UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE AMINISTRATOR
SCIENCE ADVISORY BOARD

August 3, 2020

EPA-SAB-20-009

The Honorable Andrew Wheeler
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Transmittal of the Science Advisory Board Report titled "Review of the All Ages Lead Model External Review Draft 2.0"

Dear Administrator Wheeler,

Please find enclosed the final report from the Science Advisory Board (SAB or Board). The EPA's Office of Research and Development requested that the SAB review the All Ages Lead Model (AALM) External Review Draft 2.0. In response to the EPA's request, the SAB assembled the All Ages Lead Model Review Panel with subject matter experts to conduct the review.

The SAB All Ages Lead Model Review Panel met in-person on October 17-18, 2019, and held one teleconference to deliberate on the agency's charge questions. Oral and written public comments were considered throughout the advisory process. This report conveys the consensus advice of the SAB.

While the SAB provides several recommendations within this report, the Board highlights the following. The Board finds that the AALM 2.0 is a major step forward from both technical and public policy perspectives for use in future human health risk assessments. The AALM 2.0 facilitates evaluation of exposures that go beyond those addressed by the Adult Lead Model (ALM) and the Integrated Exposure Uptake Biokinetic Model (IEUBK). There was great interest among Board members in the potential applications of this model for public health protection.

Some key recommendations from the SAB include: The EPA should identify the audience for whom the AALM is developed and apply an appropriate level of complexity to accompanying documents. The strengths and limitations of the AALM and scenarios where it can be used should be clearly described. Users would benefit if the AALM and supporting materials were more user friendly and if training materials were available. The SAB has recommended opportunities to evaluate model parameters, overall model performance and document model uncertainty, which will further enhance the utility of the model.

The Board recommends that the Agency make those changes, clarifications, corrections, and edits to the model and documentation needed to allow use of the AALM 2.0 for research and additional testing. The Board has described these actions in its Tier 1 recommendations. Given the openness and transparency that the Federal Advisory Committee Act requires, the AALM 2.0 is currently available on the SAB website. Therefore, the Board recommends that the Agency implement these Tier 1 actions as quickly as feasible, in order to provide an updated version to the public to replace the AALM 2.0 reviewed by the Board.

The Board recommends that the Agency develop and implement a plan to expand the utility of the AALM 2.0 for use in risk assessments and public health assessments. These recommendations are largely described in the Board's Tier 2 recommendations.

The Board recommends an ongoing commitment to continued maintenance of the AALM, including its parameter values and model documentation. EPA should provide support and training to the broad range of likely users of the model. This support should include continued updates to the model and to its recommended parameters as new data become available. It should also include extending the model to address aspects of exposure or pharmacokinetic biological processes that require more effort and longer time frames (included in the report's discussion of Tier 3 recommendations).

As the EPA finalizes its External Review Draft AALM Draft 2.0, the SAB encourages the Agency to address the Board's concerns raised in the enclosed report and consider its advice and recommendations. The SAB appreciates this opportunity to review EPA's AALM 2.0 and looks forward to the EPA's response to these recommendations.

Sincerely,

/s/

Dr. Michael Honeycutt, Chair
EPA Science Advisory Board

/s/

Dr. Hugh A. Barton, Chair
AALM Review Panel

Enclosure

NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board (SAB), a public advisory committee providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. Reports of the SAB are posted on the EPA Web site at http://www.epa.gov/sab.

U.S. Environmental Protection Agency
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All Ages Lead Model External Review Draft 2.0 Peer Review Panel

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ACRONYMS AND ABBREVIATIONS

AALM	All Ages Lead Model
AALM.FOR	Fortran Code for AALM
NHANES	National Health and Nutrition Examination Survey
CBLI	Cumulative blood lead index
COPD	Chronic obstructive pulmonary disease
CREM	Center for Research for Environmental Models
GSD	Geometric standard deviation
ICRP	International Commission on Radiological Protection
IEUBK	Integrated Exposure Uptake Biokinetic (lead exposure model; U.S. EPA)
MATLAB	Matrix Laboratory – proprietary programming language developed by Mathworks
MPPD	Multi-Path Particle Dosimetry
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OPPT	Office of Pollution Prevention and Toxics
Pb	chemical symbol for lead
RBA	relative bioavailability
RBC	Red blood cell
TRW	Technical Review Workgroup
TSD	Technical Support Document for AALM
SAB	Science Advisory Board
U.S. EPA	United States Environmental Protection Agency
WHO/IPCS	World Health Organization/International Programme on Chemical Safety

1. INTRODUCTION

The All Ages Lead Model (AALM) estimates the effect of lead exposures from various media (air, water, food, dust, soil) on lead concentrations in blood, bone, and various other tissues of humans from infancy through 90 years of age. The predecessor to the AALM is EPA's Integrated Exposure Uptake Biokinetic (IEUBK) Model for lead in children less than 7 years old. EPA's Office of Research and Development led efforts to create and develop the AALM. A user-friendly software program allows users to input detailed exposure information (e.g., duration of exposure and levels of lead in various media). The model is then run for the specified scenario regime and results (i.e., lead tissue burdens) are returned to the user.

EPA's expressed intent in creating the AALM is to extend EPA's modeling capabilities in order to estimate lead in blood and other tissues following acute exposures, transiently reoccurring exposures, and chronic exposures for individuals of any age. In contrast, the IEUBK model only allows for estimates of blood lead in children following chronic exposure conditions.

The AALM documentation reviewed by this Board has three parts: 1) the *Technical Support Document for the All Ages Lead Model (AALM), Version 2.0 – Parameters, Equations, and Evaluations,* May 2019; 2); the *AALM Version 2.0 Software*; and 3) the *User's Guide for the FORTRAN Version of the All Ages Lead Model* (April 2019)

The ad hoc AALM Review Panel held a public meeting on Oct. 17-18, 2019, at the Crystal City Gateway Marriott Hotel, Arlington, Virginia. At this meeting, the Panel heard presentations from staff of EPA's Office of Research and Development, which included a live demonstration of the AALM capabilities, and public comments, followed by discussion and questions for EPA staff. Dr. Hugh Barton, Chair of the AALM Panel led the Panel's discussion of their initial responses to the Charge questions. Oral and written public comments were considered throughout the advisory committee's process.

This report is organized to state each charge question raised by the agency followed by the SAB's consensus response and recommendations. Recommendations are prioritized to indicate relative importance as follows:

- Tier 1: Recommended Revisions – Recommendations that are necessary in order to improve the critical scientific concepts, issues and/or narrative within the reviewed model and necessary documentation.

- Tier 2: Suggestions – Recommendations that EPA is encouraged to adopt in order to strengthen the scientific concepts, issues or narrative within the model and documentation being reviewed by the Board, but other factors (e.g., Agency priorities or resource considerations) should be considered by EPA before undertaking these revisions.

- Tier 3: Future Considerations – Useful and informative scientific exploration that may inform future evaluations of key science issues and/or the development of future model versions or

documentation. These recommendations are likely outside the immediate scope and/or needs of the current model and documentation under review.

Minority opinions are presented within Appendix B. All materials and comments related to this report are available at:
https://yosemite.epa.gov/sab/sabproduct.nsf//LookupWebProjectsCurrentBOARD/9B019D11EF07A3FA8525831A006275A4?OpenDocument

2. RESPONSES TO CHARGE QUESTIONS

2.1. Charge Question One

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 Board would like to commend EPA on this effort and extensive and generally well-written documentation. EPA states (p. 113, lines 28-34, pdf p. 124) that the intent of the AALM is to replace or supplement the current IEUBK and adult lead models and to provide 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. Overall, the Board noted that the information presented in the technical guidance (background, model structure, equations, parameters, parameter values, and explanation of model inputs) was adequately covered; however, the Board had several recommendations that would improve the guidance document.

The audience for this guidance and model should be clearly stated by EPA. A clear description should be provided about the intended uses and applications of this model so that the varied stakeholders (risk assessors in a range of capacities, those who would use this model for litigation purposes, public health officials, and medical doctors) concerned about lead exposure can understand the model's strengths and its limitations. Even if this is intended as a broad-use model, EPA should provide examples of contexts and applications in which the AALM in its current form can be used.

The Board agreed that the details provided in the technical support document (TSD) provide a full explanation of the model structure, equations, parameters, and input variables; however, the guidance is quite technical and reflects the complexity of the model. While this document is sufficient and appropriate for those who are experienced and familiar with modeling and for lead experts, it may be a more difficult and time-consuming task for those who are not as experienced in these areas. A guidance document that is not as technical and intended for the broader potential user or stakeholder audience would be a valuable addition to the current guidance manual and should include guidance on the level of expertise appropriate to use the model.

Although the tables containing equations, default exposure parameters, and model variables are comprehensive and thorough, the organization is not easy to navigate. For example, the tables and figures are all at the end of the chapters, which makes it difficult to read and then scroll to the table or figure discussed in the text. Providing hyperlinks in the text to the figures, tables, and appendices would make it easier to move around in and use the document.

The Board questioned how the growth curves were defined and implemented and whether they were discussed in terms public health and medical practitioners could understand. A clear discussion of the O'Flaherty growth curves and parameters used should be provided in the document. They should be discussed in a context and terms that medical practitioners and public health risk assessors can comprehend.

This version of the AALM model may be described as a hybrid of O'Flaherty and Leggett models, which raises challenges for understanding the model structure, parameter value choices, and impacts on predictions. While the TSD has extensive discussion of the different models EPA developed leading to the AALM.FOR version under review, it is a challenge to fully evaluate the many aspects involved. Many of the O'Flaherty equations and parameter values have replaced Leggett's values, and in some cases altered the structure of the model (e.g. removing one of the pathways of lead elimination via urine). Hence, the AALM is not really a newer version of the Leggett (or ICRP) model. This change from version 5 of the ICRP model to a hybrid model is significant. The evolution from the original ICRP model (ICRP 1993) to the structurally altered age-specific kinetic model of lead metabolism in humans (Leggett 1993) has been difficult to convey and has remained unclear for some. The switch from a method explained in Leggett's paper of interpolating lead mass transfer values between specific ages to a method for establishing tissue growth and volumes based mostly on scaling and other equations from the O'Flaherty model needs to be more transparent. Many of O'Flaherty's equations appeared in the TSD, since the growth equations are used in AALM. For the childhood and adolescent part of the model, Leggett has a significant discussion about the uncertainty of lead mass transfer parameters in childhood and adolescence due to limited data available for calibration. In addition, given this switch from mass transfer to tissue concentrations of lead based on age and body weight scaling, it is important to revisit O'Flaherty's predictions of age- and body weight-related concentrations of lead with data as well as Leggett's predictions of age-related distributions of lead mass compared to estimates published in Leggett (1993) of lead mass in tissue groups from autopsy data.

The current strengths and limitations of the AALM should be clearly discussed. For example, there is no pregnancy model, lead exposures for neonates through breastfeeding are not accounted for (see Charge Question 3a response), and the recommended default inhalation scenario may be appropriate for environmental exposures but not occupational exposures (See Charge Question 3b text). Specifically, occupational exposure may involve larger size particles with different deposition fractions in the respiratory tract (i.e., associated with more mucociliary clearance), and simulating occupational exposures would likely require higher values for ventilation rates than for average adults. The model is also potentially applicable for public health and clinical purposes to describe impacts of interventions, but chelation therapy is turned off and modifications like inputting dust lead loading are needed. These and other examples of exposure scenarios for which the model is not parameterized or cannot account should be clearly stated. In addition, Section 2.3.3 of the guidance states that that the model simulates lead absorption from inhalation, ingestion, and dermal contact with dust. No dermal contact with soil or dust is discussed in the document; thus, the fact that dermal exposure is not accounted for should be indicated. The current strengths of the AALM and examples of exposure scenarios that it can simulate should be clearly outlined.

The figure of model structure (Figure 2-1) should be modified to be more accurate. All four compartments of the gastrointestinal tract and lung need to be explicitly shown. The model includes different rates of transfer in and out of tissue compartments. In the figure, for example, arrows pointing in both directions should be replaced by separate arrows representing lead entering and leaving compartments (e.g., the brain, liver and bone compartments). While an

arrow shows transfer of lead from diffusible plasma to bladder contents, the transfer rate is now zero so the arrow is misleading.

The TSD would benefit from additional examples of differences in uptake and predicted blood lead distributions for different model versions. Specifically compare the current proposed AALM with IEUBK (including the Stochastic Human Exposure and Dose Simulation IEUBK) and ALM model applications to the same default scenarios, inclusive of baseline, water, diet, soil and dust ingestion, and inhalation pathways. This could 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 blood lead concentrations 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 lead concentrations over time, summarized in both an Excel table and graphic format. By contrast, the IEUBK and ALM models generate probability distributions of blood lead concentrations, by applying a lognormal distribution model to the predicted mean concentrations. This utility does not currently exist in the AALM and it is not clear if the AALM outputs represent geometric mean values, though if they are users could post-process the results on their own. The TSD is silent on this point and should at least discuss this omission along with any anticipated next steps.

Charge Question 1 Recommendations

Tier 1

- The audience for the model, documentation, and guidance must be clearly stated by EPA and should reflect the breadth of stakeholders who would be interested in using this model or interpreting its results.
- EPA should provide examples of contexts and applications for which the AALM in its current form can be used with any needed cautions and clearly state situations for which it is not currently appropriate due to limited tests of the model with data, missing components in the model structure, current parameter values, or other factors.
- Figure 2-1 needs to be modified in order to more accurately describe the model structure.
- Discuss the omission of a fully developed risk characterization module, along with any anticipated steps to achieve one (e.g., recommendations for Charge Questions 7-9).
- Modify the existing documentation to address the recommendations, questions, edits, and suggestions that are provided throughout this report to improve the clarity of the considerable documentation that exists for AALM.

Tier 2

- A guidance document that is not as technical as the TSD intended for the broader range of stakeholders would be a valuable addition to the current guidance manual.
- A clear discussion of the O'Flaherty growth curves and parameters used should be provided in the document. They should be described in a context and terms that medical practitioners and public health risk assessors can comprehend. Revisit O'Flaherty's comparisons for age- and body weight-related concentrations of lead with data as well as Leggett's evaluation of

age-related distributions of lead mass compared to estimates published in Leggett (1993) of lead mass in tissue groups from autopsy data to build confidence in AALM.

Tier 3

- Providing hyperlinks in the text to the figures, tables, and appendices would make it easier to move around in and use the document.

2.2. Charge Question Two

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 literature or by reasonable extrapolation from such data. Some additional considerations are presented here as well as in responses to the other charge questions.

Relative bioavailability

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. (p. 11, pdf p. 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 compared to lead ingested in an occupational environment, lead in solid and dust ingested in a residential setting may have different solubility, particle size, and chemical composition, and by extension different RBA.

In addition, notwithstanding that 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. Further discussion of these kinds of issues is found in Charge Question 3b.

In the case of food, as opposed to soil and dust and water, the way to account for age-specific changes in overall daily food intake across the lifespan was not clear. (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, it would be helpful to include in an appendix to the model documentation suggested values for such age specific intake rates or clearly direct users to other documentation (e.g., Exposure Factors Handbook).

Post-exposure lead kinetics
In AALM, when long term exogenous lead exposure is terminated, the blood Pb concentration declines rapidly. For example, see Figure 3-2 B (p. 76, pdf page 87). 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 observations, that the decline in blood lead is not as rapid as predicted by the model in other cases.

Moel et *al.* (1986) described the decline in blood lead concentration in severely lead intoxicated children (blood lead 100 to 200 μg/dL) followed for nine to 17 years after the end of chelation treatment, when the rate of decline in blood lead was strongly influenced by slow release of lead from skeletal stores. 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. Although there was inter-individual variability, for some of the subjects presented by Schutz et *al.* (1987) the rate of decline in blood lead over the first nine months after cessation of exposure appeared to be less than what would have apparently been predicted by AALM.FOR based on Figure 3-6. 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 over a period of years.

Some of the Board felt that the rapid decline might arise because the AALM.FOR biokinetic module adapted the Leggett model paradigm in which Pb that enters "nonexchangeable" skeletal compartments only returns to the plasma compartment during bone remodeling. A new publication shows this structure can capture slower declines in blood Pb but needs modified parameter values and continued background exposure (Vork and Carlisle, 2020). 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 also should be noted that the O'Flaherty bone model structure and parameter values evolved over time as reflected in publications including those cited in the TSD from 1993 to 2000.

It would be helpful to obtain additional datasets that document the decline in blood lead concentration following abrupt cessation of long-term elevated lead exposure, so that the accuracy of the AALM.FOR model in these settings can be further examined. Some references are provided above as well as those evaluated in Vork and Carlisle (2020).

Brain and olfactory uptake modeling
The model has a simple description of a single brain compartment. This is understandable in that brain Pb concentrations are simply not available from which more extensive modeling can be

undertaken. Consequently, they are not 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 or clarified in text related to brain Pb (e.g., Section 2.3.8). For example, p. 31 (pdf p. 42) 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. Outflow from the brain to plasma 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 months 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 need to be provided. One source may be the Leggett (1993) analysis (p. 606), but this needs to be stated and it would be valuable to confirm that modeling with AALM is consistent with the data Leggett referred to (e.g., Table 3, p. 610).

One other consideration relates to intake of 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 the brain and bypass the blood brain barrier. While inhalation of Pb and regional brain Pb analyses have not been undertaken, assessments in goat tissue showed significantly higher levels in olfactory epithelium and olfactory bulb, consistent with this route (Steuerwald 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 are 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.

Charge Question 2 Recommendations

Tier 1

- Statements about brain Pb and appropriate references should be included or clarified in text related to brain Pb, especially if the inference is brain lead amounts in humans.
- Revise the model to allow for different user defined RBA values for each source of ingested medium containing Pb encountered by a receptor at different times and locations (e.g. multiple sources of soil, dust, water). Currently a single RBA applies to all intake of a specific medium.

Tier 2

- Obtain additional datasets for model evaluation documenting the decline in blood lead concentration following abrupt cessation of long-term elevated lead exposure. Evaluate AALM.FOR model predictions for blood lead decline after extended intervals of moderate to high lead exposure to characterize the accuracy of the model.
- Any uncertainties or limitations regarding the most appropriate elimination assumptions for different types of exposure scenarios should be detailed in the documentation.

Tier 3

- Enhance treatment of age-related food Pb intake by offering known or established age-dependent food intake rates (e.g. adopted from the EPA Exposure Factors handbook) or obtain new data that can be applied to various types of food ingested by a receptor at different times and locations.
- EPA should acquire more data regarding total amounts of lead in the brain from various exposure routes, such as directly through inhalation across the blood brain barrier via olfactory neurons and then modify the model as needed to address this data.

2.3. Charge Question Three

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

Overall, the theoretical model is well explained. This is discussed further in response to the subparts of this charge question. Please comment on the discussion of the following specifics regarding AALM:

2.3.1. Charge Question 3a.

Are the values specified for the intake rates as a function of age for different media adequately described?

The Board finds that the TSD provides mostly adequate and clear descriptions of how AALM is parameterized with respect to intake rates (i.e., what parameter values have been selected as a function of age for different exposure media), and why EPA selected these parameter values (i.e., the theoretical basis and justification for the choices). The TSD presents the parameters in the following specific sections and tables:

- Chapter 2.2 - Exposure Model
    - Table 2-1. Exposure Equations of AALM.FOR
- Appendix A, Table A-1. Equations of AALM.FOR
- Appendix C, AALM Exposure Parameter Values
    - Appendix C, Table C-1. List of Parameters that are Assigned Constants or are Represented by Age Arrays

The meaning of the term Intake rate is clearly presented.

As noted in the User's Guide (pp. 3-4), the original Leggett model (1993), which provides the central platform for the current AALM.FOR, referred to Intake rate as the total mass of lead intake per day (on average), in units of µg Pb/day. This was essentially an administered dose, excluding normalization by body weight. In AALM.FOR, the term Intake rate has multiple meanings, which are clearly described in the TSD. Intake rate primarily refers to a media intake rate – meaning, the total mass (or volume) of an exposure medium that is ingested or inhaled per day, on average over some user-specified age range. The units are m^3/day for air, g/day for surface dust and soil, and mL/day for water, and the model estimates the average daily lead intake rate (µg Pb/day) for a specific exposure pathway and age range by multiplying the media intake rate by the media concentration. Exceptions to this approach are noted:

- Food intake is still expressed as a total mass of lead intake per day (µg Pb/day), on average over an age range, rather than a combination of specific food item intake rates and corresponding lead concentrations.
- "Other" media is a placeholder for users to include additional exposure media, and the parameter is defined in units of µg/day; thus, users are required to calculate age-specific intakes beforehand, separate from the AALM model. This option is similar to EPA's current regulatory model used for lead risk assessment during childhood (i.e., IEUBK).

The presentation in the TSD is easy to follow because it is packaged as a series of "submodels" for exposure, with equations and parameter values listed in tables.

The TSD clearly states that the inputs are intended to represent central tendency estimates, rather than high-end (reasonable maximum exposure) point estimates or probability distributions. 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 plausible ranges and/or distributions in the TSD may constrain options for conducting a robust sensitivity analysis, since the current model framework requires somewhat ad-hoc changes to combinations of model inputs.

Intake Rates

The Board has specific questions and/or recommendations for EPA to consider. Summaries are presented below, organized by environmental exposure media in the sequence presented in the TSD (i.e., air, indoor dust, [outdoor] soil, water, food, and other).

Air Intake Rate

The Board noted that EPA uses the term ventilation rate (m^3/d) as attributed to ICRP (1994), whereas the term respiration rate (breaths per minute) is preferred in the public health and clinical/medical fields. The term "ventilation volume rate" may be an improvement over ventilation rate. Clarifying these terms would be beneficial for a broad model user audience.

The TSD (p. 10, lines 2-3, pdf p 21) states that ventilation rates in the model can reflect activity levels and that sources that support the recommended parameter values also observe associations between water intake and energy expenditure. However, it is unclear how activity levels have been explicitly considered in the recommended mean parameter values and, therefore, how to incorporate/characterize these in simulations of populations that exhibit varying activity levels.

The model does not include activity patterns as a user-specified input. Furthermore, it is unclear if different activity levels may support different assumptions regarding fractional deposition in and translocation from the respiratory tract of various particle size fractions (e.g., course, fine, ultra-fine).

The ventilation rates throughout the TSD appear to be obtained from healthy individuals. These do not necessarily apply for individuals with asthma, chronic obstructive pulmonary disease (COPD), or other disease conditions. Suggesting sources of information or recommended values would further broaden the utility of the model. Consideration of whether there would be changes in other parameters, such as deposition fractions in regions of the respiratory tract, would be essential for appropriately modeling these disease states.

For adults with occupational contact with lead, inhalation may be the most significant route of exposure. Greater flexibility is needed with AALM.FOR in order to represent inhalation rate scenarios that are more applicable to a range of worker exposure scenarios if that is an intended use of the model or such data are used in calibration or evaluation of the model. For example, the user should be afforded the opportunity to adjust the default respiratory rates for the model shown in Appendix C (pp. 282-284, pdf pp. 293-295). The model's default value for adults, 19.9 m3, is apparently intended to represent long-term average daily exposure. Short-term adult respiration rates associated with moderate or heavy exertion that may be more applicable to occupational lead exposure have been reviewed in Chapter 6 of EPA's Exposure Factors Handbook (U.S. EPA, 2011). The following are specific examples that have been proposed by EPA and California Office of Environmental Health Hazard Assessment (OEHHA):

- EPA's Exposure Factors Handbook (Table 6-50) suggests that activities requiring physical labor may be associated with a median respiration rate of approximately 1.5 m^3 per hour, corresponding to approximately 12 m^3 for an 8-hour shift.
- California OEHHA's Technical Support Document for Exposure Assessment and Stochastic Analysis (CalEPA 2012, Chapter 3, Table 3.3b) recommends 12.94 m^3 for adults engaged in moderate intensity activities for 8 hours.
- OEHHA, in the development of the Leggett Plus model for assessment occupational lead exposure and dose (CalEPA 2013), used 14.4 m^3 (30 L/min) for 8 hours for moderate workloads.

In addition, certain studies support the use of other values based on sex and body weight, in addition to age. The Board recommends expanding the options for a user to select not only the current default daily values, but also values representative of short-term occupational lead exposure. The "occupational setting" could assume a value in the range of 12 to 14 m^3 for moderate exertion during an 8-hour shift, as an initial recommended range.

AALM.FOR apportions the inhaled lead into four compartments of the respiratory tract, 1) extrathoracic (incorrectly termed intrathoracic in the document); 2) bronchial; 3) bronchiolar; and 4) alveolar, by multiplying the average mass of lead inhaled per day (µg Pb/day) by a set of deposition fractions (R) (see TSD p. 23, lines 11-20, pdf p. 34). Collectively, the deposition fractions sum to 40%, meaning each day, 40% of the total inhaled Pb is initially deposited in the respiratory tract, and the balance is exhaled. The estimates of R are summarized in a table

(copied below from p. 23, pdf p. 34) and attributed to data from five 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

Table 1 Respiratory Tract Compartments and Parameter Values (see TSD p. 23, pdf p. 34)

The table lists the four compartments, but if the numbering sequence (1 through 4) corresponds with the order of the regions described above (as presented in the TSD), then the 4% value (i.e., 0.04), assigned to region number 4 in the table, would correspond to the alveolar region, which is not the region associated with translocation to the gastrointestinal tract. Rather, the balance (i.e., 36%) initially deposited in the extrathoracic and bronchial regions would be more likely to translocate to the gastrointestinal tract suggesting the parameter CILIAR = 0.36 rather than 0.40.

In a more recent study by Lach et al. (2014), 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 gastrointestinal 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 TSD and attributed to the original Leggett (1993) model. While the TSD does already include a caveat regarding the sensitivity of the assumption of deposition fractions to the particle size distribution, the Board recommends that EPA reconsider the parameter values and their sources in light of the cited literature noted above.

Soil and Dust Intake Rate

The TSD describes soil and dust intake rates as ingestion rates of the combined (sum of) masses of soil and dust, hereafter "IRsd." In this case, dust refers to soil deposited on surfaces, not to airborne soil particles. A second term is used to apportion the total ingestion rate to separate media so that media-specific ingestion rates can be paired with matching media-specific concentration values (e.g., outdoor soil, indoor dust).

For parameter estimates for IRsd applied to childhood, the TSD (Appendix C, pp. 280-281, pdf pp. 291-92) describes two sources of information: 1) U.S. EPA's Exposure Factors Handbook , recently updated in 2017 for this exposure variable; and 2) U.S. EPA TRW's estimates as intended for use in the IEUBK model. In addition, literature sources are cited, but not summarized or discussed.

The AALM model can be run in one of two modes with respect to transitioning between consecutive age groups: 1) a step function, or 2) interpolated values between age groups. The graphics in Exhibit 1 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, and no explanation is given to explain this discrepancy. The Board recommends that EPA reconsider the basis for the

recommended parameter values for ages 2 to 15 years to either better align with the materials cited or explain the rationale for the deviation.

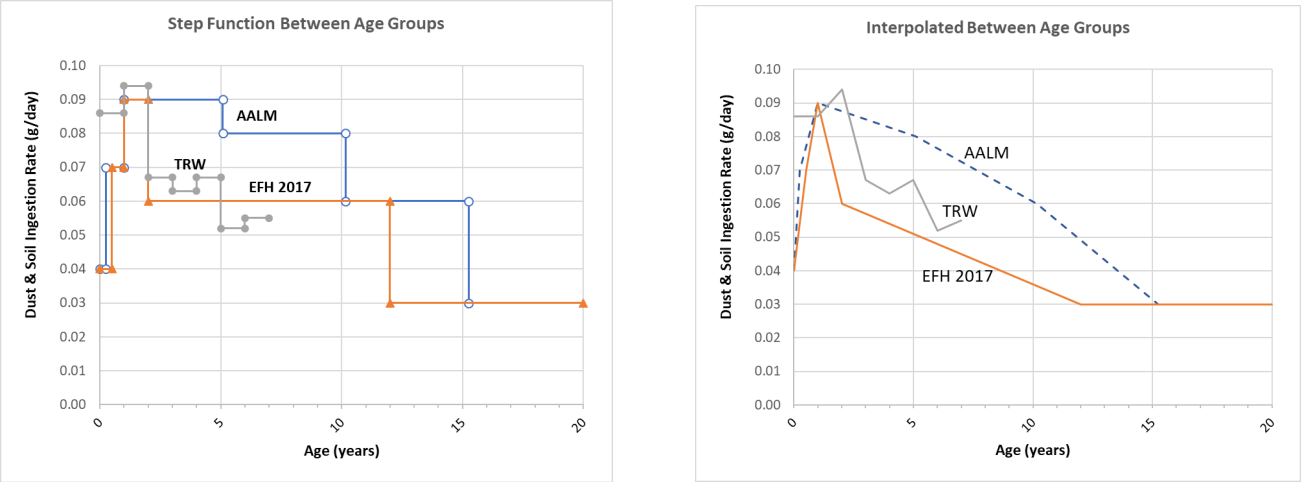

Figure 1 Age-specific parameter values for average soil and dust ingestion rates (g/day) during ages 0 to 20 years, comparing AALM with source information attributed to EPA. Graphic on left corresponds with the step function run option in A

Page 12, line 10, states, "Values for IRsoil are interpolated between inputted ages." Does this mean that a step-function option is never implemented for this exposure factor? If this is not true, and a step function is in fact one run option, the Board recommends that EPA add this clarification to this section of the TSD.

Water Intake Rate

The Board does not have any recommendations for changes to age-specific water intake rates, expressed as average daily ingestion rates (mL/day). The proposed values appear to be well supported, but further elaboration is needed on several points:

a) Describe the populations represented by these study results. Cross referencing EPA's Exposure Factors Handbook (U.S. EPA, 2011), the TSD currently states (p. 281, lines 4-5, pdf p. 292), "Water ingestion rate can be expected to vary with age, activity level and environmental factors (e.g. temperature, humidity)." EPA should clarify how (or if) specific activities are reflected in the proposed inputs.

b) Presumably the final table values (p. 282, pdf p. 293) reflect a consolidation of the two prior tables; further explanation is needed. Also, see Editorial Comments (below) for suggestions on adding an additional column to show the conversion from days to years, which will facilitate cross-walking between the various tables of source information.

In addition, the Board recommends that EPA include a baseline concentration of lead in drinking water in the TSD. A value of 0.9 µg/L represents the population weighted average of drinking water lead concentration based on data from the 2009 EPA Office of Water Six Year Review dataset (U.S. EPA, 2010a).

Like the IRsd discussed above, it is unclear in the TSD how the transition between age-specific parameters is addressed. The TSD (p. 13, lines 9-10) states, "Values for IRwater are interpolated between inputted ages." Does this mean that a step-function option is never implemented for this exposure factor? If this is not true, and a step function is in fact one run option, the Board recommends that EPA add this clarification to this section of the TSD.

Food Intake Rate

The TSD (Appendix C, pp. 278-280, pdf pp. 289-292) proposes a body weight-normalized total lead intake rate of 0.14 µg Pb/kg-day, which corresponds to an absolute lead intake rate of 10 µg Pb/day for an adult weighing 71.4 kg. The TSD presents age-specific estimates selected by the U.S.EPA TRW, an Agency workgroup that routinely updates the dietary exposure module of the IEUBK model to reflect national survey data on food consumption rates and Pb residue levels.

The Board notes that 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, the Board recommends a value of 0.128 or 0.13 µg/kg-day, which is better supported by the data cited by EPA, rather 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 considers the age-specific body weights for male and female children, as presented in the TSD.
2) The Board conducted a simple sensitivity analysis to illustrate how this error/deviation from TRW inputs changes as a function of changes in intake rates ranging from 0.120 to 0.150 µg/kg-day. (see the following page – Exhibit 2).
3) An error rate of 0% corresponds with a body weight-normalized 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 EPA has historically applied to estimates of food lead intake intakes in the IEUBK model. A slightly lower lead 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.

Also, several Board members noted that the current model structure does not appear to accommodate a nursing infant exposure scenario, whereby lead levels in breast milk may be elevated if the adult body burden of lead is elevated. While such a scenario could be evaluated using the option for the "Other" exposure pathway, the Board recommends that EPA add a

discussion to the TSD to explain that the current set of parameter inputs for Food Intake do not explicitly account for this pathway, if in fact this is true.

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 difference		**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 difference		**9.4%**

Figure 2: Comparison of differences between lead intake (µg/day) from food for ages 0 to 7 years, comparing AALM to recommendations by U.S.EPA TRW

Other Medium Intake Rate
In general, the Board finds the use of an "Other" input menu to be straightforward and useful. One of the Board's broader recommendations is that EPA include more working examples of applications of the model so that users can more quickly understand how to apply the model as noted in responses to Charge Questions 1 and 7. The Board recommends including this "other intake" module in one or more such examples.

The TSD refers to the "Other" pathway in the discussion of soil intake (p. 11-12, lines 36-37; and p. 12, line 1), stating, "The main consideration for including exposures to soil in the soil pathway rather than simulating the soil exposures in the other pathway is the determination of whether or not parameter values for soil ingestion rate (IRsoil, Equation 2.2-14) apply to the soil exposure." The Board finds the wording of this sentence to be confusing because it does not clarify conditions in which a separate evaluation, using the "other" pathway, would be warranted. And furthermore, even if there are multiple exposure pathways involving multiple soil lead concentrations, it is unclear why a different set of age specific IRsd values would be appropriate. Further clarification of these points is needed.

<u>Parameters for additional exposure variables</u>
The Board also evaluated additional exposure variables, beyond the media-specific intake rates discussed above.

Indoor dust lead
Pb in soil and indoor dust represents the most common source of non-dietary lead exposure in U.S. children whose blood lead concentration exceeds the Centers for Disease Control reference value of 5 µg/dL established in 2012, or the value of 3.5 µg/dL proposed by the ATSDR/NCEH Board of Scientific Counselors in 2016. As such, when AALM.FOR is employed, the user defined value of lead in soil and indoor dust will be of key importance.

In Appendix C (p. 276, pdf p. 287), the TSD recommends a default value for indoor dust of 175 µg/g (ppm). Appendix C further states that a value for indoor Pb dust equal to soil Pb is recommended where there are no known indoor sources of Pb in dust (e.g. lead paint or hobbies). However, Appendix C appropriately cautions, "Indoor dust Pb concentrations in residences impacted by Pb-based paint can be expected to vary considerably within and between residences and local exposure conditions should be considered to establish a representative estimate." The Board expressed concern that use of 175 µg/g as a default indoor dust Pb concentration may yield unexpected or unreliable outputs in several situations:

First, it may be noted that for indoor dust, Pb dust loading (e.g. $\mu g/ft^2$) and Pb dust concentration (µg/g) have been used as predictors of childhood blood lead (e.g. see Dixon et *al*., 2009). In a multivariable regression model developed by Dixon et al., based on interior Pb dust and child blood Pb measurements from several NHANES surveys (n = 2155), floor Pb dust and windowsill Pb dust loading were significant predictors of blood Pb (median floor dust loading in that data set was approximately 0.5 µg/ft2). In its 2018 Technical Support Document for Residential Dust-Lead Hazard Standards Rulemaking: Approach taken to Estimate Blood Lead Levels and Effects from Exposures to Dust-lead EPA, Office of Pollution Prevention and Toxics (OPPT) developed a nonlinear regression model relating Pb dust loading to Pb dust concentration based

on HUD data collected in the mid-2000s (see U.S. EPA, 2018, section 3.2.4). The extent to which this relationship might be adapted for the AALM.FOR model merits investigation.

Second, selection of a default value of 175 µg/g for Pb concentration of indoor dust concentration recommended in Appendix C appears to be too high. The calculated median Pb dust concentration from the aforementioned OPPT document on lead in residential dust (EPA, 2018; Table 3-9) was 101.2 µg/g based on a median background dust loading value of 0.7 µg/ft2. The 175 µg/g default value for indoor Pb dust, when combined with the default value for indoor dust ingestion of approximately 0.04 g per day (see Appendix C page 281), would yield a lead intake from this source of 7 µg. Further applying AALM.FOR default dust Pb RBA of 0.6, it may be seen that Pb ingestion from default indoor dust alone in young children would be 4.2 µg/day. This is approximately equal to estimated dietary lead ingestion for children (Manton et al., 2005) that has long been considered the major source of background lead exposure for the general population. Therefore, it may be prudent to use the median value of 101.2 µg/g as a default if it is necessary to use a concentration term for indoor Pb dust rather than a loading term in the AALM.FOR model.

Third, the recommendation to apply outdoor soil Pb concentration as a surrogate for indoor dust Pb in situations where no indoor Pb source is known to exist may overestimate indoor dust Pb concentration. To the extent that outdoor soil Pb is tracked indoors and contributes to indoor Pb dust it would be subject to dilution by other sources of indoor dust (such as background exfoliation of skin and dander from humans and pets). The Baseline Human Health Risk Assessment for the Vasquez Boulevard and I-70 Superfund Site, Denver, CO (EPA Region VIII, August 2001) reported the correlation between indoor house dust Pb and mean yard soil Pb at 74 properties with a range of soil lead of approximately 80 to 800 ppm. The relationship was described by CPbdust = 0.34 CPbsoil + 150, (R^2 = 0.18). In this sample, where residential soil Pb concentration exceeded 227 ppm, indoor house dust Pb was less than soil lead. It may be useful to examine additional data sets where simultaneous measurements of soil and indoor Pb dust concentration have been compared.

Charge Question 3a Recommendations (by exposure routes)

Overall and Air Intake Rate
Tier 1

- Provide a brief description of the relationship of the terms “ventilation rate” and “respiration rate” for the benefit of a broad model user audience.
- Clarify how or whether activity levels are addressed in current recommended ventilation rate values and how to integrate fractional deposition and particle sizes to insure consistency in the modeling.
- Review the fractional deposition values (table on p 23, pdf p 34) used in the inhalation modeling and make modifications to the model or the text as necessary.

Tier 2

- Provide additional guidance and examples for modeling inhalation exposures for individuals with occupational exposures if that is an intended use for the model. As noted on p 282 of

the TSD (pdf p 293) lines 12-15, appropriate interrelationships need to be addressed for particle size, clearance, deposition, and ventilation volume rates.

Tier 3

- Ventilation rates discussed are for healthy individuals and do not necessary apply for asthma, COPD, or other disease conditions. Suggesting sources of information or recommended values would further broaden the utility of the model.

Soil and Dust Intake Rate

Tier 1

- Revisit the basis for the recommended soil and dust intake rate parameter values for ages 2 to 15 years to either better align with the materials cited or explain the rationale for the deviation.

Tier 2

- Clarify in TSD text how the transition is done for values of IRsoil between inputted ages.

Water Intake Rate

Tier 2

- Clarify in TSD text, how or if activities are reflected in parameter values, how the recommended values (table p. 282) were obtained from preceding tables, and how the transition is done for values of IRwater between inputted ages.
- Include a baseline concentration of lead in drinking water in the TSD.

Food Intake Rate

Tier 2

- Re-evaluate the lead intake rate in food of 0.14 µg Pb/kg-day as the Board recommends a value of 0.128 or 0.13 µg Pb/kg-day as explained in the above text.
- Add text to documentation about intakes by age compared to TRW recommendations.
- Explain if breast milk is included in the food pathway or not. Assuming it is not, add text to explain how it would be included in the modeling.
- Clarify the TSD text about soil intake and the "other" pathway.

Indoor Dust Lead

Tier 1

- Reevaluate the default value of 175 µg/g for Pb concentration of indoor dust. The median value of 101.2 µg/g may be more appropriate as a default.

Tier 2

- Evaluate relationships between indoor dust loading and indoor dust Pb concentration for application in AALM.
- Evaluate any available data to reconsider the recommendation to apply outdoor soil Pb concentration as a surrogate for indoor dust Pb in situations where no indoor Pb source is known to exist.

2.3.2. Charge Question 3b.

Are the uptake/absorption parameters and parameters requiring modification for specific routes of exposure adequately described?

The AALM is based upon previous modeling, particularly by Leggett (1993), and relies heavily upon that theoretical approach and the methods used to estimate parameters with some updates and adjustments to further address changes in kinetics with age. Evaluating the uptake/absorption parameters is made difficult by the complexity of the documentation and differences in values reported in different parts of the documentation, e.g., the main text, Appendix D, and the EXCEL spreadsheet implementing the model.

The first issue for users or reviewers of this model 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. The AALM documents could benefit from more precise definitions and extended discussion of the approach. It would seem advantageous to EPA to use the same definitions as elsewhere, although there may be some differences with the original model developers' approaches and use of absorption terminology.

The response to this charge question will address absorption in the respiratory tract followed by the gastrointestinal tract, consistent with the presentation in the TSD. Relative bioavailability was implemented and described in the TSD as part of the exposure calculation prior to passing values to the biokinetic model. However, bioavailability largely reflects differences in the availability of the lead in different environmental media or diet for absorption, so it will be discussed following inhalation and oral absorption.

The TSD indicates that absorption from dermal exposure to surface dust is simulated (see Section 2.3.3, document p22, pdf p33), but this was not found in the description of the model. Clarification is needed for whether dermal absorption is included as a specific pathway in the model, though it is likely a minor pathway. While there is some description of how hand to mouth behaviors leading to oral exposure to dust or soil on the skin is addressed, providing examples would clarify and strengthen this aspect.

<u>Uptake/absorption in the respiratory tract (Inhalation)</u>

Review of the modeling for the respiratory tract found that the current model and recommended parameters could be appropriate for specific conditions that are not clearly specified, e.g., average individual inhalation of relatively small environmental lead particles, but that different parameter values would be needed, particularly for occupational exposures, to address varied activity levels, changes in respiration, and larger particle sizes. Variations in particle size that affect deposition in the respiratory tract and the fraction subject to mucociliary clearance to the gastrointestinal tract for absorption also need to be addressed.

Assumptions regarding absorption following inhalation of lead appear to be rather undeveloped. In section 2.3.3.1, Absorption from the Respiratory Tract, (pdf page 34, document page 23), AALM.FOR adopts the assumptions made by the Leggett model with respect to inhaled Pb aerosols, i.e. 40 percent of inhaled Pb is retained in the respiratory tract, and of this, only 4 percent is transferred by mucociliary clearance to the gut (cf. definition of CILIAR, pdf page 311) while the remainder (96 percent of deposited Pb) is absorbed. These parameter values were based on the clinical studies cited in section 2.3.3.1 where the inhaled Pb aerosols were soluble submicron particles of the type released by automotive exhaust in the 1970s. Such assumptions may continue to be reasonable for the minute amount of lead present in ambient air in the United States today (on the order of 0.01 $\mu g/m^3$, which is the default value recommended by the TSD for the AALM.FOR in Appendix C (pdf page 286 document page 275).

Significantly, the TSD states "These assumptions would not necessarily apply for exposures to larger or less soluble airborne particles" (pdf page 34, document page 23). In Appendix C, page 282 lines 10-14 state "Regional deposition and clearance in the RT will depend on numerous factors, including age, particle size, as well as various factors that affect ventilation rates (mg/day) which vary with age and physical activity. The interrelationships between particle size, clearance, regional deposition and ventilation rate should be considered in assigning values of these parameters for simulating specific populations and exposure settings, these subjects are treated in depth in ICRP (1994)."

Section 3.4 (pdf page 72, document page 62) "DATA NEEDS FOR FURTHER REFINEMENT OF THE AALM" indicates the dose of Pb particles deposited in the lung "must be calculated outside of the AALM.FOR for a given set of assumptions" (lines 40-41). This point should be made clearer in discussion of uptake/absorption parameters, Section 2.3.3.1.

The TSD does not discuss whether or how to utilize well established tools and models designed to address the impact of particle density, particle size and size distribution on regional deposition in the lung (and subsequent absorption). The Multiple Path Particle Dosimetry (MPPD) model is well established for addressing just these concerns (see Asgharian et *al.*, 2001; Miller et *al.*, 2016; *etc*.). Exposure modeling of various particle size distributions (*i.e*. lognormal distribution around a mass mean aerodynamic diameter, skewed towards larger or smaller particle sizes, bi-modal) for a set air concentration of lead (*e.g*. $\mu g/m^3$) indicate the potential for significant variability in regional deposition in the lung and subsequent absorption (see Petito Boyce et al.. 2017). As noted above in the discussion of inhalation intake (Charge Question 3a), the study by Lach et al. (2014), showed that 49% of total inhaled Pb would be deposited in the respiratory tract, of which 37% would be translocated to the gastrointestinal tract in contrast to the 4% based upon Leggett (1993).

There was difficulty understanding the meaning of the relevant respiratory parameters (e.g., R1-R4, BR1-BR4, CILIAR) and how they might be modified by a user. Inconsistencies in text, tables, and the EXCEL spreadsheet implementation of the model were noted. Examples include:
P23 (pdf p34) Line 32 defines BR*i* as a fraction when it is a rate
P25 (pdf p36) Line 2 BR*i* again described as a fraction when it is a rate

P299 (pdf p310) BR1 to BR4 – Half-life values given are rounded and converted to days in calculations of rates, which are shown as 0.693/T1/2 but in the EXCEL spreadsheet, they are calculated as LN(2)/T1/2*24 so the numbers do not match.
P302 (pdf p313) R1 – 10% value given in text (line 14), but the calculation shown, and the value used in the spreadsheet (LUNG tab) is 0.08 or 8%
P302 (pdf p313) R3 – 12% value given in text (line 26), but calculation shown, and value used in spreadsheet (LUNG tab) is 0.14 or 14%

Some discussion is recommended of how the R, BR, and CILIAR 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.

Occupational inhalation exposures

Particles encountered in occupational settings (including those encountered episodically by outdoor construction and remediation workers who are receptors of interest in EPA risk assessments) tend to be larger, sometimes less soluble, and present at much higher concentrations. Several approaches are available for addressing these issues including clearly specifying for what conditions the current AALM model parameters are appropriate and when they are not, developing modifications for the model and its parameters to facilitate its utility for these other settings, or relying on other lead modeling focused on occupational exposures for that purpose.

California OEHHA (CalEPA 2013) developed a modification of the Leggett model to account for Pb anticipated to be present in workplace air. As detailed in the OEHHA report, (subsection B.2, pp 71 et seq), it was found practical to use the Multi-Path Particle Dosimetry Model version 2 (MPPD2) to describe size dependent deposition of inhaled particles in various regions of the airway (Asgharian et *al.,* 2001; Miller et *al*., 2016). OEHHA conservatively assumed 100 percent absorption of Pb particles from the lung to the blood, which is somewhat higher than the 95% assumed by Leggett and used in AALM.FOR. Interestingly the OEHHA model found that although particle deposition in the MPPD2 module differed significantly from original Leggett model assumptions, the overall default inhalation transfer coefficient arrived at by OEHHA, 0.30, was not much different than that yielded by the Leggett model. That is because for very small size Pb aerosols (e.g. submicron), the minor fraction retained in the body (i.e. not exhaled) undergoes a high degree of transfer to the blood from deep lung regions; conversely, for larger size Pb particles, a high percentage that are inhaled are retained in the upper airway and cleared by mucociliary clearance to the gut, where percent absorption is relatively low compared to the lung. In addition to exploring the utility of MPPD2 as applied by OEHHA, the developers of AALM.FOR should explore additional modifications of the model that would allow the user to specifically indicate the RBA of inhaled particles that are cleared to the gut.
One specific route of exposure for workers is inhaled particles that are removed by ciliary action and swallowed during and after meals when absorption efficiency can increase substantially from the default of 12% oral absorption of lead from the small intestine as described below.

A lead pharmacokinetic model designed to address occupational exposures for the Department of Defense was recently reviewed by a committee for the National Academies of Science, Engineering, and Medicine (Review of DoD's Proposed Occupational Exposure Limits for Lead, PIN: DELS-BEST-18-05). The report is available online (NASEM 2020). This modeling is based upon the physiologically based pharmacokinetic model originally developed by Prof. O'Flaherty, whereas AALM is derived from the modeling by Dr. Leggett. However, the availability of a peer reviewed model for at least some occupational exposures could be a useful option for the EPA to consider for modeling solely occupational exposures, or to provide insights and parameter values for expanding AALM to address occupational exposures in a context of prior childhood exposures.

Uptake/absorption in the gastrointestinal tract (Oral)

Although gut absorption of lead is 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 (AF) should be modified to separate non-saturable and saturable components. It is not clear to what extent the AALM has considered dual components or other nonlinear approaches to modeling gastrointestinal absorption. 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.

Section 2.3.3.2. Absorption from the Gastrointestinal Tract, indicates that AALM.FOR has incorporated age dependent gastrointestinal absorption fractions, ranging from 0.39 at birth to 0.12 that do not otherwise vary based on whether Pb enters the gut without food (e.g., fasting condition), with liquids, or with food. However, as noted in the cited references (e.g., James et *al.*, 1985) and several other studies (cf. discussion in Maddaloni et *al.*, 2005 and CalEPA 2013 pp 83 et seq. and appendix A), the extent of gastrointestinal Pb absorption varies considerably depending on whether Pb enters the gut with or without food or liquids. This applies not only to Pb ingested during meals, but also Pb transported from the respiratory tract by mucociliary clearance (a relatively continuous process throughout the day). For risk assessment scenarios, there may be a basis to distinguish between Pb ingested with meals (food and water), and that

ingested during outdoor recreation or work when food is not eaten. OEHHA considered this by estimating three mean gastrointestinal absorption fractions for adults: 50% after several hours of fasting, 19% with liquid between meals, and 12% during intake with solid food (CalEPA, 2013, page 82). Further calculations provided a 24-hour time weighted average gastrointestinal absorption of 30% assuming 10 hours fasting (50% AF), 10 hours with liquids between meals (19% AF), two hours intake with solid food (12% AF), and two hours in which no lead enters the gastrointestinal tract. The impact of revising the AALM.FOR to consider this additional variability in gastrointestinal absorption of Pb based on co-ingestion with food and liquid should be examined.

The new ICRP age-specific and sex-specific model, called the Human Alimentary Tract Model may be appropriate to include in the AALM because it has been vetted and updates the gastrointestinal tract model included in the current AALM (Leggett et *al*., 2007; ICRP 2006). This newer model should be evaluated for use in future versions of the AALM and discuss the uncertainties in the data used to parameterize/evaluate the model. It is more complex and might be difficult and time consuming to implement.

Relative bioavailability for ingestion

For the INGESTION pathway, the inputs are adjusted by RBA in the SOIL, DUST, WATER, FOOD and OTHER Exposure Modules. Relative bioavailability is determined by comparison with availability with lead completely soluble in water. Each of these reduces the amount of lead entering the biokinetic model. The model user can adjust the RBAs. Default values are 60% for soil and dust, and 100% for food, water and other lead. Because these adjustments are made to the amount of lead entering the biokinetic model, this results in a material imbalance under-predicting the fecal lead content. Lead in these media delivers a combined available Pb to the gut, which is augmented by secretions from other model components (lung, bile, plasma) for transfer to the plasma by first-order absorption coefficients. Four compartments are modeled in series, the contents of the stomach, small intestine, upper large intestine, and lower large intestine (feces) with first-order transfer rate coefficients. All absorption of Pb from the gastrointestinal tract is assumed to occur in the small intestine, which is described 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 is age-dependent, and derived by formulae from historic studies.

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 under prediction 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 over predict *uptake* because the variability in fed/fasted state is not taken into account.

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 from different sources 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:

"$IN_{WATER} = PbB_{WATER} \bullet IR_{WATER} \bullet RBA_{WATER}$ 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 that human data pertaining to different bioavailability of soluble Pb versus suspended fine particulate are 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. In a bioaccessibility experiment using simulated gastric fluid to measure the dissolution of lead particulate collected from home faucets, dissolution at 48 hours was 66% in one instance and 21% in another (Triantafyllidou et *al.*, 2007). In a study examining the observed *in vitro* bioaccessibility of a spectrum of lead particulate harvested from field collection of household faucet water, median estimated RBA of the lead particulate was 33% (Deshommes and Prevost, 2012). Pediatric blood lead concentration resulting from chronic or acute exposure to lead in drinking water has recently been estimated using the IEUBK and Leggett models (Triantafyllidou et *al.,* 2014). Comparison of AALM.FOR simulations to the results of Triantafyllidou et *al.,* (2014) may be informative.

On the RBA tab of the EXCEL spreadsheet, the gastrointestinal 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 the spreadsheet and with documentation.

The RBA assumptions are not described nor justified anywhere until Appendix C (this is true for many of the parameters). It was difficult to keep going back to Appendix C to see what the values and sources were.

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 red blood cell (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, for uptake in the gut. On the other hand, the comparisons alluding to difference in absolute and RBA in the IEUBK and AALM are 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 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.

Charge Question 3b Recommendations (General)

Tier 1

- Clarify in model documentation whether dermal absorption is included as a specific pathway in the model or not.

Tier 3

- While there is some description of how hand to mouth behaviors leading to oral exposure to dust or soil on the skin is addressed, providing examples would clarify and strengthen this aspect.

Charge Question 3b Recommendations (Inhalation)

Tier 1

- Clarify when the current model structure and parameter values would be appropriately used and when they would need to be modified (e.g., occupational inhalation exposures to larger particles) to guide users to appropriately use the model and avoid inappropriate uses.

Tier 2

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

Charge Question 3b Recommendations (Gastrointestinal Tract and RBA)

Tier 1

- Change the model to quantify the total elimination in feces (e.g. fate of non-absorbed lead in soil and dust) and maintain mass balance.
- Revise the model to allow different user defined RBA values for each source of ingested medium containing Pb encountered by a receptor at different times and locations (e.g. multiple sources of soil, dust, water). Currently a single RBA applies to all intake of a specific medium.

Tier 2

- Provide model users with guidance to address differences in lead bioavailability of different media from multiple sources.
- Future revisions of the AALM should address non-linear aspects of gastrointestinal lead absorption that account for active and passive absorption mechanisms, the impact of food in the gastrointestinal tract (i.e. fasting vs. non-fasting states), the absorption of particulate lead in water compared to soluble lead in water, and lead concentration in the gut on lead absorption fraction.

Tier 3

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

2.3.3. Charge Question 3c.

Are the biokinetic parameters describing lead distribution and elimination adequately described?

In general, the biokinetic parameters described in Tables 2-3 and 3-2 of the TSD were adopted from the Leggett model and are generally well accepted.

<u>Parameter Inconsistencies and Uncertainties</u>

However, in order to recode the All Ages Lead Model (AALM) to run in MATLAB (adult parameters only) and reproduce the output from the AALM in Figure 3-10, several errors and

omissions were discovered. The FORTRAN input file named POUNDS_GUI.DAT listing input values for ICRPversion8 provided the following information that is missing from or inconsistent with Tables 2-3 and 3-2 of the TSD:

- The value for total transfer rate from exchange bone volume is 0.02311. The fraction of total transfer from the exchangeable bone directed to non-exchangeable bone is 60% of 0.02311 or 0.01387 not 0.02311 as listed in Table 2-3. The transfer of lead from "Exch Vol" to "Surf bone" is 40% of 0.02311 or 0.0092 not 0.0185 as listed in Table 2-3. (Note that in Appendix D, p. 303, the calculation of RDIFF from ln2/half-life has a typo, 0.00231.)
- Regarding the deposition fraction from Plasma-D to Kidney 2, Table 2-3 indicates a change from the original value of 0.4 to 0.8. However, in Table 3-2 the change in the Kidney 2 deposition fraction from ICRPv4 or ICRPv5 to AALM.FOR is missing.
- Changes made to the deposition fraction from Plasma-D remove the mass balance originally present in the ICRP (Leggett) model. Specifically, the deposition from Plasma-D to all destinations should add up to 2000 μg of lead. Instead it adds up to 1980.36. This mass imbalance has resulted from three changes in the fractional transfer of lead from Plasma-D to urine from 30 to 0, to kidney-1 from 40 to 50, and to kidney-2 from 0.4 to 0.8. These changes drop about 20 μg. Maintaining mass balance is essential for insuring correct model behavior.

Other changes made to the model that had to be obtained from the FORTRAN input file before Figure 3-10 could be reproduced include changes in:

- Blood volume (dL) from 0.726*body weight to 0.67*body weight
- Default adult Hematocrit was changed from 0.45 to 0.46

Findings from this limited exercise indicate that a more complete check for errors and omissions in Tables 2-3 and 3-2 describing the parameters for the entire model is needed. Nomenclature throughout the document (e.g., Table 2-3 and Appendix D) needs to be consistent so readers are certain what is being referred to. Parameter values and sources listed in documentation and model files (e.g., EXCEL spreadsheet) need to be cross-checked with the current ICRPversion8 code file. If errors are only in documentation, then documentation readily can be corrected, but it is also possible that errors have been introduced in the modeling that need to be corrected.

The AALM appears to have three adjustments to Pb mass leaving diffusible plasma (TSUM=2000) in which mass balance needs to be checked: 1) due to changing some deposition fractions (DFs) between versions of the model (Table 3-2), 2) due to adding an age-scaling equation to the model, and 3) due to changes in RBC binding rate once Pb concentration exceeds 20 ug/dLrbc. Mass balance needs to be checked and maintained after changing DFs between versions of the model and across a range of ages and levels of Pb in whole blood.
Changes were made in several deposition fractions for Pb leaving diffusible plasma such as those to urinary bladder and kidney and bone during multiple updates to the ICRP version 4 (Leggett 1993) and AALM. Given these changes, mass Pb leaving diffusible plasma could easily go out of balance. For example, TSUM is achieved when the adult Pb transfer from diffusible plasma to RBCs (TORBC) of 480 per day is increased to 500 per day in the AALM.FOR. This change is consistent with changes made to AALM.LG listed in Table 4-22 for the deposition fraction of

Pb leaving diffusible plasma to RBCs, where 0.24/day = (480/2000)/day and 0.25/day = (500/2000)/day. As noted elsewhere, applying the correct TORBC across ages and levels of blood lead is important. In addition, during multiple updates to the ICRP version 4 (Leggett 1993) and AALM, the equation for AGESCL appears in the TSD in multiple places and contains slightly different definitions for the value of Pb transferred from diffusible plasma to bone surfaces in the form of TBONE(t), TBONEL and ATBONE.

AGESCL = (1-TEVF-TBONE)/(1-TEVF-TBONEL) (equation 2.3-12)
AGESCL = (1-TEVF-TBONE(t))/(1-TEVF-TBONEL) (equation 4-5)
AGESCL = (1-TEVF-TBONE)/(1-TEVF-ATBONE) (equation in Table A-1, page 199)

On page 20 of the TSD, TBONEL is the limiting adult value for the bone deposition fraction.
On page 102 of the TSD, TBONEL is defined as the terminal value for TBONE on the last day of simulation.
On pages 262 and 298 of the TSD, ATBONE is defined as the age-specific deposition fraction from diffusible plasma to surface bone-age array.

Age-scaling may turn out differently depending on which definition is applied in the model. In addition, the age-specific deposition fractions in Leggett (1993) were derived based on the assumption that increases in Pb transferred during the growth period are proportional to increases in calcium deposition with age in childhood. Additional age-scaling seems redundant. For clarity, further explain why additional age-scaling is needed and its impact on the model.

An order of adjustment (e.g. age-scale then adjust for changes in binding rate in RBCs) is implied based on the text in Chapter 2 of the TSD. For children, and for blood lead levels exceeding 8 ug/dL whole blood (20 ug/dLrbc), adjustments are applied to the transfer of Pb leaving diffusible plasma to RBCs (TORBC) according to the equation for TOORBC in Table 2-2:TOORBC = TRBC x [1 – ((RBCONC-RBCNL)/(SATRAT-RBCNL))]^1.5

For example, TORBC listed in Table 2-3 becomes TRBC after it has been age adjusted and all other deposition fractions are adjusted based on equation 2.3-13. Also, TOORBC is TORBC adjusted downward when RBC concentrations exceed 20 ug/dLrbc. All other deposition fractions are adjusted upward based on CF = (1-TOORBC)/(1-TRBC) (Eq. (2.3-14, Table 2-2 E7) when RBC concentrations exceed 20 ug/dLrbc.

If this order is correct, state in the TSD the order of adjustment, for the sake of clarity, and to make sure future adjustments to the model preserve this order.

Red Blood Cell Binding

The assumption that saturation of binding in RBCs begins increasing the proportion of unbound lead at about 60 μg/dL RBC (25 μg/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 μg/dL and remained below the curve fit to data from DeSilva (1981) at levels above 90 μg/dL. If the alternate assumption were

made 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 the threshold constant would be set to zero and the saturation constant would be reduced from the current value of 350 µg/dL to 290 µg/dL RBCs. The latter assumption (RBC binding would begin to saturate at any level of lead in whole blood) was adopted by others (O'Flaherty and OEHHA). The description of RBC binding in the AALM should be re-evaluated for possible updating in a future version of the AALM.

Biokinetics associated with changes in hematocrit, especially at highly elevated lead levels (e.g. lead induced anemia) should also be considered, or perhaps noted, as an additional area of uncertainty. For example, a blood lead concentration of 100 µg/dL would typically be associated with a significant decrement in hematocrit due to lead-induced anemia. Accordingly, a blood lead concentration of 100 µg/dL with a hematocrit of 20% would be associated with a greater proportion of lead in the plasma fraction than would a blood lead concentration of 100 µg/dL with a hematocrit of 40%. Leggett (1993) suggested that RBC maximum capacity binding constants would be much lower for acute high exposures based upon data on urine clearance of lead from such exposures in adults. Data in Kochen et *al.*, (1973) also could be useful to consider.

Applicability of Biokinetic Parameters

Biokinetic parameters currently reflect an "average" individual, at an "average level of activity." For example, the AALM may not adequately model highly active (e.g., athletes) or less active (e.g., sedentary) individuals. Furthermore, populations with elevated lead exposures in the presence of acute (or chronic) neuroinflammatory responses may require modified biokinetic assumptions. For example, inflammation is known to influence blood brain barrier integrity and transfer biokinetics of metals and other xenobiotics.

Blood Lead Declines Following Exposure Cessation

The decline in blood lead following cessation of key exposures (e.g., occupational) was discussed in Charge Questions 2 in relation to the data available to support the model. It reflects issues of biokinetic parameters and potentially structure for describing bone distribution and clearance, so it is also important in relation to this charge question. In the previous response, several data sets and publications were noted that could be evaluated to provide a clearer understanding of how to appropriately model these situations given the structure and growth equations in the AALM.

Default Sex-Specific Body Weight

The default sex-specific body weight values (technically body mass, but commonly referred to as body weight) used by AALM.FOR (Figure 2-2) were based on O'Flaherty. These values, particularly for adults, now are somewhat lower than those observed in the latest NHANES surveys for the U.S. population. For example, based on earlier NHANES studies cited in the EPA Exposure Factors Handbook (2011), the mean body weight for males and female adults combined is 80 kg; sex-specific median adult body weights in Exposure Factors Handbook vary by decade of age but range from 75.1 to 87.8 kg for males and from 62.8 to 73.9 kg for females.

These are approximately 10 kg higher than the AALM.FOR defaults. Body weight is a key parameter in biokinetic models, because it influences blood and organ mass and perfusion. Accordingly, the default values for body weight should be updated to include the Exposure Factors Handbook 2011 ranges and consideration given to whether body mass index differences need to be addressed. The same recommendation may apply to other biometric defaults in AALM.FOR that differ substantively from those found in recent iterations of NHANES or the Exposure Factors Handbook.

Postmenopausal Changes and Age-Sex Interactions in Bone and Lead

As currently formulated, the biokinetic features of the AALM.FOR incorporate age-related changes in the uptake and release of lead from bone. However, the model does not account for significant sex-related differences in the relevant biokinetics that have been demonstrated in studies of lead in blood and bone. Numerous reports have observed that increased bone turnover and subsequent changes in bone density in perimenopausal and postmenopausal women are associated in part with age-related decline in estrogen. Several studies have found that this has a notable impact on the biokinetics of lead in blood and bone. Three large cross-sectional studies of U.S. women based on NHANES cohorts have documented that postmenopausal women have significantly higher blood lead concentration than premenopausal women, controlling for age and other factors related to exogenous lead exposure, particularly in the years soon after the onset of menopause (Silbergeld et *al.*, 1988; Symanski and Hertz, 1995; Nash et *al.*, 2005). In a large study of perimenopausal and postmenopausal women (n=1225), linear multivariate models demonstrated that biomarkers of bone turnover (N-telopeptide cross-linked collagen type I, bone-specific alkaline phosphates, and osteocalcin) were significant predictors of blood lead concentration (Machida et *al.*, 2009).

In a cross-sectional study of bone lead concentration by non-invasive K x-ray fluorescence in 101 subjects age 11 to 78 with background environmental lead exposure, a significant age•sex interaction accounted for higher tibial bone lead concentrations in men over the age of 55 years (Kosnett et al., 1994). Similar findings of an age•sex interaction in the relationship of age to tibial bone lead was observed in a more recent study conducted in subjects (n=263) from the general population of Ontario (Behinaein et *al.*, 2017). Popovic et *al.* (2005) compared blood and bone concentration in a cohort study of women with a history of occupational lead exposure to unexposed referents (n=207). Among the women with past occupational lead exposure, the ratio of blood to bone lead was substantially higher after menopause. The authors noted, "The results suggest that the endogenous release rate (micrograms Pb per deciliter blood ÷ micrograms Pb per gram bone) in postmenopausal women is double the rate found in premenopausal women" (Popovic et *al.*, 2005). Bone Pb was significantly greater in postmenopausal referent women treated with estrogen (Popovic et *al.*, 2005). Related findings were observed in a longitudinal study of bone lead concentration in postmenopausal women, in which hormone replacement therapy (HRT) was associated with higher bone lead concentration compared to women not on HRT (Webber et *al.*, 1995). Overall, the available research strongly suggests that the AALM.FOR would benefit by refinements that account for sex-related differences in bone lead accretion and release associated with changes related to menopause (O'Flaherty 2000).

Elimination pathways

The relevance of the sweat elimination pathway and its inclusion in the model should be clarified or at least qualified as a relatively minor pathway. Leggett (1993) indicates this only accounts for a small percentage of elimination.

Charge Question 3c Recommendations

Tier 1

- Errors identified in Tables 2-3 and 3-2 raised uncertainty in our evaluation and indicate a more complete check of biokinetic parameters is necessary. If errors are only in the documentation, text editing is necessary, but if there are errors in the modeling then these need to be corrected and the documentation updated accordingly.
- The equation for AGESCL appears in multiple places in the TSD with differing definitions. Also, AGE scaling to account for bone growth seems duplicative given that the original age-specific transfer rates are already based on calcium addition. This needs to be clarified or reconsidered as a necessary adjustment factor in the AALM.
- Due to multiple adjustments and updates to transfer rates for Pb leaving diffusible plasma, the mass balance on transfer of Pb leaving diffusible plasma (TSUM=2000) needs to be checked over a range of blood lead levels and ages and/or include a statement in the TSD that this specific check on mass balance has been conducted and maintained.
- Nomenclature needs to be made consistent in the documentation and the EXCEL implementation of the model (and any other computer files).
- TSD text needs to make clear that the biokinetic parameters reflect standard tendencies for an "average" individual.

Tier 2

- Assumptions regarding saturation of binding to red blood cells (RBCs) need to be re-evaluated and the implications for the modeling better described. Changes in hematocrit with lead exposure should also be discussed in more detail.
- Default sex-specific body weight values should be reconsidered considering recent data for the U.S. population, as they hold implications for blood and organ mass and perfusion, and ultimately biokinetics. Consider whether BW or BMI or both should be applied in the modeling and explain options and choices in documentation.
- Revise AALM to account for postmenopausal changes in bone turnover and age-sex interactions in bone lead and release of lead from bone.

Tier 3

- Evaluate whether to retain the plasma-D to bladder and sweat elimination pathways in the model.

2.3.4. Charge Question 3 (continued)

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 the Board found that the justifications for model assumptions were sound, we 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

These results need to be investigated and for all sensitivity analyses the direction of change needs to be indicated, that is, positive for a direct dependence and negative for an inverse dependence. For the four parameters noted above, there appears to be unusually high sensitivity, i.e., the ratio of percent change in blood concentration to percent change in parameter is much greater than 1 in absolute value, indicating significant amplification of error from the input parameter to the model output. For example, a 10% variation in one of the parameters would produce a 50% to 90% change in the predicted blood lead level. Since these parameters are in different compartments in the two models this result is unexpected. The present discussion does not provide a satisfactory explanation to account for the significant impact these parameters have on model outcomes.

Charge Question 3 (continued) Recommendations

Tier 1

- The sensitivity analysis should include the direction of the sensitivity; that is, positive for a direct dependence and negative for an inverse dependence.
- Each of the two models underlying the AALM appear to be unusually sensitive to two parameters. This dependence needs to be investigated and fully explained in the TSD or corrected if there are errors in the sensitivity analysis or the model.

2.4. Charge Question Four:

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

2.4.1. Charge Question 4a.

The predictive accuracy and reliability of the AALM based on comparisons to available data sets.

The Board discussed how to interpret the terms "predictive accuracy and reliability" used in this charge question. In both Chapter 3 (regarding AALM.FOR) and Chapter 4 (regarding AALM.CLS [sic]), the term "prediction" refers to the model output (e.g., p. 54, lines 2-6, pdf p. 65), primarily for blood and bone lead concentrations. This leads to confusion because the TSD does not distinguish between predictions based upon an established model and parameter values and outputs from simulations that were used to optimize parameters during a model calibration step. This is relevant because one outcome of model calibration is expected to be close correspondence between model output (predictions) and data. While calibration of parameter values 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. The comments herein include observations about model performance with respect to AALM.FOR.

As described in the response to Charge Question 3c, re-implementing adult modeling in MATLAB identified a series of issues about parameter values that appeared necessary to reproduce some Figures in the TSD. That has raised additional uncertainties in the review of the model results in comparison with the data in addition to the topics discussed here in response to Charge Question 4a.

Many of the simulation results, whether pure predictions or fits by adjusting parameters, are quite good. The following are notable exceptions with respect to model performance:

- Figure 3-14. Based on comparisons to data reported by Ryu et *al.* (1983), the model shows a much more rapid increase following the change in formula at age 112 days as compared to the data based on estimated mean Pb intakes.
- Figure 3-15. The fit is quite poor for the Pb intake: blood Pb relationship for infants reported by Sherlock and Quinn (1986), not only because of the difference in slope, but also the intercept, which would be an indication of a baseline blood Pb in the absence of the additional Pb intake. Also, note that the y-axis is incorrectly labeled "Blood Pb intake" when it is "Blood Pb concentration."

New equations for bone weight and bone volume have been added to the AALM. Given these additions, the adjustment for bone Pb based on bone mineral does not appear to provide the expected answer. However, ASHwt = WBONE x 0.6 based upon information provided in ICRP (2002) for bone ash density and bone volume does. This indicates values on p 63 line 10 of the TSD based upon ICRP 1981 should be reconsidered. The following discussion should be used to inform the reconsideration. The adjustment for bone Pb based on bone mineral currently in the AALM does provide a similar answer to the one proposed by the reviewers, as both derive a fraction of skeletal weight that is ash weight (see multiple ways to calculate ash weight below). However, the equation for ash concentration (G 24 in the TSD) appears to have an error in it. Specifically, the reference value from ICRP 2002 page 178 for ash weight is 29% of the total skeleton weight of a 73 kg man ranging from 27 – 31%. This is based on direct measurements and theoretical values derived from the calcium content of the skeleton.

Therefore, equation G24 (page 41 TSD) should be ASHCON = YSKEL/(0.29*TSKELWT).

Ash weight can be derived multiple ways. First, using the reference value for TSKELWT = 10500 grams, ash weight is 0.29*TSKELWT = 3045 grams. Second, ash weight can be calculated from values for bone volume and ash content density from page 174 of ICRP 2002 to get a single ash fraction of 0.6 where WBONE is 5212 grams for a 73 kg man and WBONE*0.6 = 3127 grams of ash content. This is 30% of TSKELWT. Third, ash weight from equations N16 and N 17 on page 45 of the TSD where CORTWT*0.55 and TRABWT*0.5 as proposed on page 63 of the TSD derives ash weight= 2814.6 grams or 27% of TSKELWT. Hence, each approach derives a fraction of ash content from total skeletal weight that is within the range of values

derived from direct measurements of ash content and through estimates based on calcium content.

Additional development and applications of the AALM model may continue to utilize data on bone lead concentration obtained from noninvasive K x-ray measurement of lead in bone. This is typically expressed as micrograms of lead per gram of bone mineral. AALM model development that utilizes such data may wish to reference assumptions underlying the calculation of bone lead concentrations from the instruments used and described in these studies:

- Jones KW, Schidlovsky G, Williams FH, Wedeen RP, Batuman V. In vivo determination of tibial lead by K x-ray fluorescence with a Cd-109 source. Ch 57 in "In Vivo Body Composition Studies. Proceedings of an International Symposium held at Brookhaven National Laboratory, New York Sept 28 – Oct 1, 1986."
- Ellis KJ, Yasumura S, Morgan WD (eds). Institute of Physical Sciences in Medicine, 1987 ISBN: 0904181502, 9780904181500, pp 363-373.)"

The description of the modeling of the Hattis data appears to have an error (p. 56, line 37, pdf p. 67) indicating "(20 years + duration of strike)", when presumably it is (20 years + duration of *prestrike* employment).

The empirical data that are used to evaluate model performance appear to be more heavily weighted to representing males than females. Concerns about modeling breastfeeding and post-menopausal changes in bone have been noted elsewhere and suggestions made about potential data sets to use.

Table 4-16 of the TSD presents a strategy for the sequential parameter optimization of the model using eight steps. The following observations are notable:

a. The capacity limit of 350 µg/dL RBCs may be too high.
Step 2 (plasma/RBC ratio) lists six studies that support estimates of this ratio. With respect to RBC binding capacity, the Board recommends referring to Figure 14 in Leggett (1993) and Figure 1 in Bergdahl et *al.*, (1998). Bergdahl et *al.*, (1998) reported an RBC capacity limit of 300 µg/dL – similar to previous findings by this group and others. In Figure 1 of Bergdahl et *al.*, (1998), the modeled line representing the three observed lead-binding components is closer to the line representing the DeSilva data shown in Figure 14 in Leggett (1993) and in O'Flaherty (1993). Based on the conclusions stated by these authors, perhaps the capacity limit of 350 µg/dL RBCs is too high. The issue of how to describe RBC binding also has been raised in charge question 3c.

b. Urine clearances reported in the literature are quite variable – how was this addressed in the proposed plasma-to-urine clearance estimates (Step 3)?
Step 3 lists five studies that support plasma (blood) to urine clearance. Figure 13 in Leggett (1993) shows that short term and chronic exposure scenarios can yield vastly different urine clearances relative to blood lead levels. Were exposure scenarios from all five studies similar? EPA should consider examining this variability and discussing implications for these findings on the input parameter selected for AALM.

c. AALM appears to exaggerate Pb concentrations in kidney and liver.

Step 4 lists four studies that support soft tissue/bone Pb ratios. When a 20-yr simulation with the AALM of the lead distributed to compartments representing bone, blood, liver, kidney, brain other tissue was conducted as described in Leggett (1993), results for kidney and liver were substantially higher than those estimated from autopsy data summarized in Table 3 of Leggett (1993). EPA may wish to revisit this optimization step using summaries of tissue lead distribution.

It seems possible that AALM.FOR may yield a more rapid decline in trabecular bone relative to cortical bone in adult lead workers following termination of long-term exposure. Data from Nie et *al*., 2009 presenting KXRF measurement of trabecular and cortical bone lead in retired lead smelter workers indicated that years after exposure ended trabecular bone Pb concentration exceeded cortical bone lead concentration. However, when pre- and post- retirement blood lead presented on one worker in Figure 3 of Nie et *al*., 2005 were extracted and used by one Board member to model trabecular and cortical bone lead in a MATLAB version AALM, trabecular bone lead declined to less than cortical bone lead beginning approximately 5 years post-retirement. The TSD (page 55 and page 66) noted that published and unpublished blood and bone lead data from the studies by Nie and colleagues had been made available to EPA. The TSD concluded that uncertainty regarding certain aspects of the subjects' lead exposure constrained the utility of the dataset for evaluation of the model's biokinetic parameters. Notwithstanding these limitations, future revisions of the AALM may be informed by qualitative patterns of decline in trabecular and cortical bone lead in the Nie datasets, as well as additional data on human bone lead measurements that may become available.

d. AALM appears to overestimate peak blood Pb.
Step 7 lists one study (Rabinowitz, 1976) as a source of data on blood elimination kinetics in adults. Some of these data are displayed in Figure 3-10 of the TSD, which shows strong correspondence between observed and predicted blood 207Pb concentrations, after gut absorption fractions were adjusted to match values reported in Rabinowitz. Figure 7 of Leggett (1993) shows simulations results using absorption fractions from the Rabinowitz study, as reanalyzed by Chamberlain. When the modified absorption fractions were applied using the AALM, peak blood leads were higher than previously modeled for three out of four subjects. The elimination kinetics did not change but perhaps, the body weight-based blood volume is too low.

Charge Question 4a Recommendations

Tier 1

- Use prediction in the documentation to mean a *de novo* prediction from an established set model and parameter values. Otherwise, describe the output of the model as simulations, results, or model outputs.

Tier 2

- Re-evaluate simulations shown in Figures 3-14 and 3-15. Determine if adjustments to the model can improve the fits or provide text in the documentation to assist the user in understanding implications of these fits for using the model in specific contexts.
- Review whether any additional data for females are available that could inform model parameters.

- Re-evaluate the calibration steps described in Table 4-16 considering the comments provided above. Make adjustments as deemed appropriate to the model and add explanations to the documentation for adjusting or not.
- Discuss the potential uncertainties associated with model calibration and evaluation from historical data as compared to likely contemporary exposures.

2.4.2. Charge Question 4b

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.

The similarity of results obtained with the model coded in ACSL and Fortran is a strong verification that the current Fortran version of the model is operating as expected. However, as described in Q3c, an effort to reimplement the adult model in MATLAB identified issues with parameter values.

The AALM has been successfully executed with proprietary software such as ACSL extreme, MATLAB and Excel on Windows operating systems. It has not yet been successfully executed on Apple or Linux operating systems.

Charge Question 4b Recommendations

Tier 1

- Note in documentation the operating systems that have been used (i.e., Windows) and not used (i.e., Apple, Linux) at this time.

2.4.3. Charge Question 4c

The availability of other datasets that may be useful for further model evaluation.

Some references with additional data that could be used for verification of the model are provided here, though other references are discussed in responses to specific issues in other charge questions. Comments are provided below about the issue addressed by these references (individually or as a group associated with Nie et *al.*, 2005) for consideration in evaluating model performance. It would be useful to evaluate how well the AALM predicts the results from these data sets. If the model does well, then it provides more verification of the model. If the model is far off it is important to understand why. No model is perfect, and no model can be expected to recover all collected data. However, it is important to know the limitations of the model and this data would serve as an important test since it was not used in the development.

- Christoffersson JO, Ahlgren L, Schutz A, Skerfving S, Mattson S. Decrease of skeletal lead levels in man after end of occupational exposure. Arch Environ Health 41:312-318; 1986.

Comment Christoffersson, et al.: After approximately 25 years of occupational exposure, decline in blood lead following cessation of further exposure exhibited a two-compartment pattern, with slow phase T1/2 of approximately 7 to 8 years.

- Hodgkins DG, Hinkamp DL, Robins TG, Schork MA, Krebs WH. Influence of high past lead-in-air exposures on the lead-in-blood levels of lead-acid battery workers with continuing exposure. J Occup Med 33:797-803; 1991

Comment Hodgkins et al.: High airborne lead exposures sustained more than 5 years in the past exert a significant influence on contemporary blood lead of workers despite interval reduction in air lead. Study does not report T1/2 of blood lead, but rather the relative contribution of current air lead to blood lead as a function of seniority (past lead exposure).

- Hryhorczuk DO, Rabinowitz MB, Hessl SM et *al.*, Elimination kinetics of blood lead in workers with chronic lead intoxication. Am J Indust Med 8:33-42; 1985

Comment Hryhorczuk et *al.*: Slow phase blood lead elimination half-lives in patients with chronic occupational lead intoxication followed for more than 5 years after removal from exposure ranged from 1,658 to 7,189 days.

- Manton WI, Angle CR, Stanek KL et al. Acquisition and retention of lead by young children. Environ Research. Section A. 82:60-80; 2000.
- Roberts JR, Reigart JR, Ebeling M, Hulsey TC. Time required for blood lead levels to decline in nonchelated children. J Toxicol Clin Toxicol. 2001;39(2):153-60.

Comment Manton et *al.,* and Roberts et *al.*: Data on children with relatively long T1/2 of lead in bone after earlier life prolonged lead exposure.

- O'Flaherty EJ, Hammond PB, Lerner SI. Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fund Appl Toxicol 2:49-54; 1982.

Comment O'Flaherty et al.: Decline in blood lead after cessation of exposure is markedly longer in adult males with long history of exposure, consistent with strong effect of slow release of lead in bone.

- Brito, J. A., McNeill F.E., Stronach I., Webber C.E., Wells S., Norbert R., Chettle D.R., 2001. Longitudinal changes in bone lead concentration: Implications for modelling of human bone lead metabolism. J Environ Monit 3:343-351. DOI: 10.1039/b101493p PMID: 11523432
- Brito, J. A., F. E. McNeill, D. R. Chettle, C. E. Webber, C. Vaillancourt. 2000. Study of the relationships between bone lead levels and its variation with time and the cumulative blood lead index, in a repeated bone lead survey. J Environ Monit 2:271-276. DOI: 10.1039/b002855j PMID: 11256712
- Fleming, D. E., D. Boulay, N. S. Richard, J. P. Robin, C. L. Gordon, C. E. Webber, D. R. Chettle. 1997. Accumulated body burden and endogenous release of lead in employees of a lead smelter. Environ Health Perspect 105:224-233. DOI: 10.1289/ehp.97105224 PMID: 9105798
- Fleming, D. E., D. R. Chettle, J. G. Wetmur, R. J. Desnick, J. P. Robin, D. Boulay, N. S. Richard, C. L. Gordon, C. E. Webber. 1998b. Effect of the delta-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers. Environ Res 77:49-61. doi: S0013-9351(97)93818-4 [pii]10.1006/enrs.1997.3818.

- Fleming, D. E., D. R. Chettle, C. E. Webber, E. J. O'Flaherty. 1999. The O'Flaherty model of lead kinetics: An evaluation using data from a lead smelter population. Toxicol Appl Pharmacol 161:100-109. doi: 10.1006/taap.1999.8790 S0041-008X(99)98790-2 [pii].
- Nie, H., D. R. Chettle, C. E. Webber, J. A. Brito, J. M. O'Meara, F. E. McNeill. 2005. The study of age influence on human bone lead metabolism by using a simplified model and x-ray fluorescence data. Journal of environmental monitoring: JEM 7:1069-1073. doi: 10.1039/b507749d.

Comment In Chapter 3 section 3.3, authors stated that they were able to obtain blood and bone lead measurements along with dates of hire and birth dates for 209 smelter workers. However, authors concluded that the data was not suitable for model evaluation. The authors state:

> "*Data that were available from the Nie study consisted of three longitudinal blood and bone XRF measurements for 209 adult Pb workers. The measurements were made in 1991, 1999 and 2008. This period included a nine-month strike (July 1990 to May 1991), during which exposures at the plant were interrupted. The available data also included birth dates and dates of hire. There were no data on actual exposures at the plant. Although attempts were made to reconstruct exposures so that blood and bone Pb concentrations could be predicted and compared to observations, ultimately, it was concluded that the data were not suitable for model evaluations because of the uncertainty in the exposures that preceded the blood and bone Pb measurements and that occurred during the measurement period. Exposures prior to 1991, including the period of the strike, had to be reconstructed with no basis for verification other than the observed blood and bone Pb measurements.*"

This dataset appears to have as much or more detail as those datasets that appear in Figures 4-18 and 4-19 (pages 177-178 TSD 2019). The exposure history of the cohort from 1968 – 1995 appears in Brito et al. 2000 and 2001 and in Fleming et al. 1997. It appears that this group level blood lead data – by absence of these references – was not considered. An initial assessment of the 9 retired workers in Nie et al. 2005 by a Board member indicates that lead in trabecular bone on a ug lead/g bone mineral basis, remains higher than in cortical bone for four or more years after removal from occupational exposure. However, predictions from the current AALM inverts this relationship.

Charge Question 4c Recommendations

Tier 1

- Compare AALM simulation results with the data sets provided to further assess the capabilities of the model. Particular attention should be paid to the comments provided with each reference or the group of references associated with Nie et al., 2005 for evaluating whether the model captures the behaviors described.

2.5. Charge Question Five:

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?

2.5.1 General Comments Responding to Question Five

The Board found that the AALM is functional, but not particularly user-friendly. User-friendly in this context refers to the Excel software interface and whether it is easy to use, and not difficult to learn or understand. User-friendly interfaces should be simple, well-organized, intuitive and reliable; should provide a positive experience; and not cause undue frustration for the user. User-friendly model interfaces are typically more successful and widely used than those with complex, convoluted difficult interfaces.
Several Board members noted throughout the review that the perception of user-friendliness, and indeed the effectiveness of the model predictions, depend on the intended use of the model and the experience level of the user. There seemed to be a consensus that the interface is sufficiently functional for skilled modelers, but nevertheless requires internet searches to overcome Excel and operations systems glitches. However, as an Application Guide for a broader range of potential users (e.g., state or local public health official or risk assessors, medical doctors), the User's Guide probably discourages those who might otherwise find the model a useful tool.
An illustrative measure of "User Friendly" is a comparison of time expended (and frustrations vented), by Board members before and during the open meeting, on making the model run versus running the model and assessing its effectiveness in blood lead predictions. Only a minority of members were able to implement and use the model. A disproportionate amount of time, although useful and instructive, was spent during the meeting toward making the AALM operational. The Board requested a tutorial session on how to implement the model to develop a better understanding of model capabilities and the types of output that can be produced. The live demonstrations by EPA Staff were immensely helpful. EPA should consider developing a companion video if releasing the User's Guide in its current format. Additionally, an appendix could be added to the User's Guide that uses screen shots to provide several examples of typical uses of the AALM, including exposure pathways beyond drinking water and the user entries that would be required. Training videos for different aspects of the model, such as each exposure pathway, would be valuable.

The Board indicated some confusion as to the intended purpose of the User's Guide. U.S.EPA staff clarified in the meeting that Charge Question 5 does not address the functionality of AALM in the context of, or comparison to current U.S.EPA regulatory models (e.g. the IEUBK model for lead in children that contains a far more extensive Users Guide or the Guidance Manual produced for the 2005 version of the AALM). In that regard this current guide would not be functional.

EPA Staff indicated that Question 5 refers to the internal technical specifications 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."

In that context (its purpose being to implement a FORTRAN Program using an Excel Interface); the User's Guide is functional, assuming the User has substantial knowledge and familiarity with similar models. Uninitiated Users would have considerable difficulty and frustration in making the model operational, making informed modifications, and storing and interpreting the results. There is little guidance provided, in either of the documents, regarding how to save, connect and interpret the input and output summaries.

There is also confusion as to how and what would be released by EPA should AALM be endorsed for use by the Agency. It is unclear whether the earlier support documents and previous "… the more extensive AALM.CSL documentation …" part of the package, as item 3 above would suggest. There were references to Batch Mode simulations and other options available in the ACSL edition not available in the FORTRAN version and indications that there were additional compartments in some of the biokinetic modules.
As these materials were not provided to the Board, it was difficult to assess the adequacy of the User's Manual in this context.

2.5.2 Specific Comments and Suggestions by Section

Front Material: The Cover Page does not include Authors, Project Officers, responsible Agency Division, Contract References or Contact information. There is no link to an "Assistance or Help" resource. 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 TSD and were provided in the Draft 2005 Guidance Manual. However, in some cases the descriptions in the TSD 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. Numbering the figures and tables would help users quickly find the correct one without searching through the text.

Section 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 TSD. In this case, the User must refer to the TSD without references or refer to documents from earlier versions of the AALM. The Board suggests adding a sub-section to the Introduction describing Model Limitations, identifying where data are missing or weak, and where simplifying assumptions are made.

It is unclear if the final sentence in this section applies to the original Leggett model, or to this document:
This approach was designed to provide maximum flexibility and versatility rather than user-friendliness.

Section 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 referenced or explained. Board members were not able to locate the "Leggett text files" indicated. The executable file is problematic in that it gives no other indication it is functional other 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 and it was initially unclear 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. If the executable program is not functioning, the buttons do not work, and there is no message as to the source of the error, 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 advisable.
The Note under Step 3 in the guide, particularly the last sentence, is disconcerting. Particularly when the first attempt to run the program returns errors:

"However, the code returned errors in the compilation during our testing."

This suggests the user should be looking for the proprietary compiler. These types of editorial messages, apparently provided to model developers, should be removed.

Section III. Setup and Run

The reviewed document's Subsection 1 provides instructions to unzip the files and place in folders with read/write permissions. Brief descriptions of read/write permissions and how to modify permissions would improve the document. This section also contains numerous references to the "Excel File" however 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 file is vital to execute the model. The instructions to add a runtime library to this Excel file are confusing. Several Board members indicated the screen shots were dissimilar to those in the User's Guide.

These instructions might also be more user-friendly if implemented in steps. The first step would include a screen shot of the Excel File. Step 2 should be to 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. The VB acronym (and others in the document) is never defined. 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. It is unclear if these cautions apply to Excel in total, or to one or both Excel files? Also, are these instructions applicable to other operational systems?

Step 2a would 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 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.

The reviewed document's 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.

Several Board members endorsed U.S.EPA internalizing the entire Time Step procedure and with an appropriate algorithm that would allow the User to simply select the simulation Time Step for the model and the frequency of the output. This would avoid having to include confusing statements such as:

One final nuance: TSTOP and the total number of cycles may not actually match each other based on user input, and the FORTRAN code will use whichever is shorter. If TSTOP = 80, the actual simulation period will be 80 days. On the other hand, if TSTOP = 180, the actual simulation period will be 137.5 days (the number of cycles specified in the time step input table).

The historic note regarding computer capacity to run the Leggett model in the early 1990s is interesting but perhaps better in a footnote or Appendix, as the recommendation for current use is the important message here. There are several "asides" throughout the document referring to nuances and notes regarding situations the programmers encountered in converting the codes that might be moved to a Notes section in the Appendices.

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 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? Should 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. However, there is no apparent way to save a 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.

In the discussion of interpolated versus stepwise exposure time series, the term "time stamps" is used but never defined. When selecting either stepwise or interpolated exposures it is unclear if the selection applies to all exposures.

The reviewed document's Subsection 3. Exposure Input Tabs describes the inputs for the exposure modules. Each of these Tabs is relatively straight forward. There is 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. It is unclear how the discrete component relates to the Baseline in the Pulse exposure. Step 2 is not 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.

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" bioavailability for (e.g., food) and then RBA for the other media compared to food. This description could be at odds with the use of the term RBA in other U.S.EPA applications, usually related to particular lead salts dissolved in water. The discussion here should be amended to reflect bioavailability determinations consistent with other EPA models and Programs.

The discussions regarding nuances of the AALM.CSL versus AALM.FOR are likely of concern to the programmers doing the conversion but inclusion of the notes in a User's Guide is not necessary, e.g.:
The user interface has to translate these profiles into the format used by the Leggett model. Again, this process is seamless in AALM.CSL but is fairly intricate in AALM.FOR.

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. This Section references the Pounds.dat output file that has never been described throughout the document.

Charge Question 5 Recommendations

Tier 1

- Make revisions and edits to the User's Guide as described herein. Decide on the role for each document (e.g., TSD, User's Guide) to provide clarity to the text. Numerous suggestions and edits have been provided here for consideration in these revisions.

Tier 2

- Build up a library of training materials (pdfs of presentations, videos of tutorials) over time designed for a broad user audience. These would address topics such as getting started with the model and using the model to address a range of exposure scenarios. Updating or extending these training materials needs to be considered a part of any tasks to update or extend the model.
- Develop an application manual for the broad range of potential users that is less technical and historical than the TSD and excludes details on the computer set-up and running that are in the User's Guide. The manual should focus on describing the current model structure and parameter values, how to use them and interpret the results, and strengths and limitations, including uncertainties, of the modeling results obtained.

Tier 3

- Develop a more "modern dashboard" interface if the model goes forward in a substantially modernized format.

2.6. Charge Question Six:

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

Throughout its responses to previous charge questions, the Board has noted features that could improve the predictive accuracy of the model.

Fecal Excretion and Mass Balance

While it would only impact matching fecal data and calculating mass balance, it appears that correcting for the RBA (p8 lines 2-4, pdf p 19) 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 to obtain the output. Similarly, corrections would be made to the mass balance equations. This was not an issue in AALM.CSL but arose in AALM.FOR (Table 3-3 p 72, pdf p83) and the functionality/output affected.

Addressing Particle Size

The absence of airborne Pb aerodynamic particle diameter is a limitation as noted previously especially in Charge Question 3b. 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, resuspended dirt, Pb paint spray, and Pb powder dispersion) will be well above 1 micrometer and well above 10 um mass median aerodynamic diameter (MMAD) and have high bronchial deposition (with little blood access), and in many cases no deposition in alveoli (Petito Boyce et *al.*, 2017). Adding particle size categories (e.g., ultrafine, fine and coarse) would significantly improve accuracy and applicability to realistic exposures. It will also tie into EPA's air monitoring network.

Integration Algorithm

A variable-step predictor-corrector algorithm such as the Adams method or the Gear implicit method would help insure appropriate model use. These methods specify the acceptable error in the simulation. This is a feature that would make the model more user friendly as noted in Charge Question 6, but it also would help to ensure that spurious results are not obtained due to incorrectly setting the integration step size. Until such change is made, it would assist users to further explain the approach for controlling numerical integration error during the model simulations, as described in section 2.3.1.

Post-Exposure Kinetics

In Figure 4-19 (p 178 of the TSD, pdf p 189), the predicted decline in cortical bone lead predicted from the AALM.LG appears to be very close to the decline observed in retired workers. However, predicted blood lead tends to be lower than observed. This is particularly the case in the first few years post-retirement where the difference between predicted and average observed blood lead level is substantial (observed is about 14.5 ug/dL and predicted is about 10.4 ug/dL).

Although the AALM has been compared with the Hattis data to see whether measured relative to model-predicted post-strike blood lead levels in chronically exposed workers are on average similar (Figure 3-7 p 81, pdf p 92), further examination of the bone/blood relationship following the methodology presented by Hattis (1981) is needed. Hattis emphasized that it is also important to examine the model's performance relative to the number of days of workplace exposure prior to the cessation of workplace exposure. 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 (i.e. a near zero slope of the blood lead level relative to days of workplace exposure).

Hattis's method for examining model performance relative to length of job tenure could also be helpful (see page 25 of Hattis 1981). This is a check on whether model predictions are dependent on length of employment. For example, predictions from the original Leggett model (Vork and Carlisle. 2020) and the O'Flaherty model (Sweeney 2015), show some tendency to predict blood lead levels after a 273-day strike that are too low on average for workers with shorter job tenures with a trend toward predicting higher blood lead levels on average for workers with longer tenures. The goal is to have no trend across the range of job tenures and predicted blood lead levels. Hattis (1981, page 25) suggests that such a trend might indicate that "…less lead might be stored in slow-exchanging pools than called for in the model, or the rates at which the slow-exchanging pools accumulate, and release lead might be somewhat off."

Body Weight and Body Mass Index

Using age and sex (i.e., standard growth curve data) to define exposed subjects has some problems as initially discussed in charge question 3c. 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.

Pregnancy, Fetal and Infant Exposures

Addition of a gestation model for the fetus could be considered. 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 its blood, that should be added to the lifetime exposures. Otherwise the calculated blood levels and risks will be underestimates. Existing pregnancy models for other chemicals would serve as a good starting point, although factors that are important for lead pharmacokinetics may need additional research to include them in the pregnancy modeling, e.g., red blood cells and hematocrit, serum binding proteins.

Chelation Modeling

The technical guidance indicates that chelation can be simulated with the model (Section 2.3.1.2). When a reader gets to page 301 and Table D-1, page 313, however, the definition of ICHEL indicates that in the EXCEL implementation of the model, chelation is turned off. The Excel file indicates that these parameters are fixed for no chelation and the cells in the sheet are not highlighted, indicating that these parameters cannot be changed. This functionality (or lack thereof) was confusing and needs to be further explained at least, but preferably would be made active in the model. Further, it is not clear whether the modeling of ATSDR data described in Section 3.3.8 (p 61) was done with or without chelation being modeled. This model has the potential to be useful for characterizing, even predicting, changes in blood lead following public health and clinical interventions (e.g., removal of exposure, chelation treatment). There are concerns whether it clears lead too rapidly as noted above (Charge Question 2 – Post-exposure lead kinetics). The model and appropriate parameter values, the documentation, and the validation against data need to be clarified and strengthened.

Charge Question 6 Recommendations

Tier 1
- Correct mass balance errors and fecal lead output.
- Adjust adult bone lead parameters if indicated by re-evaluation of post-exposure kinetics.

Tier 2
- Add algorithm to provide user-friendly integration step size selection and error control.
- Add option to input and process particle size information.

Tier 3
- Describe methods to obtain initial values for blood and tissues to start simulation (e.g., child at birth). Further check the initialization of mother model.
- Add a pregnancy model, which could be based on existing models for other chemicals. Include amniotic fluid for biomarker measurements. Include capability to assess fetal exposure.

- Activate or add capability to simulate chelation. The model and appropriate parameter values, the documentation, and the validation against data need to be clarified and strengthened for potential public health or clinical predictions.

2.7. Charge Question Seven:

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

The Board discussed a wide range of ideas to improve the model's overall functionality as well as applicability for a broader range of scenarios. Many Board members found it challenging to navigate the user interface. The Board members have a range of opinions with respect to the choice of model platforms (i.e., Excel). Some members appreciate the transparency of the Excel worksheet environment, where equations and parameter values are easily accessible. Other members recommended that EPA switch platforms altogether, citing the example of EPA's Benchmark Dose Software (BMDS) – presumably referring to earlier versions, given that the current version utilizes an Excel workbook interface.
The Board felt that it would be beneficial for the broad range of stakeholders to be able to use this model. It is highly likely that it could have quite valuable roles in public health practice and research, as well as in risk assessment and risk management. For the model to be broadly accessible and user friendly, it needs to be structured to readily accept the kinds of information that are available to public health professionals (e.g., dust lead loading, as reported by public health agencies in mcg/ft^2), and researchers as well as risk assessors.
In addition, as noted in charge question 5, well-developed training materials would be beneficial to anyone trying to learn to use a model of this complexity. The tutorial provided the Board was very helpful and availability of such presentations as pdfs as well as videos of tutorials would be useful. Such materials would help guide users toward appropriately applying and using good modeling practices given the complexity of this model.

The following are specific examples for EPA to consider in refining the model to improve its functionality and utility.

Charge Question 7 Recommendations

Tier 1

- Create a library of input files (or example Excel workbooks) that correspond with example scenarios. Then use those scenarios as part of the User's Guide and other training materials to coach new users on various common scenarios, and how to populate the dialogue boxes. The current User's Guide gives an example for water intake. The Board recommends providing at least one example for each exposure pathway and environmental medium.
- Improve the consistency in naming conventions for model input variables between the user interface (Excel file) and the accompanying documentation.
- Create additional user options to specify parameters for the RBA term. Currently, a single RBA applies to all intakes for a specific exposure medium as previously noted in charge question 3b. 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 in different occupational, residential, and public setting may have different solubility, particle size, and chemical composition, and by extension, different RBA.

Tier 2

- Create a single worksheet in which figures are automatically generated for some of the more common x-y scatter plots (e.g., time series for blood, plasma, bone, etc.; blood vs plasma; intake vs blood Pb; etc.)

- Eliminate the user option to change the step size and rely on a predictor-corrector algorithm.

- Provide a plausible range of input values (for the central tendency estimates), at least for selected parameters for which source information is uncertain.

- Create a single worksheet for risk characterization. It might apply an assumed lognormal distribution model and generate a plot automatically (also see response for charge question 9 on approaches to addressing variability and uncertainty). 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 geometric standard deviation (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. This should allow entry in units that arise in a range of different settings, including for example amount of Pb per square foot for dust ug/ft2 in addition to the currently entered ug/g.

- Consider including the Adult Lead Model 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.

- How to effectively implement age-related changes in food intake needs to be clarified in the model documentation and examples created. EPA should consider including an appendix to the model documentation of suggested sources or values for age specific intake rates or other parameters needed for implementing this pathway.

- Since this is a life-stage model and simulations can be started from birth, accounting for breast milk exposure would be essential. Add text to explain how it can be done.

Tier 3

- One application of the AALM might be to assist clinicians in estimating and interpreting the future pattern of blood lead in a patient who presents with an elevated value and is ostensibly removed from further exposure. If the blood lead did not decline as predicted by a physiologically based pharmacokinetic model such as the AALM, this might raise suspicion of occult ongoing exposure that merits further investigation. To enhance potential use of the AALM for this purpose, future versions may be able to use available information on a subject's current blood lead, age, and approximate exposure history to create a modeled version of the subject in which each tissue compartment has been primed with compatible estimates of lead mass. An application like this, would also need to be compared to appropriate data to demonstrate its reliability.

- Consider a module that allows for exposure or kinetics parameters to be modified to account for co-exposures to other chemicals. 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 sufficiently model Pb exposures in most scenarios, although it 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.

2.8. Charge Question Eight

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

The Board agreed that the model documentation and development processes for the AALM have generally been consistent with the EPA Center for Research for Environmental Models (CREM) guidance. The guidance document presents 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. In addition, EPA has conducted peer reviews of past versions of the model and they are now conducting this peer review. The CREM guidance provides extensive lists of recommended practices. Many of these have been addressed for AALM such as the summary of recommendation for model development at the beginning of Section 3 and aspects to be peer reviewed (p 24 and Box D2 p 63 of CREM Guidance).

The model will likely be further optimized by continued testing and rigorous calibration efforts utilizing additional data sets from the real world. The Agency should continue to identify and apply the model to real world situations, as well as to controlled studies and designed experiments. The Board has the following recommendations that would aid in the AALM conforming to CREM guidance.

The link for the guidance document given in the charge question did not work. However, Board members were able to find it at: https://www.epa.gov/sites/production/files/2015-04/documents/cred_guidance_0309.pdf. EPA should correct the link.

CREM guidance indicates that a primary step in model development includes the need to "(a) specify the environmental problem (or set of issues) the model is intended to address and develop the conceptual model (EPA 2009 CREM guidance, page vii). This is currently absent in the review version of TSD for AALM.FOR. A revision should include a detailed discussion of intended model applications that describes when use of the AALM is appropriate or is not appropriate, or when the model parameters would require modifications. Applications where the model is believed to have the strongest and weakest predictive capabilities should be identified. If this model is used for a scenario or with data that it was not designed to address, the outcomes may not be valid, and this should be clearly explained. For example, as discussed above in the response for Charge Question 3b, the strengths and weaknesses of applying the model to occupational inhalation exposures should be highlighted. For example, compared to airborne environmental lead exposures, occupational exposures could be characterized by larger particles with different deposition locations in the respiratory tract, as well as ventilation rates that exceed defaults for most adults with community lead equations.

Given the high sensitivity of the model to some parameters as discussed in the response for the final part of Charge Question 3, the Board recommends performing uncertainty analyses. A weakness of this model, like other complex pharmacokinetic models, is deriving parameter values from data requiring underlying assumptions. Elements that are recommended for inclusion as part of the uncertainty analysis:

Tables of key uncertainties of inputs and outputs: These tables should make key uncertainties clear to model users and risk assessors.

It should be clearly conveyed to users that uncertainty in model outputs will vary. For example, there are simply more data sets available with measured blood lead versus brain lead levels and there is thus more uncertainty around the prediction of brain lead.

The WHO/IPCS PBPK Guidance (WHO/IPCS 2010), containing tables for characterizing uncertainty and variability, could be useful in uncertainty evaluation for the AALM. It is recommended that the Agency evaluate this document and include similar tables in the documentation for the AALM. Specification of uncertainties should then focus future research efforts to address those needs.

Bayesian statistical analysis using Markov Chain Monte Carlo methods incorporates parameter correlations and should be performed on at the very least, blood lead, in order to obtain uncertainty estimates in kinetic parameters. Separate analyses should be performed for biokinetics and for the exposure module in order to obtain uncertainty estimates for the two separate parts of the model. MCSim, which is free software, can be used to perform Bayesian analyses and can be found at: https://www.gnu.org/software/mcsim/ (accessed March 12, 2020).

There are numerous parameter values included in this model, and many of the variable value selections should not be made in isolation. In addition to uncertainty analyses, 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.

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 U.S. exposure levels. This model is also 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 U.S.

It may be useful to compare the data used in Leggett's original model and the updated AALM to develop and/or update parameters values with criteria listed in the CREM guidance on study quality. Attributes of study quality are also addressed in a series of articles on this subject written by Leggett and colleagues; these articles should be evaluated by the Agency (Harrison et al. 2001, Leggett 2001, Leggett 2003, Leggett 2007). In addition, comments about the quality of data used to calibrate and test model parameters from the original Leggett (1993) publication should be extracted and commented on in the technical guidance. The assumptions, rationale, and limitations of parameter values listed in the original Leggett model should also be checked and commented on.

Charge Question 8 Recommendations

Tier 1

- Develop a clear statement of model applications considered appropriate for the current status of the model and the available parameter values. Providing examples of these applications would also benefit users.

Tier 2

- Assess AALM parameters and outputs using CREM guidance on study quality and consideration of comments in Leggett (1993). Add results of analysis to model documentation.
- Develop a plan to characterize uncertainties in the model outputs, along with those in model inputs, and begin implementing the plan. Initial steps would likely be more qualitative, e.g., table recommended in the WHO/IPCS PBPK Guidance. Later steps would be increasingly quantitative, e.g., Monte Carlo or Markov Chain Monte Carlo analyses.

2.9. Charge Question Nine

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?

2.9.1. Evaluating lead concentrations in exposure media associated with benchmark changes in blood lead

Risk managers and other stakeholders occasionally encounter risk management questions for which it is desirable to examine the isolated contribution to blood lead (or another biomarker of lead burden) arising from a certain medium and/or route of exposure. For example, risk managers may be interested in discerning the isolated contribution of a certain concentration of lead in soil to blood lead concentration in a certain demographic group, such as a two-year-old toddler or an outdoor adult worker. In a notable peer-reviewed article, scientists with the California Office of Environmental Health Hazard Exposure (OEHHA) expressed their opinion that with respect to environmental lead exposure, an increase in blood lead of 1 µg/dL to a young child would constitute a reasonable benchmark change for environmental decision-making (Carlisle et al., 2009).[1] OEHHA then utilized the California Department of Toxic Substances Control's slope-factor model, LeadSpread, to calculate that a concentration of lead in soil or dust equal to 77 µg/g would yield a benchmark blood lead increment to a child of 1 µg/dL at the 90th percentile (CalEPA 2009). In like manner, OEHHA applied EPA's Adult Lead Model (EPA, 2005) to calculate that exposure of a pregnant adult worker to a soil concentration of 320 µg/g would yield a 1 µg/dL increment in the blood lead concentration of the neonate at birth (CalEPA 2009). For each of the foregoing assumptions, OEHHA entered various default values in the respective models for parameters such as exposure frequency, soil intake rate, and geometric standard deviation. Intake of lead from other pathways was considered to be zero. For the adult worker scenario, the geometric mean background blood lead concentration was assumed to be 0.6 µg/dL.

It may be envisioned that the AALM could be utilized to address questions of a similar nature relating soil exposure to estimated increment in blood lead. The design of the AALM requires assumptions about prior lifetime lead exposure history and the corresponding lead content of various tissue compartments. This could be addressed by developing certain generic datasets or libraries of past lead exposure depicting representative lifetime lead exposure patterns for various receptors, such as a two-year-old child, or a 25-year-old male or female adult. When used in conjunction with the AALM, these datasets could be used as a point of departure to solve for a certain concentration and pattern of soil lead exposure (e.g. exposure to X ppm of lead in soil for 90 consecutive calendar days, or 250 consecutive work days) that would be associated with a benchmark increment in blood lead concentration (e.g. 1 µg/dL). As currently structured, the AALM would yield an exposure that would apply to a benchmark blood lead increment at the

[1] This was based on the assessment that at the upper bound of the slope of the blood lead – IQ relationship in young children in the pooled study by Lanphear et *al.* (Lanphear et *al.*, 2005), a 1 µg/dL increment in blood lead was associated with a 1 IQ point decline. The authors noted, " …at present, the effect of changes less than 1 µg/dL are too uncertain to use as the basis for regulatory action." (Carlisle et *al.*, 2009).

central tendency, or median. Application of methods to estimate variability around the central tendency, e.g. by use of an assumed GSD or Monte Carlo modeling, could be added to the AALM to yield medium-specific lead values that would yield a benchmark change in blood lead to the 95th percentile receptor.

2.9.2. Population variability in AALM outputs to facilitate use in risk assessment and risk management

As noted above, the current construction of the AALM.FOR yields outputs for tissue compartments, such as blood lead, that represent central tendency estimates derived from the selected exposure inputs and biokinetic settings. While these central tendency estimates are informative, risk managers often require outputs that also present tissue concentration such as blood lead at the upper end of a population distribution, e.g. the 95th percentile. For example, the IEUBK model is used in risk assessment to calculate the geometric mean blood lead concentration, the 95-percentile confidence interval about the geometric mean, and the 95th percentile of the lognormal distribution. The latter value represents the blood lead concentration that will be exceeded by no more than 5% of children subject to the exposure inputs (e.g. soil lead concentration) of the modeled situation. IEUBK calculates the 95th percentile using a GSD that is intended to capture the variability in everything except the concentration term. Specifically, the GSD incorporates variability inherent in behavior that contributes to the exposure (such as hand to mouth activity), RBA of lead in soil, and biokinetics. EPA has long recommended the default GSD of 1.6, although use of a site-specific GSD is permissible (U.S. EPA, 1994; Marcus and Elias, 1998). USEPA's guidance on the GSD for older age groups is limited to women ages 17-45 years, based on a reanalysis of the most recent six years of blood lead data reported from NHANES 2009-2014 (U.S. EPA 2017).

Several approaches would be possible to depict variability around central tendency estimates generated by AALM.FOR. As with the IEUBK, it would be possible to assume that the population distribution is lognormal and can be calculated using an assigned GSD. Some Board members cautioned that unlike the long term experience with IEUBK that has validated the use of a default GSD of 1.6 for childhood blood lead, there is insufficient data and experience with the AALM.FOR to identify a default GSD valid for the myriad of settings and age ranges for which the model is intended.

Probabilistic methods, incorporating Monte Carlo simulations for exposure and biokinetic parameters, would represent an alternative approach to estimation of variability in AALM.FOR. Monte Carlo modules have been developed for use with IEUBK (Goodrum et *al.*, 1996), for the O'Flaherty model applied to childhood blood lead (Beck et *al.*, 2001), and for the O'Flaherty model applied to adults with occupational lead exposure (Sweeney, 2019). Board members suggested that variability in the AALM.FOR outputs could be generated using either conventional (random seed) Monte Carlo methods, or Markov chain methods, applied to both exposure and biokinetic parameters.

2.9.3 Multiple user-friendly model outputs

A key area of research is to develop a better understanding of what measures of lead in the body best relate to neurotoxicological outcomes. Since AALM calculates lead levels in blood and different tissues, it could assist in research on such questions. What measures of lead in blood (e.g., circulating unbound lead levels, average daily lifetime blood lead level, area under the curve for blood concentration, cumulative blood lead levels), brain, or bone would be most informative about health outcomes? Would expansion of the brain model beyond a single compartment be useful? Is there an "ideal" bone for measuring lead deposits, what contributes to the differences, and what role does bone injury play in re-exposure to deposited lead?

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.

In like manner, a few epidemiological studies have found that CBLI is a significant predictor of adverse health effects. This metric may grow in use in the future. It would be useful for AALM.FOR to calculate CBLI (essentially the area under the curve of blood lead by time plot) as an output. For example, this may be helpful in illustrating how infrequent exposure to high levels of lead in air, e.g. during infrequent maintenance work, might result in considerably more cumulative lead exposure than regular daily exposure at lower levels.

For example, the consider two scenarios evaluated by the OEHHA Leggett+ model. The area under the curve (AUC) in the model represents CBLI for this time interval.

Scenario I. A 25 year old worker who starts work with a blood lead level of 1.5, and whose only lead exposure for the next year is one 8 hour day, once a month for 9 months, engaged in heavy work (breathing rate of 8.67 m^3/8 hour) where the airborne lead is 500 ug/m^3. The second scenario is the same worker, but this time he begins work characterized by moderate exertion, 5 days a week, for 12 months, at an air lead concentration of 10 ug/m^3. Over the course of one year, AUC for scenario 1 = 3075 ug-day/dL, for scenario 2 it is 2477 ug-day/dL. This illustration depicts the pitfall of exempting workers with only infrequent lead exposure from medical surveillance.

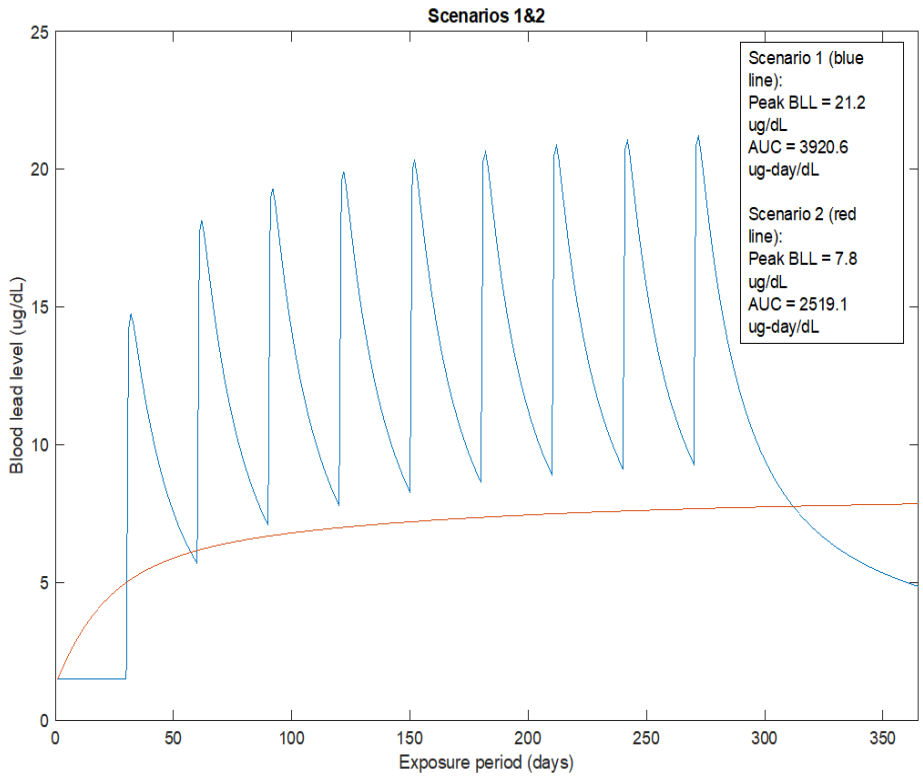

Figure 9-1: Simulations of blood lead concentration for two different exposure scenarios over the course of a year: one day of high exposure each month for nine months, versus 5 days a week lower level exposure, using the 2015 OEHHA Leggett + model.

2.9.4. Comparison of multiple model simulations

Users will likely want to compare blood lead (and other tissue lead) levels across multiple exposure scenarios simultaneously (e.g., varying the exposure terms, varying exposure frequency or periodicity, varying exposure cessation). To the extent possible, the Board recommends that this functionality be made available and easy to use. For example, the option to run multiple exposure scenarios with blood or tissue lead levels reported on a single graph would enhance efficient communication of results. Capabilities for batch runs and plotting the results could also be valuable.

2.9.5. Assessing exposure due to paint

Guidance on how to estimate and assess lead exposure from lead-based paint would be useful (maybe in the context of presenting some examples with real-world exposures/exposure patterns). Estimates of how much paint children might ingest at different ages and examples that estimate lead intake based on 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 evaluate cases with paint exposures or lead from other sources (pottery, dishes, etc.) would be helpful.

Charge Question 9 Recommendations

Tier 1

- Augment the current model outputs to include metrics that are under active research investigation, such as cumulative blood lead index (CBLI) and concentration of lead in cortical and trabecular bone (ppm) and evaluate whether model outputs of values or graphs can be made more user-friendly.

Tier 2

- Facilitate comparisons across multiple exposure scenarios by providing user-friendly automated graphing options or, at least, clear documentation so users with a broad range of skills can set up their desired results reporting.
- Implement methods to characterize population variability and uncertainty for AALM outputs, such as blood lead, to provide estimates like 95^{th} percentiles that would be useful in risk assessment and risk management.
- Develop a library of representative lifetime exposure scenarios (e.g. childhood exposure; environmental adult exposure; occupational lead exposure) that could be used to provide the "background" lead exposure for purposes of investigating additional exposures (e.g., soil or air or water exposure) and the predicted model outputs, such as blood lead concentrations that could be compared to benchmark changes in blood lead (i.e., 1µg/dL increase in a child or adult).

Tier 3

- Provide guidance on addressing exposures arising from the presence of lead in paint.

3. REFERENCES

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APPENDIX A: EDITORIAL CORRECTIONS

The SAB recommends that the following editorial corrections be made to the AALM Technical Support Document.

P 3 line 1: strike "A Brief History of"
P 3 line 14: delete "minimal"
P 3 line 14: Title line –Setup or Set Up ?
P 8 line 9: options or option ?
P 9 line 8: is age 20 missing from series?
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 10 Inset: Change "word to Wise" to "Warning"
P 10 Inset, last line: Delete "slightly"
P 13 line 17: Add "at" before "different"
P 15 lines 1 and 3: use a better descriptive term or define "tool"
P 15 lines 8: should be "water" pathway not "air"?
P 18 line 7: For completeness, add 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 11 – There are small errors in the Table.
P 23 line 29 – The equation for UPTAKERT did not provide the expected results, which were obtained from UPTAKERT = (1-CILIAR) x sum(YRi x (1-e^-BRi)). Note that other equations appear to have a similar error and need to be corrected.
P 23 line 32: BRi is a rate not a fraction
P 27 line 4: Correct Eq. 2.3-35 to match to equation in Table 2-2.
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

Throughout the document, "CLS" should be changed to "CSL" when discussing ACSL model files. For example, on p. 1 (lines 17-19; pdf page 12), "AALM.CLS" should be "AALM.CSL."

Page 303 Appendix D: Calculation of RDIFF from ln2/half-life has a typo, 0.00231.

Editorial Comments Relevant to Charge Question 3(a)

1. 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:

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

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

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

2. 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

3. 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.

dusts for a statistical sample of U.S. residences. Based on a sample of approximately 2000 homes, the mean Pb loading (µg/ft²) 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/ft²

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."

track in from contaminated soil). A value of equal to the soil Pb concentration (see section on *Soil Lead Concentration*) 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).

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	30
(8, 44)[a]	(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 the following notes:
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 7 Appendix D does not have B1-B4, presumably this should be BR1-BR4

j. 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

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

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

l. 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.

m. 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.

n. Table C-1, confirm that term "indoor soil" is intentional – is it better defined as simply "soil"?

p. 291

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	

APPENDIX B: MINORITY OPINIONS

The Board agreed, by voice vote, to include this appendix representing a minority opinion based upon the comments of Dr. John Guckenheimer.

The All Ages Lead Model v2 (AALM) estimates lead concentrations in blood, bone and other body organs resulting from changing lead concentrations in the environment. The model evolved from three models created in the early 1990's: the IEUBK model for lead concentrations in children ages 0-7, a model Leggett developed at Oak Ridge National Laboratory in connection with studies of biological accumulation of radionuclides , and a physiologically based model developed by O'Flaherty, initially fit to experimental data on rats. The original AALM Fortran model has been modified over time, reimplemented in the proprietary acslX language and given an Excel interface for users Computers and computer software have changed dramatically during the twenty-five years since the AALM was first created, but the evolution of the model has taken relatively little advantage of these improvements. Open source software (including packages specifically designed for investigation of dynamical models) and high-level programming languages like Python, Julia and Matlab (or its open source alternative Octave) make it far easier to implement models of moderate complexity and enable much more extensive exploration of their properties.

Dynamic models like the AALM create time series of interacting variables. The simplest models are either systems of ordinary differential equations that express the rates at which state variables change, or discrete time iterations that give rules for how the state variables change in a single time step. Much more complicated models are also possible, for example hybrid models that include both discrete and continuous time phenomena, and stochastic models that track evolving probability distributions of variables rather than deterministic values. The core of the AALM is a system of differential equations. Solutions of the equations are visualized as trajectories evolving in a multidimensional state space. Numerical integration algorithms are used to compute approximate trajectories step by step. An inherent feature of this process is that errors can accumulate so that the accuracy of the computed trajectory diminishes in time, typically at an exponential rate. The development of numerical integration algorithms and their error analysis is a long standing, mature research area in applied mathematics. A weak point of the AALM is that it uses poor, ad-hoc methods for numerical integration (section 2.3.1 of the TSD). This deficiency has been noted repeatedly in reviews, but fixing it requires a thorough reworking of the model. The acslX version of the model was one attempt to do that, but the language is proprietary and obscure.

The numerical integration issue is a fundamental weakness of the AALM. Abstractly, differential equation models have the form $x'=f(x)+i(t)$ where x is a vector encoding the state variables (e.g., amounts of lead in each body compartment), f is the "right-hand side" which expresses the rates of change in the state variables and i(t) is a vector of inputs (lead from the environment). Approximate trajectories are computed in discrete time steps. Numerical integration algorithms require the user to code the right-hand side which evaluates f(x) and specify initial values of x at the start time and the input function i(t). The AALM is not organized in this way. The model

incorporates an explicit low order formula (Eq. 2.3-2 in the TSD) for its time stepping that is intermingled with the formulas that evaluate the right-hand side. This yields unacceptable run times for simulations having sufficient accuracy, prompting further ad-hoc modifications to the software. Furthermore, the current version of the AALM buries the integration algorithm beneath an Excel spreadsheet that calls Fortran libraries with a run-time library that is specific to the Visual Basic Language used by Excel. The review panel attempted to extract f(x) for use in a Matlab reimplementation with standard numerical integration algorithms, but they encountered difficulties in making this work. Almost all modern computational science software includes fully implemented and documented examples that can be used to test the software on different computers. The lack of such examples and the arcane computing environment required by the AALM are serious deficiencies.

General modeling principles recommend using models of minimal complexity that capture the essential aspects of the system being studied. Ideally, a lead model should incorporate scientific understanding of the key processes in its biokinetics. The Leggett model begins with the assumption that the right-hand side of the model is linear. This limits the number of parameters required to specify the model and yields solutions given by sums of exponential functions. Engineering systems are often linear. When data give poor fits to the engineering models, a common strategy is to add more state variables that yield more terms in exponential sum with additional time constants. For the AALM, this results in splitting single compartments into multiple compartments solely for the purposes of fitting the data. However, physiological processes are seldom linear, leaving the Leggett model with weak scientific foundations.

The models created by O'Flaherty are much better in this regard, but the AALM still follows the Leggett approach at its core. When time series of lead concentrations are not fit by single exponentials, new compartments are created to yield sums of exponentials with more terms and more time constants. No pretense is made to establish biological principles for the extended models. Thus, the Leggett model can be viewed as "data driven" with a tenuous relationship between model variables and identified physical quantities.

The O'Flaherty model could provide a starting point that focuses upon the interchange of lead between blood, plasma, trabecular bone and cortical bone within the body. Systematic analysis of models that are not too large or complicated can quantify the sensitivity of model output to changes in model inputs and parameters. Such analysis may also identify aspects of the system that a small model is unable to reproduce and point toward improvements. Even with small models, the number of quantities to be measured or estimated is large enough that ad hoc "tuning" of model simulations is unlikely to find optimal fits of model and data. Systematic sensitivity analysis is usually a more effective strategy. This is likely the case for modeling lead concentrations in the body

The deficiencies of the AALM strongly suggest that the EPA stands to benefit far more from creating a new model to simulate the biokinetics of lead than by investing more resources into the AALM. The Air Force Research Laboratory has pursued further development of the O'Flaherty model as part of its efforts to establish limits for occupational exposure to lead. See the National Academy of Sciences report "Review of the Department of Defense Biokinetic

Modeling Approach in Support of Establishing an Airborne Lead Exposure Limit (2020).” The Agency could also support an interdisciplinary team to create and implement a new model while simultaneously conducting empirical studies to calibrate and test their model. Joint programs of the NSF and NIH to support collaborations that span the interface between mathematics and biology have demonstrated the effectiveness of this strategy in quantitative modeling of biological systems.

APPENDIX C: TABLE OF BOARD RECOMMENDATIONS

Topics of Recommendations/Charge Questions	Q1 Documentation	Q2 Model support	Q3a Intake rates	Q3b Absorption	Q3c Distribution & Elimination	Q3 Model assumptions	Q4a Predictive accuracy	Q4b Code verified	Q4c Other data	Q5 AALM Fortran Guide	Q6 Improve predictions	Q7 User friendly	Q8 CREM Guidance	Q9 Model applications & outputs
Model users and applications														
Clarify audience	Tier 1													
Create "Application" Manual	Tier 2									Tier 2				
Specify appropriate model applications	Tier 1			Tier 1									Tier 1	
Training materials										Tier 2				
Variable step size algorhythm											Tier 2			
Modernized interface										Tier 3				
Editorial														
Editorial and Clarifying Changes in Documentation	Tier 1		Tier 2											
Consistent nomenclature					Tier 1							Tier 1		
Distinguish "prediction" and "output"							Tier 1							
Fix Model Structure Figure	Tier 1													
Edit Users Guide for AALM.FOR										Tier 1				
Hyperlinks in documentation	Tier 3													
Inhalation														
Ventilation rates and activity			Tier 1											
Particle size				Tier 2							Tier 2			

Topics of Recommendations/Charge Questions	Q1 Documentation	Q2 Model support	Q3a Intake rates	Q3b Absorption	Q3c Distribution & Elimination	Q3 Model assumptions	Q4a Predictive accuracy	Q4b Code verified	Q4c Other data	Q5 AALM Fortran Guide	Q6 Improve predictions	Q7 User friendly	Q8 CREM Guidance	Q9 Model applications & outputs
Particles to GI (fraction deposited)			Tier 1											
Inhalation parameters for disease states			Tier 3											
Oral														
GI absorption - various aspects				Tier 2&3										
RBA		Tier 1		Tier 1								Tier 1		
Soil & dust intake rates and ages			Tier 1&2											
Water intake rates, activity, and ages			Tier 2											
Food intake rates and age		Tier 3	Tier 2									Tier 2		
Clarify hand to mouth modeling				Tier 3										
Dermal														
Dermal				Tier 1										
Distribution/Elimination														
Brain lead description		Tier 1												
Bone kinetics and post-exposure blood kinetics		Tier 2							Tier 1		Tier 1			
Inhalation & nasal olfactory uptake		Tier 3												
Fecal elimination & mass balance				Tier 1							Tier 1			
Cortical-trabecular bone levels							Tier 2a*		Tier 1					
RBC parameters					Tier 2		Tier 2a							
Kidney & liver distribution					Tier 3		Tier 2a							
Growth curves	Tier 1													

Topics of Recommendations/Charge Questions	Q1 Documentation	Q2 Model support	Q3a Intake rates	Q3b Absorption	Q3c Distribution & Elimination	Q3 Model assumptions	Q4a Predictive accuracy	Q4b Code verified	Q4c Other data	Q5 AALM Fortran Guide	Q6 Improve predictions	Q7 User friendly	Q8 CREM Guidance	Q9 Model applications & output
BW, BMI					Tier 2									
Sweat elimination					Tier 3									
Variability in urinary clearances							Tier 2a							
Peak blood lead modeling							Tier 2a							
Initial values for blood and tissues											Tier 3			
Exposures														
Additional exposure examples												Tier 1		
Constant media concentration & background or baseline exposures			Tier 1&3- dust,soil Tier 2 - water									Tier 2&3		Tier 2
Soil and dust			Tier 2	Tier 2										
Lead in paint modeling														Tier 3
Occupantional Exposure			Tier 2				Tier 2a							
Chelation											Tier 3			
Sex, life stage, & health														
Reassess data for females							Tier 2							
Infants - reevaluate Figs 3-14&15							Tier 3							
Breast feeding (Lactation)			Tier 2									Tier 2		
Pregnancy											Tier 3			
Menopause & bone kinetics					Tier 2									
Inhalation and respiratory diseases			Tier 3											

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Model Evaluation														
Model reproducibility uncertainty					Tier 1									
Model sensitivity						Tier 1								
Model calibration - Table 4-16							Tier 2							
Evaluate model against data sets provided									Tier 1					
CREM & Leggett study quality criteria													Tier 2	
State operating systems useable for AALM								Tier 1						
Model outputs & risk characterization														
Clarify outputs for "average" individual					Tier 1									
Output Metrics												Tier 2		Tier 1
Compare multiple model runs														Tier 2
Risk characterization - population variability & uncertainty	Tier 1											Tier 2	Tier 2	Tier 2
Compare to IEUBK or Adult Lead Model												Tier 2		
Coexposures or mixtures												Tier 3		

*Tier 2a: A single recommendation covers these topics