM.FOR model in these settings can be further examined.

<u>What additional information (if any) about AALM might be useful to users who want to assess a hypothetical or real-world risk assessment problem, in order to facilitate the correct application of the model and to communicate its modeling outcomes correctly and efficiently?</u>

Pb in bone, as measured by non-invasive K x-ray fluorescence (KXRF) has been shown in various studies to be a biomarker of an individual's blood lead level over time (cumulative blood lead index, or CBLI). As reported in several publications from the Normative Aging Study, a person's bone lead concentration at mid to late life, or an increment bone lead concentration across a given age strata, are better predictors than blood lead (or change in blood lead) of significant health endpoints such as cardiovascular morbidity and mortality and cognitive function. The ability of the AALM to include bone lead concentration as an output is likely to be helpful for risk assessment. By reference to investigations such as the Normative Aging Study, this information may facilitate assessment of the health risks associated with cumulative lead exposure.

The validity of KXRF as a biomarker of cumulative lead has primarily been established by favorable comparison of a single KXRF measurement to long term blood Pb biomonitoring in occupational cohorts. In most cases, the Pb exposure of these cohorts has been relatively stable for many years, (sometimes with a gradual decline over time). Based on this data, Person A with a cumulative blood lead index (CBLI) of 300 µg/dL•years will predictably have a higher KXRF bone lead concentration than person B with a CBLI of 200 µg/dL•years where Person A sustained 20 years of blood lead of 15 µg/dL and person B sustained 20 years of blood lead of 10 µg/dL. However, it's not clear how the KXRF bone lead measurements would compare if Person B's CBLI of 200 µg/dL•years were instead accrued through 15 years of blood lead of 5 µg/dL followed by 5 years of blood lead of 25 µg/dL. Outputs from the AALM that include estimated bone lead burden is likely to facilitate research into the utility of KXRF as a biomarker of cumulative lead exposure.

Dr. Anne Loccisano Preliminary Responses to AALM Charge Questions

Dr. Anne Loccisano Draft responses to charge questions

1. Are the features of the AALM adequately described in the "Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations?"

The way I went about this question was asking myself, as a user of this model, does the technical support document provide everything I need to know about this model and does it provide the information needed to explain how it works, assumptions, parameters, etc?

I think the answer to that is, for the most part, yes. I had to read through the document a few times to grasp everything, but as long as one has the patience to go back and search the various sections and really comprehend all the information, the features, equations, parameters, and assumptions are described. It was helpful to have both text explanations as well as equations and equation/parameter tables.

The document is pretty lengthy (I'm not complaining there—better to present all the information than not include it) and although this is personal preference, it was distracting having to go back and forth between the text and tables/figures (I had to keep 2 copies of the document open). Maybe there's a better layout for this (i.e., place the table or figure where it's discussed). Also, the equations in the tables (e.g., Table 2-2) are not presented in the order that they are discussed in, which is confusing

The model structure and most of the equations and descriptions of uptake, transfer, etc are described and those tables in the appendices with the equations and parameters are pretty thorough. However, there are some elements that are not described (which I pointed out in some of the answers to the questions below; for example, why is an intake rate for food not implemented and why is breast milk exposure not accounted for) that probably warrant explanation

2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?

This model is basically the Leggett model with growth/tissue volumes being incorporated by use of the O'Flaherty equations. Both are accepted models; however, the O'Flaherty model has a more physiologically-based structure (blood flows, etc) while Leggett has those transfer rate coefficients that do not seem to be based on anything other than fitting to data (although predictions are in pretty good agreement with data). O'Flaherty has some fitted/optimized parameters but I think Leggett probably has more of those. Also, the O'Flaherty model structure seems less complex with blood flows rather than all the transfer rates/deposition fractions that Leggett has. The technical guidance discusses some advantages of the O'Flaherty model

(especially with regard to how bone is described). Overall, I think the features are supported by the available literature; even with parameters that are fitted, EPA did that in order to fit available data

3. In general, is the theoretical basis for the model adequately described in Chapter 2 (Theoretical Framework, Parameters, and Equations)? Are the following specifics regarding AALM, also adequately described?

a. Values specified for the intake rates as a function of age for different media.

Most of this looked OK to me; intake rates appear to be those recommended in EPA guidance documents (and equations follow standard EPA methods of estimating intakes) and if they are not, justification/sources were provided. However, I did not understand the food intake. For all the other media, the intake is calculated from Pb concentrations in the media and intake rates (air, dust, soil). Why is this not done for food? I can understand why this might not be done for the "other" category as there are probably not good estimates for media like paint chips or something.

Since this model is supposed to simulate Pb exposure from birth, why is breast milk exposure not incorporated? Or is that somehow incorporated into food intake? It wasn't clear to me

b. Uptake/absorption parameters and parameters requiring modification for specific routes of exposure.

The relative bioavailability parameter (RBA) was confusing. In the technical guidance, it is stated that "The application of RBA as an adjustment to Pb intake rather than an adjustment to the GI absorption fraction is a simplification that results in an underprediction of fecal excretion of unabsorbed Pb and negative mass balance…when RBA < 1." If this results in a negative mass balance, what was the justification for this simplification? Was this done so that the relative bioavailability does not have to be adjusted for age (from the guidance document, that is supposed to be constant over the whole age range simulated)? How difficult is it to code it so that does not occur?

This is minor, but the RBA assumptions are not described/justified anywhere until Appendix C (this is true for many of the parameters). As I read through the document, I had to keep going back to that to see what the values and sources were (I just found this inconvenient).

In the absorption section (2.3.3), the technical guidance states that the model simulates Pb absorption from inhalation, ingestion, or dermal contact with dust—unless I'm missing something, I did not see a description of how dermal contact is simulated/accounted for. Is an adherence factor or hand-to-mouth contact factor built in or accounted for somewhere? This wasn't clear to me

For the respiratory tract, EPA states (and describes) the 4-compartment respiratory tract—a figure should be included for this. In section 2.3.3.1, it is stated that "these assumptions [referring to the assumptions on deposition fraction in the lung and % transferred by mucociliary clearance to the stomach] would not necessarily apply for exposures to larger or less soluble airborne particles." Some explanation (even a few sentences) would be helpful to the user on this

For the GI tract, EPA states (and describes) the 4-compartment GI tract—a figure should be included for this.

I thought that the equations used were described well and justification was given for the parameter values (largely Leggett and data cited within)

If they adjusted/fitted parameters, they cited data that they relied on for that.

c. Biokinetic parameters describing lead distribution and elimination.

The technical guidance indicates that chelation can be simulated with the model, but the spreadsheet model indicates that these parameters are fixed for no chelation and the cells in the sheet are not highlighted, indicating that these parameters should be changed. Why is this covered in the technical guidance if the user cannot use this function?

Is a sweat pathway really needed (or is there no other way to account for that elimination)? Even Leggett 1993 indicates that is a small percentage of elimination (and how well-characterized is the % eliminated in sweat?). Was this tested with sensitivity analysis? Just trying to suggest some potential simplification

Additionally, please comment on any strengths or weaknesses in the justification provided for model assumptions (data inputs, methodology, etc.) and the quantitative impact of those assumptions on the model and its results.

I'll put some more thought into this one before the meeting

4. What are the Panel's views of Chapter 3 (Evaluation and Development of AALM.FOR) with regard to the:

a. Predictive accuracy and reliability of the AALM based on comparisons to available data sets.

A strength is that the user is told that a limited number of data sets was used to test this model (especially for blood concentrations), the details of the data sets used for testing are given, and EPA gives examples of data that would be useful in further testing/reducing uncertainty/improving prediction consistency. From the data they compared the predictions to,

those looked OK. EPA states that there are several studies that have reconstructed Pb intakes for kids using exposure models but were not considered in this evaluation—these would be useful to include in the evaluation (it is not clear to me why they were not included)

Maybe I missed something with this, but for the worker studies used in the model evaluation, it was not clear to me if these cohorts had oral or inhalation exposure and how their exposures were input into the model

b. Extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms.

From what I saw from the comparisons of different versions/programs, the model appears to work as expected. Also, from using the spreadsheet version (in my limited testing of it), it appeared to do what it was supposed to

c. Availability of other datasets that may be useful for further model evaluation.

At this point, I don't know of any specific data sets (although I will try to look for something before the meeting), but I think what would be useful here are additional data sets for kids/adults that have BLLs in the 5-10 ug/dL range (CDC guideline levels) and known (or estimated) exposures (I guess the Rabinowitz and Ryu data sets have that but it would useful to have data that also span a lower range than that—if any of those neurodevelopmental researchers (or anyone trying to compare to outcomes associated with low BLLs) want to use this model, they will likely want to look at small changes in a low BLL range). There would be increased confidence knowing that the model can predict well in that guideline range and below that

Since this model incorporates inhalation exposure, some data sets where the subjects largely had inhalation exposure (known or estimated) might be useful for testing

5. Is the "AALM Fortran Users Guide" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved?

On p. 5 of the user guide, it is stated that the Leggett model text file that was compiled to create the Leggett executable is available as a "supplementary file". It was not clear to me where this file can be found (it is stated that this file may be needed if someone wants to make changes to model algorithms)

On p. 13 where they discuss using stepwise or interpolated exposures: When you choose one or the other (stepwise or interpolated) and you have more than one exposure source (i.e., food, water, and air) that this applies to all of those exposures (this is stated in the technical guidance

as well). What if someone wants to interpolate for food and then have stepwise exposure for water?

I was able to follow the user guide, reproduce the figures they had, and mess with the model for different scenarios. For the most part, I think the user guide is OK, but some more examples with different exposure scenarios should be given. As a modeler, I think I can probably use this thing OK, but for folks who are not, it would be useful to have some different exposure scenarios with different ages, different sources, different time steps, etc . Maybe include some real-world scenarios (exposure patterns that would have been encountered at a particular site or something) and advise on assumptions to make when there are data gaps. Not saying that people will actually run all of these (although I probably would because I like make sure the model works), but it'd be useful for people who are interested in testing the model and learning more about how to use it.

6. How could specific features of the AALM be further refined to improve its predictive accuracy?

7. How could specific features of the AALM be further refined to make it more user-friendly?

I'll think about this one…I thought it was OK and didn't have any issues using the interface or anything

As a modeler, I don't like that some parameters are not supposed to be modified. Maybe provide a range of values for those parameters so that users can see how changing those affects model outputs

8. Is the AALM consistent with the Agency's Regulatory Environmental Model Guidance found at URL:http://cfpub.epa.gov/crem/?

This is a general guidance document for development of environmental/human health models. The disclaimer statement in this document state that "it may not apply to a particular situation" and that "the EPA retains the discretion to adopt, on a case-by-case basis, approaches that differ from this guidance."

The basic process/elements outlined in the document for best practices include: problem ID and specification (specifying modeling objectives), model development (develop model structure, equations, code the thing), model evaluation (testing code to make sure it works and compare outputs to data), and model application (running the model to inform decision). As this document is a guidance document, it is open to interpretation (what am I saying—legally binding documents are open to interpretation), my opinion is that EPA should generally follow their own

guidance (consistency) but this may not apply to every situation and they do not necessarily need to follow this to the letter depending on the model being developed.

Broadly, EPA has accomplished most of these objectives in the technical guidance document: the model objectives are defined and EPA has developed the model over time (and they have explained the evolution of the AALM.FOR). In the guidance document, they present evaluations of the AALM.FOR (and other AALM versions—AALM.OF and AALM.LG) against (some) existing data and compared the AALM.FOR to the IEUBK model and the Adult Lead Methodology. To my knowledge, this model has not yet been applied to a real-world scenario to make some sort of decision. This model is still in development (isn't that the point of this panel?), so successfully applying it and providing an example in decision-making is premature (although it would help it provide examples with some measured exposures).

Other elements of the guidance EPA followed: They have conducted peer reviews of past versions of the model and they are now conducting another peer review, they have conducted sensitivity analyses (have they done a sensitivity analysis with the spreadsheet version?), and they have acknowledged some uncertainties and data needs

Chapter 3 of this document contains guidance on the model development aspect. I have a few comments here:

This chapter covers model complexity and the fact that models tend to uncertainty as they become more complex or increasingly simple. I think there are elements of the AALM that could be simplified—did EPA conduct sensitivity analyses for these (e.g., sweat excretion)?

This chapter also covers coding verification. While I messed with the code and was able to run different scenarios (and probably others on the panel did this), was independent testing of the spreadsheet model conducted (to find out what parameter ranges the code is stable in, etc)?

9.What additional information (if any) about AALM might be useful to users who want to assess a hypothetical or real-world risk assessment problem, in order to facilitate the correct application of the model and to communicate its modeling outcomes correctly and efficiently?

Guidance on how to estimate and assess paint exposures would be useful (and maybe some examples with real-world exposures/exposure patterns). Estimates on how much paint kids might ingest at different ages and how to estimate the lead content of paint from XRF

measurements would be much appreciated. There is probably a lot of uncertainty around these types of data but even some guidance on recommended values would be helpful. Any guidance on how to treat cases with paint exposures or lead from other sources (pottery, dishes, etc) would be helpful.

Since this is a life-stage model and simulations can be started from birth, incorporation/accounting for breast milk exposure would be useful.

This may be asking a lot, but maybe incorporate the pregnancy life stage. Bone resorption kinetics (and other physiology) changes a lot during this period, which will obviously affect blood and tissue lead levels and excretion. And I could see this scenario being something that risk assessors may want to simulate.

Dr. Steven Marcus Preliminary Responses to AALM Charge Questions

Question 2: Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings

It is difficult to answer 2. It would be unethical to truly study the model in real time, with real subjects. It is reasonable to use some animal data and some 'ecological" data to support the models. I expand o my feelingsbelow.

Difficulty in finding literature to support the rapid release of lead from children's bones.

> Gwiazda [i] (2005) reported 3 cases in which stable isotope measured lead levels suggested a rapid rise in bone-sourced lead in blood, but they did not really know the isotope ratios in bone and assumed that the reduction in the apparent environmental lead isotopes in the blood with rise in total blood lead was from the introduction of bone lead, but then where did the lead in the bone originate in the first place. In the studied cases the blood and fecal isotope ratios differed initially; they used heparinized blood collection tubes, a bit of a problem.

Need the model to enable a user to plug in a given BLL and look at effects of lowering or raising lead exposures

> Difficulty in finding literature regarding the effect of ingestion on actual blood levels in infants and children. There are limited reports which can be directly used to validate any model. The literature is based on a few studies which attempt to ascertain the effect on BLL from certain ingestions. They are both limited in number and study design which limits the ability to say they validate the model, except as "guestimates." There is some evidence of a multiple compartment model but this is not clearly represented in the model.

Lead exposure is probably more often related to intermittent exposures at relatively igher levels of dose than at baseline. The models do not take this into account.

> According to Lorenzana [ii]: The ICRP model was used to compare the outcomes (blood lead concentration) of various time-averaging adjustments for approximating the time-averaged intake of lead associated with various intermittent exposure patterns. Results of these analyses suggest that standard approaches to time averaging (e.g., U.S. EPA)(1) that estimate the long-term daily exposure concentration can, in some cases, result in substantial underprediction ofshort-term variations in blood lead concentrations when used in models that operate with EMATs exceeding the shortest exposure duration that characterizes the

intermittent exposure. Alternative time-averaging approaches recommended for use in lead risk assessment(2) more reliably predict short-term periodic (e.g., seasonal) elevations in blood lead concentration that might result from intermittent exposures. In general,risk estimates will be improved by simulation on shorter timescales that more closely approximate the actual temporal dynamics of the exposure.

The models seem to prefer a linear relationship between exposure and effect even given a previous elevated blood lead level from prior exposure. The assumption is that there may be a ceiling level from absorption, but there is limited, none, data to support this effect in infants/children.

The Glascow [iii] (1986) study of effect of dietary lead intake in infants suggests a closer fit to the cube root of the concentration of dietary lead, and not a linear relationship.

Davies et al [iv]: significant relationship with house dust lead loading and overall rate of touching things, to water and to parent's smoking. These factors are not well considered in the models

It is note that "it is not the goal of the IEUBK model to match the measured blood lead level of a specific child. The IEUBK model is primarily a probabilistic model, not a substitute for medical evaluation of a particular child." That being said, how can you use the model if it cannot be validated by specific cases?

Hogan study "This is the most extensive comparison of a biologically based blood lead model with real-world data of which we are aware. Within the scope of these comparisons, IEUBK-predicted blood lead levels agree with observed blood lead levels within 1 pg/dl, and IEUBK-predicted risk of blood lead greater than 10 pg/dl agrees with observed population exceedances within 4%. We conclude that this is reasonably close agreement." "One plausible explanation is that the exposure estimates both under- and overestimated individual children's cumulative lead exposure due to the cross-sectional measurement of lead levels from limited areas of each child's sphere of activity."

i. Gwiazda R, Campbell C and Smith D. *Env Hlt Persp*. (2005) 113(1)104-110
ii. Lorenzana RM, Troast R, Klotzbach JM et al. *Risk Analysis* (2005) 25(1) 169-178
iii. Sherlock JC, Quinn MJ. *Food Additives and Contaminants* (1986) 3(2) 167-176
iv. Davies DJA, Thornton I, Watt JM et al. *The Science of the Total Environment* (1990) 90 13-29.

Dr. Clyde Martin Preliminary Responses to AALM Charge Questions

Question 4.b. The extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms. [Dr Martin, Dr Vork]

The Staff has done an admirable job of preparing the documentation of the overall model. However as with any large program there will be glitches when trying to run the program on a different system. This is inevitable and occurs no matter who wrote the program and documentation. When I was a NASA I was involved with writing simulations for various aircraft control systems and I feel that this model has the same complexity as did those simulations. We solved the problem by insisting that the simulations be run on the NASA simulators and companies were free to use the simulators to test the program on different aircraft. Eventually Boeing used the models to develop control systems for their commercial aircraft. I would assume that they basically had to rewrite the code for their computer systems. I feel that the model developed here will have the same problems but will be used as a guide for preparing code by eventual users. The overall model is wonderfully developed and described.

Question 5. Is the AALM Fortran Users Guide sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved? [Dr.von Lindern, Dr. Clewell, Dr Martin]

I do not see any non-normal problems.

Dr. Isaac Pessah Preliminary Responses to AALM Charge Questions

1. Are the features of the AALM adequately described in the "Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations"?
   [*Dr. Loccisano- all other writing leads providing input*]

- Although not an expert in modeling, I found that the AALM Technical Support Document clearly explained the parameters included and the dynamics of their interactions.
- The modeling of kinetic fluxes among tissue compartments by route of exposure and age at exposure seems, to me, more than an incremental improvement in the overall modeling approach. Examples include, age-dependent simulation of absorption from the gastrointestinal tract and form inhalation using first-order fractions and first-order rate coefficients both within the GI and lungs, as well as summation of transfer rates from inhaled and ingested Pb to yield a total rate of transfer (µg Pb/day) to the central plasma compartment. The model accounts for rates of new Pb exposures (intakes) as well as Pb transferred to the gastrointestinal tract from the respiratory tract (i.e., mucocilliary clearance), and from the liver (i.e., biliary secretion). This seems to be a strength of the AALM.
- Another strength of the model is flexible for incorporating various exposure and absorption scenarios and accounts for transfer to the major target tissues (red blood cells and blood plasma (including a pool of Pb in plasma that is bound to proteins), brain, cortical and trabecular bone, kidney, liver, and other soft tissues.
- I defer to panel members having more expertise in building and evaluating the modeling equations used in AALM.

2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?
   [*Dr. Cory-Slechta*, Dr. Kosnett, Dr. Marcus]

3. In general, is the theoretical basis for the model adequately described in *Chapter 2: Theoretical Framework, Parameters, and Equations*?
   [*Dr. Weitzman*, Dr. Cory-Slechta, Dr. Phalen]

   Please comment on the discussion of the following specifics regarding AALM:

   a. Are the values specified for the intake rates as a function of age for different media adequately described?
      [*Dr. Goodrum*, Dr. Cohen]

b. Are the uptake/absorption parameters and parameters requiring modification for specific routes of exposure adequately described?
[*Dr. Vork*, Dr. Loccisano, Dr. von Lindern]

c. Are the biokinetic parameters describing lead distribution and elimination adequately described? [*Dr. Cohen*, Dr. Pessah, Dr.Vork]

Additionally, please comment on any strengths or weaknesses in the justification provided for model assumptions (data inputs, methodology, etc.) and the quantitative impact of those assumptions on the model and its results.
[*Dr. Clewell*, Dr. Cory-Slechta, Dr. Phalen]

1. Uptake/absorption parameters and parameters requiring modification for specific routes of exposure seem are adequately described and seem to permit flexibility for multiple exposure scenarios.
2. It is not clear whether the AALM permits adequate modeling of certain contemporary scenarios of extremely high exposures, such as those that may be encountered by fire fighters working in actively burning areas, inside firefighting vehicle cabins and within fire stations in close proximity to burns.
3. Some recent studies suggest levels of lead and other metals (chromium, nickel, copper, zinc, and manganese) orders of magnitude higher compared to more typical concentrations measured in non-fire settings.
4. It is not clear whether the model can account for simultaneous exposures to other metals that may have additive, multiplicative, or more complex influences on uptake/absorption parameters for Pb.
5. It is not clear whether the AALM accommodates scenarios of Pb adhered to microplastic particles, which could influence overall predictions on adsorption and distributions rates. Adherence of heavy metals, including Pb, can vary significantly among different plastic types and locations.
6. It is not clear whether the AALM accommodates more general interactions of Pb and other metals adhered to fine particles (eg, $PM_{2.5}$), including soluble and exchangeable fractions, carbonates, oxides, and Pb bound to organic matter, all know to occur in particulate matter samples.
7. It is unclear whether AALM can accommodate for the relationship of decreased pH, atmospheric deposition and increases in the exchangeable Pb (3.3-26.1%) in surface soils. These parameters have been suggested to increase health risk index (HRI) of (for example) rice consumption, which accounted for 40.0% and 35.5% of Cd and Pb at the high deposition site, respectively. Should the AALM include parameters with potential influences of atmospheric deposition on the soil-crop system to human exposures?

8. Exposure to lead typically occurs in conjunction with simultaneous exposures to other heavy metals of concern to human environmental health, especially susceptible populations. AALM may be sufficient to model Pb exposures in most scenarios although seems monolithic in that it cannot model exposures to real-life exposures to multiple metals. This should be viewed as a limitation of the model, possibly significant, especially when one considers the weight of evidence in the published scientific literature that Pb, Mn, Hg and other metals may converge on absorption, transport, metabolic, and neurotoxicity pathways.

What are the Panel's views of *Chapter 3: Evaluation and Development of AALM.FOR*) with regard to:

a. The predictive accuracy and reliability of the AALM based on comparisons to available data sets.
[*Dr. Goodrum*, Dr. Clewell, Dr. Cohen, Dr. Weitzman]

b. The extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms. [*Dr Martin*, Dr Vork]

c. The availability of other datasets that may be useful for further model evaluation.
[*Dr. Marcus*, All panelists, Chair to facilitate discussion]

4. Is the *AALM Fortran Users Guide* sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved? [*Dr.von Lindern*, Dr. Clewell, Dr Martin]

5. How could specific features of the AALM be further refined to improve its predictive accuracy? [*Dr Phalen*, Dr Marcus]

7. How could specific features of the AALM be further refined to make it more user-friendly? [*Dr. Barton*, Dr. Goodrum]

As discussed above under Q2 (point 8) and repeated here for clarity:

1. Exposure to lead typically occurs in conjunction with simultaneous exposures to other heavy metals of concern to human environmental health, especially susceptible populations. AALM may be sufficient to model Pb exposures in most scenarios although seems monolithic in that it cannot model exposures to real-life exposures to multiple

metals. This should be viewed as a limitation of the model, possibly significant, especially when one considers the weight of evidence in the published scientific literature that Pb, Mn, Hg and other metals may converge on absorption, transport, metabolic, and neurotoxicity pathways.

Dr. Robert Phalen Preliminary Responses to AALM Charge Questions

CQ-3:
The descriptions of the model are thorough and clear.

CQ-6 There are several ways to refine the AALM to improve it's accuracy and applicability to real-life Pb scenarios.

1. Using age and sex (i.e., standard growth curve data) to define exposed subjects has some problems. It assumes that all women are smaller than all men, which is a limitation. Parameters such as body weight, and BMI determine respiratory, water and food intakes, organ sizes, blood content and partitioning in fat, muscle and water compartments of the body. Also growth curves differ among ethnic groups.

2. The absence of airborne Pb aerodynamic particle diameter is a limitation. Pb from engine exhaust is sub-micrometer in diameter, so it has high deposition in the alveoli (and access to macrophage degradation, and proximity to a rich blood supply), while Pb from other sources (paint sanding and removal, metal grinding, re suspended dirt, Pb paint spray, and Pb powder dispersion) will be well above 1 micrometer aerodynamic diameter and have high bronchial deposition (with little blood access), and in many cases no deposition in alveoli.
Adding particle size categories (e.g., ultrafine, fine and coarse) would improve accuracy and applicability to realistic exposures. It will also tie into EPA's air monitoring network.

3. I did not see the fetus in the model. Blood levels in the fetus relate to that of the mother, and the pre-birth exposure routes are maternal blood and amniotic fluid. If a child starts life with Pb in it's blood, that should be added to the lifetime exposures. Otherwise the calculated blood levels and risks will be underestimates.

CQ-7: The Users Guide could be simplified, and thus improved, by omitting non-essential comments (e.g., to Leggett, and alternative model
structures) in the program input/output instructions. These topics are fairly well covered in section 1. Also, it would be helpful to include a web-based or e-mail link for the user to get help when all else fails.
As a former FORTRAN programmer, I know that situations will arise where the help of someone intimately familiar with the program will be needed.
Without a path to get help, users face failure to obtain Pb data for risk assessments, or other applications. The figures and tables could be numbered to help users quickly find the correct one without searching through the text.

Also, I have about 20 comments and edits on the User's Guide that I could pass on to the author(s).

Dr. Ian von Lindern Preliminary Responses to AALM Charge Questions

3b. Are the uptake/absorption parameters and parameters requiring modification for specific routes of exposure adequately described? [*Dr. Vork*, Dr. Loccisano, Dr. von Lindern]

General Comments

AALM.FOR model simulates Pb absorption from inhalation, ingestion, or dermal contact with surface dust. The presentation in the AALM.FOR support document suggests a rather narrow definition for absorption; i.e., described as the transfer of Pb intake (µg Pb intake/day), computed in the exposure model, to a rate of entry of Pb into the diffusible plasma compartment of the biokinetics model (µg Pb absorbed/day). Absorption from each exposure pathway is simulated as first-order processes governed by absorption fractions and/or first-order rate coefficients (per day). Extensive presentation of absorption is apparently limited to the Respiratory Inhalation RI, which has been enhanced in this version, and GI tract ingestion that integrates soil, dust, water, food, other sources in the small intestine for a single combined absorption step. There seems to be no discussion or application of dermal absorption. Relative Bioavailability(RBA) has been added as a Tab that has significant "absorption" implications.

Limited to this definition, most of the absorption parameters are first order plasma membrane rate coefficients, based on historic studies conducted thirty years ago when the models were developed. These studies have been recognized, utilized, and extensively critiqued and peer-reviewed for decades, as these were critical to the development of predictive models that influenced large resource expenditures to meet environmental and health regulations. As such, the documents' strategy of routing the readers/users to the historic literature is likely appropriate, although that is not easily accomplished for those without historic files or access to HERO.

The extent to which these coefficients can be updated or refined, however, is not discussed directly in the document. Moreover, if refinements are to be proposed, these should be discussed with appropriate cautions, including thoughtful consideration to any effect that changing a single co-efficient might have on other rate drivers in the model. Many of the partitions developed in these early studies were based on experimental designs and material balance considerations that could be distorted by perturbations in other partitions or coefficients. It is also unclear if these empirical descriptors are "double counting" some absorption mechanisms, as the modules and compartment-to-compartment transfers are accomplished, and intakes are simultaneously "adjusted" by addition of the Relative Bioavailability Tab.

Additionally, the comparison of different models and versions is sometimes confusing. With respect to overall absorption, there are absorption-related components throughout the model in both the exposure modules and the biokinetic compartments. It is not clear how these

components interact through the overall process, nor which inputs are controlling variables or rate drivers. Much of this could likely be extracted from the discussions and summaries of applications and sensitivity analyses in Chapter 4, although these are challenging to comprehend in a short review without a more thorough understanding of the inherent interactions. The document would benefit from an executive or bullet point summary of the grand lessons from these analyses.

With respect to the application of absorption related parameters in each of the compartments:

Respiratory Tract and Inhalation.

For the AIR Exposure module, overall absorption seems controlled by the empirical 40% value retention value derived from studies based on small particle inhalation studies. The model then partitions the retention among four lung compartments by reference to the historic studies; the model then apparently assumes all of the deposited lead is absorbed (excepting 4% sent to the gut) and assigns transfer coefficients (BRi) that ostensibly would be the "absorption parameters" with a direct route to the plasma compartment. The 4% fraction routed to the gut undergoes partial absorption together with other ingested bioavailable lead sources. With respect to bioavailability, the RI tract apparently assumes 100% bioavailability of all the material retained in the lung, as there is no provision for unabsorbed lead. The RBA Tab allows for assigning values other than 100% bioavailability, but is unclear as to the disposition of the any material if the bioavailability were assigned any value less than 100%.

The rate control parameters affecting absorption are modifiable in the LUNG Tab of the FORTRAN Input Module. These are described on the Tab as:

Deposition fraction and rate of removal from 1) extrathoracic, (R1, BR1); 2) bronci (R2, BR2), 3) bronchioles (R3, BR3); 4) alveolar regions (R4, BR4); this is the total deposition multiplied by the fraction in the compartment. The parameter CILIAR is also modifiable but is defined identical to BR1. The BR variables are partitioned according to historical findings referenced in the document.

However, there is no discussion in the User's Guide or Excel file regarding these parameters. These parameters are discussed in the Technical Support Document, as noted above, with limited qualification (i.e., applies only to adults breathing small particles in experimental settings). Some discussion is recommended of how the R and BR parameter values were derived (other than citing the original studies), the assumptions and factors that would need to be considered in changing these variable values, and whether the values need to be changed concurrently to not upset material balances in the model. Also, are there more recent studies and findings that can inform these selections for any of these parameter selections?

Gastro-intestinal Tract and Ingestion

For the INGESTION pathway, the inputs are adjusted by RBA in the SOIL, DUST, WATER, FOOD and OTHER Exposure Modules. Each of these effectively "adjusts" or reduces the amount of lead entering the biokinetic model components as discussed above. The model user can adjust the RBAs. Default values are 60% for soil and dust and 100% for food, water and other lead. As with the AIR bioavailability adjustment, there is no indication of the disposition of the "non-bioavailable" lead were RBAs set to less than 100%. Discussions with regard to soil and dust suggest this results in a material imbalance in the model under-predicting the fecal lead content. This results in delivery of a combined available Pb to the gut, which is augmented by secretions from other components (lung, bile, plasma) and all is transferred to the plasma by first-order absorption coefficients. Four compartments are modeled in series, to the small intestine, upper large intestine, lower large intestine, and feces at rates represented by first-order rate coefficients. All absorption of Pb from the gastrointestinal tract is assumed to occur in the small intestine, and is represented by an absorption fraction (AF), representing the fraction of Pb mass in the small intestine that is transferred to the diffusible plasma compartment. The remainder is passed to the large intestine and eventually excreted in the feces. The absorption fraction AF given by is age-dependent, and derived by formulae from historic studies.

Although gut absorption of lead is exceedingly complex and depends on numerous factors, absorption from the gut in the AALM approach seems simplified to a first-order fraction of the contents of the small intestine, based on a single age-dependent coefficient. As a result, characterization of the absorption parameters for the AALM would reflect the appropriateness of the original formulae developed earlier as cited in the document. However, the extent to which the model emulates understanding of the processes and concentration-dependent rate characteristics bears further discussion.

The extent to which overall absorption or the amount of total intake that eventually reaches (or is accessible to) tissue compartments has long been debated among researchers, practitioners and the regulatory community. Several alternative explanations have been advanced in application of these models to health response and regulatory actions, often with considerable impact on outcomes. The IEUBK model support materials noted some years ago that, in order to more accurately model lead uptake from the gut at higher intake rates, absorption fractions should be modified to separate non-saturable and saturable components. That is apparently not considered in this approach or if non-linear absorption is addressed. The IEUBK Technical Support Document extensively discusses both bioavailability application and gut absorption, and their role in applying combined passive/active absorption mechanisms to mimic non-linear uptake. It is not clear how non-linear uptake is accomplished in the AALM, especially with respect to which variables and parameter values specify or influence age-dependent and concentration dependent parameters; or whether there is "double counting" of absorption factors in applying bioavailability as an intake adjustment.

The first confounder may be definitional. Generally, in discussing absorption and absorption parameters in models integrating exposure, biokinetics, pharmacokinetics, and adverse health effects; the terms absorption, absorption fraction, bioavailability, bio-accessibility, relative

bioavailability, bioactivity etc. have somewhat different meanings to various disciplines. The IEUBK Technical Support Documents provided specific definitions as to how these were applied in the model development and use. These documents could benefit from more precise definitions and extended discussion of the approach. It would seem advantageous to EPA to use the same definitions, although there may be some differences with the original model developers' approaches and use of absorption terminology.

Among the more consequential uncertainties regarding overall absorption is the application of bioavailability. The general application, as has been appended to the AALM, has been to apply bioavailability as an intake adjustment, basically denying the absorption membranes access to the toxin, thus rendering it essentially inert. However, it is clear that absorption processes often choose to ignore available metals based on a number of considerations that are poorly understood or, at least, poorly quantified. Applying bioavailability as an intake adjustment must be recognized a major consequential assumption with respect to absorption. As such, this application should be addressed more thoroughly, perhaps similarly to the discussions in the IEUBK and ISA. The AALM document currently offers the following:

> *Further refine the gastrointestinal tract model*. AALM.FOR allows the user to input values for RBA of Pb in exposure media. This is important for risk assessment applications because the absorption fraction Pb is known to vary with the environmental medium in which it is contained (e.g., Pb in soil can have a lower absorption fraction than Pb dissolved in water). However, in the current version of AALM.FOR, the RBA adjustment is applied to the media-specific Pb intake rather than to the absorption fraction (*F1*) in the small intestine (see Section 2.2.3). In this configuration, Pb that is not absorbed when RBA is <1 does not appear in feces. This will result in an underestimation of fecal Pb excretion and a negative mass balance (excretion < intake).

It seems that the feces imbalance could be simply handled by routing the assumed inert Pb through to the excretion compartments to satisfy the material balance equations. Also, in the interest of a testable model, the total fecal concentration would be of interest, and an accurate accounting of total lead content in the lower tract may be of interest to health effects and pharmacokinetic investigators. However, this imbalance is likely not the most significant consideration. The important questions are: Was this lead invisible (never available) to the transfer mechanisms (i.e., truly inert), or was it accessible, but ignored, remaining in its original chemical/physical state; was there a physical/chemical change, but no uptake; or were there exchanges internal to the compartments?

On the backside of the "absorption" membrane, the amount of lead transferred to and from the plasma seems to be dependent on parameters in the blood compartments and particularly the exchange of Pb from the RBC and plasma components. The discussion related to the influence of the RBC parameters on childhood blood lead predictions, in comparison to the IEUBK model in Section 4, suggests that downstream mechanisms may have significant influence on "absorption", at least, uptake in the gut. On the other hand, the comparisons alluding to difference in absolute and relative bioavailability in the IEUBK and AALM is intriguing and

could contribute to the prediction differences. Section **3.3.9. Comparison to IEUBK Model for Pb in Children states:**

> Figure 3-19 compares predictions of the AALM and the IEUBK model for a continuous dust Pb intake of 10 µg/day. In both models, the relative bioavailability (RBA) for Pb in dust was assumed to be 60%. This corresponds to an absolute bioavailability of approximately 20% at age 2 years in the AALM and 30% in the IEUBK model. At age 2 years the IEUBK model predicts a blood Pb concentration of 1.18 µg/dL; the AALM predicts 1.25 µg/dL.

It seems there should be no difference in absolute bioavailability as that should be a fixed characteristic of the substrate, and the RBA is referenced to the absolute bioavailability of lead in water, which should also have a single value. The statement above indicates that bioavailability is age-dependent and differs in the two applications. This divergence, perhaps, refers to the differences in AI assumptions that EPA assigns in the models, as those relate to an absolute value expressed as an RBA. The age-dependent differences in blood lead predictions could be related to the apparent "age-related" differences in bioavailability generated by the intake "adjustments". It would be best to discuss, if not resolve, these differences as these models are released.

The report does address this question in Section 3.4 with the recommendation that:

> A model that adjusts the absorption fraction by RBA would provide a more accurate representation of medium-specific absorption and excretion of Pb. This would be similar to the modeling approach to RBA that is contained in AALM.CSL.

This refinement, together with appropriate discussion and definitions, should be supported to reflect evolving research findings, and to help resolve the non-linear, concentration dependent, and preferential (cofactor dependent) absorption considerations in the GI tract. The Technical Support Document would also benefit from an enhanced generalized discussion and clarification of terms.

5. **Is the *AALM Fortran Users Guide* sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved? [*Dr.von Lindern*, Dr. Clewell, Dr Martin]**

The evaluation and discussion of the "user friendliness" of the instructions for carrying out model runs depends on the underlying context of the question. It was not clear to this Reviewer whether the document should be reviewed in the context of utilizing the AALM as a regulatory or research model with broad application similar to the IUBK distributed by EPA for the last 25 years, or in context of the goals stated on page 4 of the User's Guide:

1) To maintain the format and functionality of the AALM.CSL Excel interface, particularly with respect to exposure estimation,
2) To adapt the tool to create the input files for the AALM.FOR and to call the FORTRAN executable directly to allow the user to run the Leggett AALM algorithms without acslX, and
3) To provide a rudimentary user's guide to help users to understand how to setup and run the simulations in this version, given the more extensive AALM.CSL documentation as a resource.

Assuming "rudimentary" being the key word, the User's Guide itself and the SAB Charge document might have explicitly indicated that the User's Guide was simply advice on how to implement a FORTRAN Program using an Excel Interface. In that context, the User's Guide is functional, assuming the User has substantial knowledge and familiarity with the predecessor models. Uninitiated Users would have considerable difficulty and frustrations in making the model operational, making informed modifications, and storing and interpreting the results. However, even if one is successful in getting the model to run, there is little guidance provided, in either of the documents, regarding how to save, connect and interpret the input and output summaries.

The **Table of Contents** is minimal and does not contain a Preface, List of Tables, Figures, Screens, or a Glossary. These are ostensibly available in the Technical Support Document. However, in some cases the descriptions in the Technical Support Document are insufficient to aid in implementing the model, and it is cumbersome to move between two documents that are seemingly connected, but not referenced to each other.

I. Introduction is brief and, for an uninitiated reader, provides minimal information as to the background, purpose, development, informative descriptions, historical evolution, intended or potential uses. biological and physical plausibility, computational accuracy, validation, empirical comparisons. Summary descriptions of these attributes would typically be expected in a User's Guide with specific reference to the Technical Support Documents. In this case the User must refer to the Technical Support Document without reference.

II. Overview of the Excel User Interface discusses the Excel user interface file, an input file template, the Leggett executable, and supplemental files (User's Guide and Leggett model text file). The explanation of the "pieces" is confusing. There are other Tabs in the interface file that are not discussed. It is not clear that that the "input file template" are some of the Tabs in the interface file. There is a second Excel file called the Intermediate Exposure Time Series file that is not reference or explained. This reviewer has not located the Leggett text files, and would not have an idea what to do with those if located. The executable file is problematic in that it gives no other indication it is functional than a "blink" of a black rectangle on the screen.

Exhibit 1 does describe the 3 Steps. However, it is not explicitly stated that the buttons are the activators of the Steps. If the executable program is not functioning, the buttons don't work. When this happens on the initial efforts to implement the Program, the User may not realize

these are active buttons and spend considerable time looking for the Step Initiators. A "dashboard" Screen Shot of the Simulation Control Sheet with descriptors and arrows would be of immense help.

The Note under Step 3 in the guide, particularly the last sentence: "However, the code returned errors in the compilation during our testing" is disconcerting, particularly if the first attempt to run the program returns errors. This suggests the User should be looking for the proprietary compiler.

III. Setup and Run

Subsection 1 provides instructions to unzip the files and place in folders with read/write permissions. It would be helpful if some description of read/write permissions and how to modify permissions, if necessary, were provided. This section also contains numerous references to the "Excel File" although there are two Excel files provided and the instructions apply alternatively to both. Nowhere in the Guide does it describe the purpose and function of the Intermediate File, except as a summary of the lead input to the biokinetic module. although it does suggest this, it is vital to execute the model. The instructions to add a runtime library to this Excel file is confusing.

These instructions might also be more user-friendly if implemented in steps. The first step should have a screen shot of the Excel File – the one provided is dissimilar to any that appeared on this reviewer's screen. Step 2 should be load the VB Editor. An explanation of runtime library, VB (or VBA as later abbreviated) Editor and the purpose of the Function would be helpful. It is also noteworthy that the Alt F11 key does not work unless the user is in the Excel file, and that these functions and screen shots are different for different versions of Excel. Does this apply to Excel in total or to one or both of the Excel files? Also, are these instructions applicable to Mac systems? Step 2a should be Select Tools with an appropriate reference to the Dropdown Menu, then a second shot Step 2b showing the Dropdown menu with the appropriate Box to check. The Tools menu is not on the control ribbon in some versions of Excel and must be accessed through Options. Also it should be noted that a new window will appear called "References-VBAProject" and that the proper entry must be checked in this Box. The Step 3 should be close the VB(A?) Editor.

A caution should be added to enable Macros in all Excel files after enabling editing. This should be mentioned before trying to implement the VB Editor. A screen shot indicating the yellow bar etc. would be helpful.

Subsection 2 addresses completing the Simulation Control Tab. EXPAGE, NDELT, TSTOP should be defined in the text. The entire concept of Simulation Time and Time Steps is sometimes confusing in both the User's Guide and Support Document. A clarification of both the rationale for time steps in modeling and the mechanics of implementing time steps to make the model perform accordingly would help uninitiated users. The historic note regarding computer

capacity in the Leggett era is interesting but perhaps better in a footnote or Appendix, as the recommendation for current use is the important message here. Some description of the considerations for TSTOP would be advisable.

Discussion regarding changing the NDELT is confusing. The reference to entering the value of DELT in cell H20 (not to be confused with water) is somewhat confusing as the DELT value is entered in cell I20. Also, the text indicates that Time Steps 2, 3 etc. should be entered in H21,H22 etc., but these are not colored yellow to indicate allowable input. Should the user do the Step numbers in these cells? The example on page 11 indicates NDELT=3 (two different time steps). Should this not be 3 total time steps or 2 additional time steps? Shouldn't there be a warning issued regarding the "one final nuance"?

The variable CINT should be defined including units if any. The cell defining CINT (D35) defaults to the inverse of cell I20 after each run. This results in the output being produced for each inverse of the DELT value (which was highly recommended to be a fraction of a day) resulting in cumbersome output. Obtaining a reasonable output frequency seems to require overriding the default and entering some fraction of the ICYC. Additionally, program errors have occurred on some runs referencing the CINT value as division by 0, if an actual number is not entered.

Saving the Intermediate Exposure Time Series.csv file does summarize the inputs to the Leggett biokinetic modules. Is there a summary Table indicating inputs to the Simulation Control Tab and Exposure Tabs, and Model Run Parameters corresponding to the output file; as opposed to summarizing the calculated inputs to the biokinetic model (which is also useful)?

In the discussion of interpolated versus stepwise exposure time series, what is the term "time stamps"?

Subsection 3. Exposure Input Tabs describes the inputs for the exposure modules. Each of these Tabs is relatively straight forward. However, there has been limited opportunity to execute runs that involve both the discrete and pulse functions. There is some confusion related to the discrete and pulse fractions concerning whether the combination of these must total one or if a pulse can overlap a discrete exposure. If this is permissible, how does that relate to the Baseline in the Pulse exposure? The text indicates that, presumably internal, programming to translate exposure profiles into the Leggett model is intricate and refers to a "tool" that accomplishes this translation. It is unclear why this is of interest to the user or what tool this references.

The reference to the "tool" also discusses the application of the RBA tab. The text indicates that the user should specify a "generic" bioavailabity for (e.g., food) and then relative bioavailability for the other media compared to food. This description could be at odds with the use of the term relative bioavailability in other applications, that is usually related to particular lead salts dissolved in water. The implication a determining a generic bioavailability food seems to be a throwback to the days when the first code was developed. Substantial development in the

understanding of lead bioavailability in the gut has ensued since. See the discussion regarding absorption in Question 3b. The discussion here should be amended to reflect bioavailability determinations consistent with other EPA models and Programs.

Section 4. Necessary Changes to the Biokinetic Input Tabs briefly notes the location of biokinetic parameters, but provides little information regarding these variables. Any considerations for changing these values would be referred to the Support Documentation which, in some instances, is insufficient to support any changes.

8. Is the AALM consistent with the Agency's Regulatory Environmental Model Guidance found at URL:http://cfpub.epa.gov/crem/? [*Dr. Loccisano*, Dr. Kosnett, Dr. von Lindern]

The referenced document, *Guidance on the Development, Evaluation, and Application of Environmental Models (*EPA/100/K-09/003, March 2009) (http://www.epa.gov/osp/crem/library/whitman.PDF), suggests the following aspects of a model should be peer-reviewed to establish scientific credibility:

- Appropriateness of input data. *The input data are specified and discussed. The input data have been appropriately presented and utilized through the historic development and use of the parent models. However, the presentations in the document supplied for this review assume substantial familiarity with the historic literature supporting the model. When introduced to the next generation of researchers and regulators, the presentation should be reordered to both point out the current relevance and the underpinnings of the some of the key assumptions. There are some recent additions to the model, particularly the inclusion of bioavailability inputs to the Exposure modules, that would benefit from a more thorough discussion of potential interactions with other modules and compartments.*

- Appropriateness of boundary condition specifications. *Boundary conditions are not explicitly describedbut can likely be presented and discussed appropriately in subsequent presentations. Boundary conditions discussions should be applied to both the overall model, but also to the individual input variables where appropriate.*

- Documentation of inputs and assumptions. *The purpose and significance of the input variables are adequately presented throughout the documents. However, this model is a reconstruction and update of historic models developed by others over a long history. Many of the key assumptions and justifications are found in the parent literature that in many cases is decades old. The document would benefit from a Table and brief description of those key assumptions and their continuing applicability. The current User's Guide indicates summary input tables can be*

requested to correspond with the output results. However, it was not clear how to produce or archive these summaries.

- Applicability and appropriateness of selected parameter values. *There are numerous parameter values included in these models. Many of the variable value selections should not be made in isolation. Additional sensitivity analyses might be conducted that examine the effects of multiple variable interactions. These findings might lead to additional guidance cautions about the appropriate ranges and other parameter settings that might be considered in altering input values.*

- Documentation and justification for adjusting model inputs to improve model performance (calibration). *The current document discusses interesting findings related to comparisons to other models currently accepted for regulatory applications. Additional investigations, relating these findings to plausible biological processes and discussions of additional research activities that could advance understanding of the underlying mechanisms, would be an important addition to both scientific understanding and eventual application of these models.*

- Model application with respect to the range of its validity. *An understated strength of this model is that it can be applied across a large range of biological effects, age and exposure/dose considerations. There is an unfortunate tendency in Agency efforts to focus modeling and research efforts on current US exposure levels. This model, particularly with its genesis in late 20th century US exposures, is particularly applicable to the higher levels of lead intoxication observed globally in vulnerable populations. It could be of immense service to international institutions implementing health and environmental responses. The calibration and verification efforts should continue to be across the full range of lead intoxication levels previously observed in the US.*

- Supporting empirical data that strengthen or contradict the conclusions that are based on model results. *The current documents and historic applications of these models has proven the applicability and usefulness. These efforts have been successful in both verifying the model's applicability and performance. The model will best be developed by continued testing and rigorous calibration efforts utilizing available data sets from the real world. The Agency should continue to identify and apply the model to real world situations, as well as controlled studies and designed experiments.*

Elements of External Peer Review for Environmental Regulatory Models (EPA 1994b)

Regulatory Decision Making Model Purpose/Objectives

What is the regulatory context in which the model will be used and what broad scientific question is the model intended to answer? *Not clearly indicated in the documents, but likely to be explained in subsequent presentations. The regulatory significance seems indeterminate at this point. The model has significant research potential and can be an important tool in exposure investigations. However, the numerous opportunities to direct outcomes through manipulation of variable inputs make it vulnerable to regulatory mischief.*

What is the model's application niche? *Not clearly indicated in the documents, but likely to be explained in subsequent presentations. Identification and investigation of outside data sets to aid in the understanding the relationships between environmental exposure and biological effects is recommended.*

What are the model's strengths and weaknesses? *There is sufficient information in the presentations for the Committee to develop a response. Obvious strengths are the integration of numerous multi-disciplinary factors in a logical, coherent and biologically plausible format, that allows exploration of complex interactions. Weakness is the large number of interactions and the interdependence on input data and underlying assumptions.*

Major Defining and Limiting Considerations

Which processes are characterized by the model? *Adequately described.*

What are the important temporal and spatial scales? *Adequately described.*

What is the level of aggregation? *Adequately described.*

Theoretical Basis for the Model — formulating the basis for problem solution

What algorithms are used within the model and how were they derived? *Adequately described.*

What is the method of solution? *Adequately described.*

What are the shortcomings of the modeling approach? *There is sufficient information in the presentations for the Committee to develop a response.*

Parameter Estimation

What methods and data were used for parameter estimation? *Adequately described.*

What methods were used to estimate parameters for which there were no data? *Adequately described.*

What are the boundary conditions and are they appropriate? *Not clearly indicated in the documents, but likely to be explained in subsequent presentations.*

Data Quality/Quantity Questions related to model design include:

What data were utilized in the design of the model? *Adequately described, but does rely heavily on references to historic data that a modern audience may not be familiar with or unable to access.*

How can the adequacy of the data be defined taking into account the regulatory objectives of the model? *Not clearly indicated in the documents, but likely to be explained in subsequent presentations. The history of these models in past regulatory forums is testimony to the appropriateness of the data used in developing and that applied and investigated.*

Questions related to model application include: *Adequately described.*

To what extent are these data available and what are the key data gaps? *Adequately described.*

Do additional data need to be collected and for what purpose? *Adequately described, but can be enhanced by considering applications beyond the Agency's immediate needs.*

Key Assumptions

What are the key assumptions? *Adequately described, but would be better presented in a summary format indicating the significance of the assumptions across the entire model, in addition to local considerations within individual compartments.*

What is the basis for each key assumption and what is the range of possible alternatives? *Adequately described, but would be better presented in a summary format indicating the significance of the assumptions across the entire model, in addition to local considerations within individual compartments.*

How sensitive is the model toward modifying key assumptions? *Needs more discussion in the presentation documents.*

Model Performance Measures

What criteria have been used to assess model performance? *Adequately described, but not quantified.,*

Did the data bases used in the performance evaluation provide an adequate test of the model? *Adequately described and promising, but additional applications should be encouraged.*

How does the model perform relative to other models in this application niche? *Adequately described, notable concurrences and differences detected and discussed. Follow-up and additional investigations should be encouraged.*

Model Documentation and Users Guide

Does the documentation cover model applicability and limitations, data input, and interpretation of results? *Adequately described, but subsequent presentations could be developed in format more appropriate to uninitiated audiences.*

Retrospective

Does the model satisfy its intended scientific and regulatory objectives? *Adequately described. The model will be an asset to both scientific and regulatory programs. However, it is not sufficiently developed to replace or substitute for the current models used under Agency Directives.*

How robust are the model predictions? *Adequately described. These are state of the art predictions in recent applications that can be improved through modest efforts integrating more recent scientific findings, other modeling strategies, and more user-friendly interactive modules.*

How well does the model output quantify the overall uncertainty? *Not clearly indicated in the documents, however, the sensitivity analyses are promising and should be enhanced to develop a cogent description of uncertainties, that would greatly benefit the user.*

Dr. Kathleen Vork Preliminary Responses to AALM Charge Questions

Preliminary draft responses to charge questions to the All-Ages Lead Model Review Panel

US EPA Science Advisory Board

For the Review of:

All-Ages Lead Model: Technical Support Document and Model Software

Prepared by US EPA Office of Research and Development

Sent Sept. 24, 2019

After many years of study, the AALM has emerged as a coordinated effort to combine concepts and capabilities from previous models developed and implemented for specific purposes. The newest version of the AALM is presented as a model primarily intended for use in risk assessment and computational toxicology. It is assumed that the new AALM will be used to predict lead levels in the tissues and fluids of humans at any age under a broad spectrum of exposure scenarios.

The AALM incorporates the systemic structure (compartment representation and mass transfer after absorption) presented in Leggett (1993). The latest version of the AALM has been adjusted to reflect new information provided by additional studies of exposed populations and from additional insights provided by multiple evaluations of the Leggett and other models. Although I have been assigned charge questions

In general, it appears that during adulthood the AALM predicts a given BLL after chronic exposure to a lower air concentration than predicted by the original Leggett model.

My comments on the all-ages lead model mostly focus on the adult systemic transfer rates (after absorption to blood), exposure parameters (up to and including absorption) and the model's use related to adult exposure scenarios.

Here are some major points:

- Changes to key adult model parameters produce much larger percentages of lead distributed to important target tissues relative to autopsy findings
- Lead uptake and release in trabecular bone relative to cortical bone mineral has remained greater on a ug/g basis for chronically exposed workers which departs from AALM predictions
- An assessment of model performance relative to job tenure as described in Hattis (1981) suggests that model performance may be influenced by the length of employment and that the transfer of lead in the bone compartments may need for attention

- Gut absorption of swallowed lead particles removed by ciliary action can vary widely over a 24hr period based on what else is in the stomach.
- Inhaled particles that are swallowed can contribute a significant amount of lead to blood (larger mass that is not measured by standard workplace sampling protocol).
- Breastmilk transfer of lead from the mother can be added to the model based on the mother's blood lead level.

Additional details are provided under specific charge questions.

Charge to the All-Ages Lead Model Review Panel:

The Environmental Protection Agency's Office of Research and Development (ORD) seeks peer review and advice from the All Ages Lead Model (AALM) Panel regarding the scientific soundness of the AALM. ORD requests that the Panel address the following charge questions during its review:

1. Are the features of the AALM adequately described in the "Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations?"

The model structure includes arrows depicting separate rates of transfer in and out of tissue compartments when other transfer rates are different. For example, arrows pointing in both directions should be replaced by separate arrows representing lead entering and leaving compartments (e.g. the brain tissue compartment).

2. Are the model features supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings?

Papers by Fleming et al and Nie et al provide a reasonable historical account of blood lead levels among exposed smelter workers during years 1965 to 1995. In addition, Nie provides bone lead levels measured at two time periods in retired workers. Bone lead relative to bone mineral alone was consistently higher in trabecular compared to cortical bone (on average about twice as high). These findings suggest that declining bone lead distant in time from the end of exposure are not well characterized in the AALM if applied to worker exposure scenarios.

3. In general, is the theoretical basis for the model adequately described in Chapter 2 (Theoretical Framework, Parameters, and Equations)?

No comments at this time.

Are the following specifics regarding AALM, also adequately described?

a. Values specified for the intake rates as a function of age for different media.

No comments at this time.

b. Uptake/absorption parameters and parameters requiring modification for specific routes of exposure.

One specific route of exposure for workers is inhaled particles that are removed by ciliary action and swallowed during and after meals where absorption efficiency can increase substantially from the default of 12% oral absorption of lead from the small intestine.

An infant exposure route through lead in breastmilk is worthy of consideration. As stated in Castellino et al (1995) on page 473 correlations were established through several studies relating breast milk to maternal exposure. Studies by Moore et al (cited in Castellino et al (1995)) lead concentrations in breast milk are about 10 times lower than blood lead levels in the mother and related as follows:

Milk lead = 0.0223+0.0868 x maternal blood lead.

An independent assessment of this relationship was published by OEHHA (2012).

c. Biokinetic parameters describing lead distribution and elimination.

Additionally, please comment on any strengths or weaknesses in the justification provided for model assumptions (data inputs, methodology, etc.) and the quantitative impact of those assumptions on the model and its results.

The assumption that RBCs reaches begins increasing the proportion of unbound lead at about 60 ug/dL RBC (25 ug/dL whole blood levels) was introduced by Chamberlain (1985) based on research published by Manton and Cook (1984) and subsequently adopted by Leggett. Leggett's equation depicting this nonlinear increase predicted plasma lead levels in-line with Manton and Cook data at whole blood lead up to about 90 ug/dL and remained below the curve fit to data from deSilva (1981) at levels above 90 ug/dL. If the alternate assumption that there is a nonlinear increase in the proportion of lead in plasma relative to whole blood at any level of lead in whole blood, then threshold constant would be set to zero and the saturation constant would be reduced to 280 ug/dL RBCs. The latter assumption (a nonlinear increase increase at any level of lead in whole blood) was adopted by others (O'Flaherty and OEHHA).

4. What are the Panel's views of Chapter 3 (Evaluation and Development of AALM.FOR) with regard to the:

a. Predictive accuracy and reliability of the AALM based on comparisons to available data sets.

Leggett pooled autopsy data into age ranges and tissue groups (Table 3 of Leggett 1993). In his article, Leggett argued that model predictions of mass distribution after chronic exposures would likely fall within the bounds of lead levels presented in Table 3 for six tissue groups.

Leggett represented the transfer of lead from plasma to urine as a combination of slow, moderate and rapid elimination processes. However, the AALM has eliminated the rapid transfer of lead through the kidney represented by a fractional deposition of lead from plasma directly to the bladder, increased by 25% the fractional deposition of lead from plasma to the kidney compartment representing the moderate rate of transfer of lead through the tubular pathway of the kidney and substantially increased the retention of lead (reduced the elimination rate to 10% of its original value) in the slowest compartment of the kidney.

Leggett also argued that the liver involved a rapid and tenacious turnover with diffusible plasma and an intermediate rate of transfer from the liver to the small intestine through the bile pathway (liver1 to small intestine). However, the AALM increased the retention time (reduced the rate of elimination to 30% of the original elimination rate) of lead in liver2 that subsequently returns to diffusible plasma.

Consequently, deposition and transfer rates were substantially altered in the AALM changed the pool size so that the AALM kidney and liver compartment burdens of lead are about 2.2 times greater than the upper end of the range found in the tissue groups of autopsied adults (see Table 3 last column in Leggett (1993)). In an initial assessment of predictions from the AALM compared to levels of lead found in postmortem data indicate that the original compared to the AALM retains 0.3% versus 0.9% respectively of the total body burden in the kidney and 3% versus 7.5% respectively in the liver.

Bergdahl et al (1998) presented three curves representing the plasma/whole blood relationship based on their analysis of data from 42 male and female active lead battery workers. Results from all three curves further informs the plasma/whole blood relationship. In Bergdahl et al (1998), the middle curve indicates that twice as much lead is found in plasma at higher levels of lead in whole blood than indicated in the pooled study analysis shown in Figure 3-13 of the draft TSD for the AALM. The middle curve represents additional binding suggesting that saturation begins to occur at lower levels of lead in whole blood. The middle curve in Bergdahl et al (1998) is in closer alignment with results from deSilva (1981) as modeled in Figure 14 of Leggett (1993). A discussion of additional finding from deSilva and Bergdahl appear to have been omitted from the TSD.

b. Extent to which the computer code implementing the model has been adequately verified and is operating as expected, based on the results comparing model predictions between applications of the AALM implemented in distinctly differing platforms.

I have not found any problems yet.

c. Availability of other datasets that may be useful for further model evaluation.

Articles published by researchers in Canada presented results from bone and blood measurements from chronically exposed workers are informative and provide additional

information about bone lead and distant past blood lead levels (Fleming et al 1998, Nie et al 2005). As indicated in Table x of Nie et al, lead levels in bone mineral from nine retired workers sustain ratios above about 1.5 of trabecular to cortical bone mineral years after removal from workplace exposure. However, the predicted decline of lead in trabecular bone mineral by the AALM diminishes substantially after removal from workplace exposure to ratios well below 1.0 of trabecular to cortical bone mineral.

5. Is the "AALM Fortran Users Guide" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved?

I've been told by some toxicologists who do site assessment that they are unable to run the AALM.

6. How could specific features of the AALM be further refined to improve its predictive accuracy?

Examine the bone/blood relationship following the methodology presented by Hattis (1981). Hattis emphasized that it not only important to evaluate the measured relative to model predicted post-strike blood lead levels in chronically exposed workers, but to also examine the model's performance relative to the number of days of workplace exposure prior to the strike. He presented a reasonable method for assessing the influence of workplace exposure tenure on the model's ability to predict blood lead levels on average as expected (i.e. near zero difference) without a significant difference relative to days of workplace exposure.

7. How could specific features of the AALM be further refined to make it more user friendly?

No comments at this time.

8. Is the AALM consistent with the Agency's Regulatory Environmental Model Guidance found at URL:http://cfpub.epa.gov/crem/?

No comments at this time.

9.What additional information (if any) about AALM might be useful to users who want to assess a hypothetical or real-world risk assessment problem, in order to facilitate the correct application of the model and to communicate its modeling outcomes correctly and efficiently?

No comments at this time.

Dr. Michael Weitzman Preliminary Responses to AALM Charge Questions

3. In general, is the theoretical basis for the model adequately described in chapter 2?

The theoretical model is very well explained. It is so well explained, in my opinion, that it facilitated my ability to perceive the following problems with it:

1. The theoretical basis for the model ignores several important facets pertaining to lead exposure, deposition and bioavailability that should be addressed:

Re: Inhalation of lead. Ventilation rates (in the public health and clinical literature "ventilation rates" is not a term that is used. Rather, this construct is referred to as their "respiratory rates." It is difficult for me to understand how one would categorize a respiratory rate as one that responds to being at "rest," "moderate activity" and "strenuous activity**." It is possible to picture how one would go about, using an appropriate sample, resting respiratory rate, but it is more difficult to picture how one would estimate "moderate activity" and "strenuous activity" by age and gender. Moreover, how does one validly take into account potential pulmonary diseases that affect very large percentages of the population and vary by age and severity, e.g. asthma, COPD, etc.)? Also, it has always been my understanding that GI rather than respiratory pathways are far more important sources of lead exposure.**

Re: GI absorption. On pg 25, the report states that even though absorption occurs from the small intestine absorption fraction, it is accounted for in the equations for inflow of lead to the upper large intestine. Given that we know this is inaccurate, **we should improve the model to reflect the level of absorbed Pb from the small intestine.**

Re: Uniformity of soil lead. The model assumes that values of soil lead have equivalent relative bioavailability (RBA) and assumes the same relative level, bioavailability and chemistries across soil types, which is inherently inaccurate. **There should be a way to titrate the model for exposure to multiple soil types similar to how this feature exists for dust.**

Re: fetal lead levels. The fetal model assumes lead mass in each neonatal compartment based on maternal blood concentration at birth. What data exists to support that maternal blood lead at birth is reflective of fetal levels? **Should maternal blood lead be monitored throughout pregnancy to better estimate fetal body burden at birth? Is one trimester more predictive of this?**

Re: age-related bone turn-over. It is well established that bone turnover decreases with age. However, bone degradation may contribute to elevated levels of lead in diffusible plasma in adults over 30. **Given that lead is a neurotoxicant and neurodegeneration concerns increase with age shouldn't we consider this lead sink as a potential source of lead exposure in aging adults?**

Re: bone-remodeling. Despite acknowledging that bone resorption is an important time for lead release into the plasma, there is no acknowledgement of bone-remodeling due to injury. This important sink, which can store as much as 90% of the body's total lead burden, **should be included in the model as this can be an important source of re-exposure even in the absence of notable lead in the immediate environment.**

Re: brain deposition. The brain is treated homogenously in the model, which is acknowledged as an oversimplification. Given that the most important toxicity associated with lead is believed to relate to neurological dysfunction, better models of brain deposition may be necessary. **Brain "constitutes relatively small site of deposition," which suggesting that deposition level either isn't driving toxicity but diffusible plasma levels may be better indicators of brain exposure needs more exploration.**

4. The predictive accuracy and reliability of the AALM based on comparisons of available data sets (chapter 3).

The data sets used to validate the AALM are limited in scope and applicability, which limits the wide-spread applicability of this model for accurately predicting lead exposures in all ages and populations. The model seems to work best when modeling high, consistent lead exposure (i.e. Rabinowitz study, subject 1), and falters when modeling multiple windows of exposure or varying levels of lead concentrations.

Re: Cohort limitations. Most of the data sets evaluated are from adult males and in occupational exposure scenarios. **The few female cohorts to which this model has been applied are inaccurate, which is probably due to sex-differences and female-based physiological assumptions that haven't been taken into consideration when building the model.**

Re: blood versus bone predictive reliability. While blood is the easiest matrix from which to measure lead, the model seems to better predict levels measured in bone deposits. **However, there are discrepancies between lead deposits across multiple bone types, which raises the question: what is the correct bone to use to predict previous lead exposure?**

Re: the use of soft-tissue: bone lead level ratios. The Barry study evaluated the kidney: tibia and liver: tibia ratios. **The model was more predictive when using liver: tibia ratios, but consistently overestimates female exposures more so than males**, again arguing that the model heavily skews towards predictive values in males over females. **However, given that the liver is estimated to be a sink for 2% of total lead in adults and the kidneys are estimated to contain less than 1% of the body's lead, it's unclear why these tissues were selected and how predictive either of these are.**

Re: using adult data to predict childhood exposures. In the few cases of evaluating the model for childhood data sets, the model often overestimates childhood exposures. **In this instance, the**

model appears to conservatively estimate childhood exposures and body burdens of lead, which may be advantageous as the resulting outcome would likely prompt efforts to reduce future exposures and possible intervention (via chelation or alternative).

9. What additional information about the AALM might be useful to users who want to assess hypothetical or real-world risk assessment problem, in order to facilitate correct application of the model and to communicate its modeling outcomes correctly and efficiently.

- Understanding the role of bone injury on re-exposure to deposited lead.
- Understanding if circulating unbound lead levels correlate with neurotoxicological outcomes or if lead deposits in specific brain regions are the problem.
- Understanding what the "ideal" bone for measuring lead deposits are, and what contributes to these differences.
- Understanding the release of bone-lead in pregnant women and understanding how that lead is deposited (which compartment and how much) in the developing fetus.
    - Are subsequent children more or less protected from maternal lead?
    - Can pregnant women chelate released bone lead to protect developing fetus?
- Are there foods or other exposures that are naturally occurring chelating agents?
- Explaining the limitations of the model: re multiple independent exposures/varying concentrations.