

April XX, 2020

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EPA-SAB-xx-xxx

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 Scientific Advisory Board (SAB). 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 includes several recommendations within this report, we would like to highlight the following. The Panel finds that the AALM 2.0 is a major step forward from both technical and public policy perspectives for conducting 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 Panel members in the potential applications of this model for public health protection.

The Panel recommends that the Agency’s highest priority is to 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 Panel has described many of 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 Panel recommends that the Agency implement these Tier 1 actions as quickly as feasible, in order provide an updated version available to the public to replace the AALM 2.0 reviewed by the Panel.

1  
2 The Panel recommends that the Agency develop and implement a plan to expand the utility of the  
3 AALM 2.0 for use in risk assessments and public health assessments. These recommendations are  
4 largely described in the Panel’s Tier 2 recommendations and in some Tier 3 recommendations. This  
5 effort would include: limited modifications of the existing model or its parameters (e.g., to provide  
6 occupational inhalation scenarios, for input of typical lead dust loading measurements, or to include  
7 nursing infants); provide user-friendly outputs useful for risk assessment and public health  
8 evaluations and additional documentation to address the needs of a broad range of users. The Panel  
9 also notes that the U.S. EPA should carefully consider how and why results are similar or different  
10 for scenarios that can be simulated in ALM or IEUBK as well as AALM 2.0; this will be important  
11 for considering risk assessment applications of these models. Ideally, differences in results among  
12 these models would arise from an improved scientific basis for the modeling (e.g., updated  
13 parameter values or improved model descriptions of exposure or pharmacokinetic processes) rather  
14 than differences in modeling approaches. In the latter case, clear justification for changing the  
15 modeling approach would be essential for creating understanding and credibility with stakeholders.  
16  
17 Finally, EPA should have an ongoing commitment to continued maintenance of the AALM,  
18 including its parameter values and model documentation. EPA should provide support and training  
19 to the broad range of likely users of the model. This support should include continued updates to the  
20 model and to its recommended parameters as new data become available. It should also include  
21 extending the model to address aspects of exposure or pharmacokinetic biological processes that  
22 require more effort and longer time frames than recommendations noted above (included in the  
23 report’s discussion of Tier 3 recommendations).  
24  
25 As the EPA finalizes its External Review Draft AALM Draft 2.0, the SAB encourages the Agency to  
26 address the panel's concerns raised in the enclosed report and consider their advice and  
27 recommendations. The SAB appreciates this opportunity to review EPA’s AALM 2.0 and looks  
28 forward to the EPA’s response to these recommendations.

Sincerely,

Dr. Michael Honeycutt  
Chair  
EPA Science Advisory Board

Dr. Hugh A. Barton  
Chair  
AALM Review Panel

29  
30  
31 Enclosure:  
32

**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>.

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## ACRONYMS AND ABBREVIATIONS

AALM	All-Ages Lead Model
AALM.FOR	Fortran Code for AALM
CDC	Center for Disease Control
NHANES	National Health and Nutrition Examination Survey
COPD	Chronic obstructive pulmonary disease
CREM	Center for Research for Environmental Models
EFH	Exposure Factors Handbook (US EPA)
ICRP	International Commission on Radiological Protection
IEUBK	Integrated Exposure Uptake Biokinetic (lead exposure model; US EPA)
MATLAB	Matrix Laboratory – proprietary programming language developed by Mathworks
NTIS	National Technical Information Service
OEHHA	Office of Environmental Health Hazard Assessment
RBA	relative bioavailability
TRW	Technical Review Workgroup
TSD	Technical Support Document for AALM
SAB	Science Advisory Board
U.S. EPA	U.S. Environmental Protection Agency
WHO/IPCS	World Health Organization / International Programme on Chemical Safety

5

## 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 exposure 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 relatively steady-chronic exposure conditions.

The AALM documentation reviewed by this Panel 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 *Users 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 – Key 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 are encouraged for EPA to adopt in order to strengthen the scientific concepts, issues and/or narrative within the model and documentation being reviewed by the Committee, but other factors (e.g., Agency need) 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

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

3

4 All dissenting opinions (if any, or additional comments provided at the concurrence step) are  
5 presented within Appendix C. All materials and comments related to this report are available at:  
6 [https://yosemite.epa.gov/sab/sabproduct.nsf//LookupWebProjectsCurrentBOARD/9B019D11EF  
7 07A3FA8525831A006275A4?OpenDocument](https://yosemite.epa.gov/sab/sabproduct.nsf//LookupWebProjectsCurrentBOARD/9B019D11EF07A3FA8525831A006275A4?OpenDocument)

8

9

## 2. RESPONSES TO CHARGE QUESTIONS

### 2.1. Charge Question One: Features of the All Ages Lead Model (AALM).

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

The Panel 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 ALM 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 Panel 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 Panel had several recommendations that would improve the guidance document.

The audience for this guidance and model itself 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 and its limitations. Even if this is intended as a broad-use model, EPA should provide examples of contexts and applications in which use of the AALM in its current form can be used.

The Panel agreed that the details provided in the technical guidance 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.

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 Panel had questions about the growth curves used in the AALM: what they are, how they are used, how they are implemented, and whether growth is discussed in terms that 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.

1 This version of the AALM model may be described as a hybrid of O’Flaherty and Leggett  
2 models, which raises challenges for understanding the model structure, parameter value choices,  
3 and impacts on predictions. While the TSD has extensive discussion of the different models  
4 EPA developed leading to the AALM.FOR version under review, it is a challenge to fully  
5 evaluate the many aspects involved. Many of the O’Flaherty equations and parameter values  
6 have replaced Leggett’s values, and in some cases altered the structure of the model (e.g.  
7 removing one of the pathways of lead elimination via urine). Hence, the AALM is not really a  
8 newer version of the Leggett (or ICRP) model. This change from version 5 of the ICRP model  
9 to a hybrid of model is significant. The evolution from the original ICRP model (ICRP 1993 pub  
10 67) to the structurally altered age-specific kinetic model of lead metabolism in humans (Leggett  
11 1993) has been difficult to convey and has remained unclear for some. The switch from a  
12 method explained in Leggett’s paper of interpolating lead mass transfer values between specific  
13 ages to a method for establishing tissue growth and volumes based mostly on scaling and other  
14 equations from the O’Flaherty model needs to be clear. Many of O’Flaherty’s equations  
15 appeared in the TSD, being the growth equations used in AALM. For the childhood and  
16 adolescent part of the model, Leggett has a significant discussion about the uncertainty of his  
17 lead mass transfer values in childhood and adolescence due to limited data available to calibrate  
18 such values. In addition, given this switch from mass transfer to tissue concentrations of lead  
19 based on age and body weight scaling, it would be important to revisit O’Flaherty’s check on  
20 age- and body weight-related concentrations of lead with data as well as Leggett’s check on age-  
21 related distributions of lead mass compared to estimates published in Leggett (1993) of lead  
22 mass in tissue groups from autopsy data.

23  
24 The current strengths and limitations of the AALM should be clearly discussed. For example,  
25 there is no pregnancy model, lead exposures for neonates through breastfeeding are not  
26 accounted for (see Charge Question 3a response), and the recommended default inhalation  
27 scenario may be appropriate for environmental exposures but not occupational exposures (See  
28 Charge Question 3b text). Specifically, occupational exposure may involve larger size particles  
29 with different deposition fractions in the respiratory tract (i.e., associated with more mucociliary  
30 clearance), and simulating occupational exposures would likely require higher values for  
31 ventilation rates than for average adults. These and other examples of exposure scenarios for  
32 which the model is not parameterized for or cannot account for should be clearly stated. In  
33 addition, Section 2.3.3 of the guidance states that that the model simulates lead absorption from  
34 inhalation, ingestion, and dermal contact with dust. No dermal contact with soil or dust is  
35 discussed in the document; thus, the fact that dermal exposure is not accounted for should be  
36 stated as a limitation. Similarly, the current strengths of the AALM and examples of exposure  
37 scenarios that it can simulate should be clearly outlined/stated.

38  
39 The figure of model structure (Figure 2-1) should be modified to be more accurate. All four  
40 compartments of the GI tract and lung need to be explicitly shown. The model includes different  
41 rates of transfer in and out of tissue compartments. In the figure for example, arrows pointing in  
42 both directions should be replaced by separate arrows representing lead entering and leaving  
43 compartments (e.g. the brain, liver and bone compartments). The model structure has been  
44 altered by removing the transfer of lead from diffusible plasma to bladder contents (i.e. the  
45 transfer rate is now zero).

46

1 The technical guidance would benefit from additional examples of differences in uptake and  
2 predicted blood lead distributions for different model versions. Specifically comparing the  
3 current proposed AALM with IEUBK and ALM model applications to the same default  
4 scenarios, inclusive of baseline, water, diet, soil and dust ingestion, and inhalation pathways.  
5 This would largely be captured in additional appendix materials, but summaries of the key  
6 similarities and differences in model performance could be carried forward in existing chapters  
7 of the main text.  
8

9 While the AALM currently remains a research tool that predicts blood lead concentrations over  
10 specific ages, it stops short of presenting a fully developed risk characterization module. Each  
11 simulation generates a single time series of predicted mean blood lead concentrations over time,  
12 summarized in both an Excel table and graphic format. By contrast, the IEUBK and ALM  
13 models generate probability distributions of blood lead concentrations, by applying a lognormal  
14 distribution model to the predicted mean concentrations. This utility does not currently exist in  
15 the AALM, though users could post-process the results on their own. The guidance document is  
16 silent on this point and should at least discuss this omission along with any anticipated next  
17 steps.  
18

## 19 **Charge Question 1 Recommendations**

### 20 **Tier 1**

- 21 • The audience for the model, documentation, and guidance must be clearly stated by EPA and  
22 should reflect the breadth of stakeholders who would be interested in using this model or  
23 interpreting its results.
- 24 • EPA should provide examples of contexts and applications for which the AALM in its  
25 current form can be used with any needed cautions and clearly state situations for which it is  
26 not currently appropriate due to limited tests of the model with data, missing components in  
27 the model structure, or current parameter values.
- 28 • Figure 2-1 needs to be modified in order to be more accurate.
- 29 • Discuss the omission of a fully developed risk characterization module, along with any  
30 anticipated steps to achieve one (e.g., recommendations for Charge Questions 7-9).
- 31 • Modify the existing documentation to address the recommendations, questions, edits, and  
32 suggestions are provided throughout this report to improve the clarity of the considerable  
33 documentation that exists for AALM.  
34

### 35 **Tier 2**

- 36 • A guidance document that is not as technical intended for the broader range of stakeholders  
37 would be a valuable addition to the current guidance manual.
- 38 • A clear discussion of the O’Flaherty growth curves and parameters used should be provided  
39 in the document. They should be described in a context and terms that medical practitioners  
40 and public health risk assessors can comprehend. Revisit O’Flaherty’s check on age- and  
41 body weight-related concentrations of lead with data as well as Leggett’s check on age-  
42 related distributions of lead mass compared to estimates published in Leggett (1993) of lead  
43 mass in tissue groups from autopsy data to build confidence in AALM.  
44  
45

1 **Tier 3**

- 2 • Providing hyperlinks in the text to the figures, tables, and appendices would make it easier to  
3 move around in and use the document.  
4  
5

6 **2.2. Charge Question Two: are the model features supported by available research**  
7 **findings in published peer-reviewed literature or by reasonable extrapolations from**  
8 **such findings?**

9 For the most part, the model features are supported by available research findings in published  
10 peer-reviewed literature or by reasonable extrapolation from such data. Some additional  
11 considerations are presented here as well as in responses to the other charge questions  
12

13 **Relative bioavailability**

14 With respect to relative bioavailability (RBA) it would be helpful for the developers to explain  
15 why for most media, e.g. Pb in soil, Pb in dust, Pb in water, only a single RBA applies to all  
16 intake relative to that medium. For example, in Section 2.2.3.3. (p. 11, pdf p. 22) the narrative  
17 states, “The model accepts a single inputted value for RBA which represents soil from all  
18 sources, in all exposure settings.” The same provision for a single RBA applies to all Pb in  
19 indoor dust (Section 2.2.3.2). This seems counter to the model’s flexibility in allowing for  
20 multiple values of Pb intake in soil or dust at different times of the day (or week). It seems likely  
21 that compared to lead ingested in an occupational environment, lead in solid and dust ingested in  
22 a residential setting may have different solubility, particle size, and chemical composition, and  
23 by extension different RBA.  
24

25 In addition, notwithstanding that human data pertaining to different bioavailability of soluble Pb  
26 versus suspended fine particulate is sparse, it is conceivable that a receptor could be  
27 simultaneously exposed (during the course of a day) to a given mass of soluble and particulate  
28 lead. How would the model account for the possibility that these two different types of Pb in the  
29 same sample might have quite different RBAs? This scenario is plausible in domestic tap water,  
30 where intermittent releases of particulate Pb may greatly exceed baseline soluble lead. Further  
31 discussion of these kinds of issues is found in Charge Question 3b.  
32

33 In the case of food, as opposed to soil and dust and water, the way to account for age-specific  
34 changes in overall daily food intake across the lifespan was not clear. (The narrative states: “The  
35 model *does not* calculate food Pb intakes from inputted data on Pb concentrations in food and  
36 food consumption rates”). Is it up to the user to estimate and incorporate “pulses” of age-related  
37 changes in food intake (e.g. after consulting the EPA Exposure Factors Handbook or other  
38 sources)? If so, it would be helpful to include in an appendix to the model documentation  
39 suggested values for such age specific intake rates or clearly direct users to other documentation  
40 (e.g., Exposure Factors Handbook).  
41

42 **Post-exposure lead kinetics**

43 In AALM, when long term exogenous lead exposure is terminated, the blood Pb concentration  
44 declines rapidly. For example, see Figure 3-2 B (p. 76, pdf page 87). This output appears to fit

1 well with the empiric data shown in Figure 3-6 for a lead worker whose exposure was interrupted  
2 during a strike. However, there is concern, based on other observations, that the decline in blood  
3 lead is not as rapid as predicted by the model in other cases.

4  
5 Moel *et al.* (1986) described the decline in blood lead concentration in severely lead intoxicated  
6 children (blood lead 100 to 200  $\mu\text{g}/\text{dL}$ ) followed for nine to 17 years after the end of chelation  
7 treatment, when the rate of decline in blood lead was strongly influenced by slow release of lead  
8 from skeletal stores. Manton *et al.* (2000) published data that demonstrated blood lead half-  
9 times between 20 to 38 months in young children exposed to lead dust from residential home  
10 remodeling. In the case of adults with occupational lead exposure, Hodgkins *et al.* (1991)  
11 presented data that demonstrated an impact of past air lead levels on contemporaneous blood  
12 lead concentration more than 5 years after large reductions in air lead exposure had been  
13 achieved. Schutz *et al.* (1987) presented data on former lead workers indicating that the decline  
14 in blood lead following cessation of exposure followed a two-compartment model – a fast  
15 compartment with a half-time of 1 to 2 months, and a slow compartment with a median half-time  
16 of 5 years. Although there was inter-individual variability, for some of the subjects presented by  
17 Schutz *et al.* (1987) the rate of decline in blood lead over the first nine months after cessation of  
18 exposure appeared to be less than what would have apparently been predicted by AALM.FOR  
19 based on Figure 3-6. Hryhorczuk *et al.* (1985) observed that for workers with chronic lead  
20 intoxication and normal renal function, the median blood lead elimination half-time was 619  
21 days over a period of years.

22  
23 Some of the committee felt that the rapid decline might arise because the AALM.FOR biokinetic  
24 module adapted the Leggett model paradigm in which Pb that enters “nonexchangeable” skeletal  
25 compartments only returns to the plasma compartment during bone remodeling. A new  
26 publication shows this structure can capture slower declines in blood Pb but needs modified  
27 parameter values and continued background exposure (Vork and Carlisle, 2020). It can be noted  
28 that a biokinetic feature of the O’Flaherty model with respect to bone lead compartments allows  
29 for diffusion of lead in all bone compartments to plasma at an age-dependent rate. This might  
30 predict a slower decline in blood lead concentration following cessation of extended periods of  
31 elevated lead exposure. It also should be noted that the O’Flaherty bone model structure and  
32 parameter values evolved over time as reflected in publications including those cited in the TSD  
33 from 1993 to 2000.

34  
35 It would be helpful to obtain additional datasets that document the decline in blood lead  
36 concentration following abrupt cessation of long-term elevated lead exposure, so that the  
37 accuracy of the AALM.FOR model in these settings can be further examined. Some references  
38 are provided above as well as those evaluated in Vork and Carlisle (2020).

#### 39 40 **Brain and olfactory uptake modeling**

41 The model has a simple description of a single brain compartment. This is understandable in that  
42 brain Pb concentrations are simply not available from which more extensive modeling can be  
43 undertaken. Consequently, they are not available for use in risk assessment scenarios. However,  
44 it is critical to remember that brain Pb is the basis of the neurodevelopmental toxicity in children  
45 and could contribute to the increasing effects of Pb described in relation to neurodegenerative  
46 diseases. For that reason, statements about brain Pb and appropriate references should be

1 included or clarified in text related to brain Pb (e.g., Section 2.3.8). For example, p. 31 (pdf p.  
2 42) makes the statement of ‘non-uniform distribution of Pb in brain tissues. It is not clear where  
3 this assertion comes from. If it was based on studies done in rodents, it is critical to recognize  
4 that studies citing greater accumulation of Pb in hippocampus suffer from the fact that  
5 concentrations in different regions were based on regional dry weights, which artifactually  
6 increases levels in some regions, and when based on wet weights, as appropriate, there is a  
7 uniformity of concentrations across regions.

8  
9 Furthermore, the text then goes on to cite numerous parameters of Pb in relation to e.g., transfer  
10 rates and the percent of outflow from plasma into brain with no references provided for any of  
11 these statements. Outflow from the brain to plasma is of potential significance at least based on  
12 information for other essential metals, e.g., iron that appear to remain in brain for at least 9  
13 months in rats, which when extrapolated to humans is on the order of decades. While some  
14 studies have cited a half-life of 2 years of Pb in brain (e.g., Garza *et al.*, 2006), citations in  
15 support of that statement need to be provided. One source may be the Leggett (1993) analysis  
16 (p. 606), but this needs to be stated and it would be valuable to confirm that modeling with  
17 AALM is consistent with the data Leggett referred to (e.g., Table 3, p. 610).

18  
19 One other consideration relates to intake of air Pb. The document currently includes 4 different  
20 respiratory compartments from air Pb to plasma. What is not considered in the model, and again  
21 likely cannot be as no real data is available, is the extent to which nasal olfactory uptake of Pb in  
22 ultrafine particles may contribute to the brain Pb compartment. As these particles are taken up  
23 via olfactory (or trigeminal or vagal) nerves, they directly enter into the brain and bypass the  
24 blood brain barrier. While inhalation of Pb and regional brain Pb analyses have not been  
25 undertaken, assessments in goat tissue showed significantly higher levels in olfactory epithelium  
26 and olfactory bulb, consistent with this route (Steuerwald *et al.*, 2014). Consequently, levels in  
27 brain of such metals are not reflected in peripheral (e.g., blood) measures of the metal. While  
28 data that could be used to model this is clearly not available, it is probably useful to include this  
29 possibility in the document, given the potential for incorporation of such information should it  
30 become available and to fully characterize limitations of the model.

## 31 32 **Charge Question 2 Recommendations**

### 33 34 **Tier 1**

- 35 • Statements about brain Pb and appropriate references should be included or clarified in text  
36 related to brain Pb, especially if the inference is brain lead amounts in humans.

### 37 38 39 **Tier 2**

- 40 • Explain why with respect to relative bioavailability (RBA) for most media, (e.g. Pb in soil,  
41 Pb in dust, Pb in water) only a single RBA applies to all intake relative to that medium.  
42 Obtain additional datasets that document the decline in blood lead concentration following  
43 abrupt cessation of long-term elevated lead exposure. Evaluate AALM.FOR model  
44 predictions for blood lead decline after extended intervals of moderate to high lead exposure  
45 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 creating a model approach, method and data.
- 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.

## **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 Committee finds that the Technical Support Document (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 following aspects of the summaries in the TSD are well done:

#### 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  $\mu\text{g Pb/day}$ . 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  $\text{m}^3/\text{d}$  for air,  $\text{g/day}$  for dust and soil, and  $\text{mL/day}$  for water, and the model estimates the average daily lead intake rate ( $\mu\text{g}$

1 Pb/day) for a specific exposure pathway and age range by multiplying the media intake rate by  
2 the media concentration. Exceptions to this approach are noted:

- 3 • Food intake is still expressed as a total mass of lead intake per day ( $\mu\text{g Pb/day}$ ), on average  
4 over an age range, rather than a combination of specific food item intake rates and corresponding  
5 lead concentrations.
- 6 • “Other” media is a placeholder for users to include additional exposure media, and the  
7 parameter is defined in units of  $\mu\text{g/day}$ ; thus, users are required to calculate age-specific intakes  
8 beforehand, separate from the AALM model. This option is similar to EPA’s current regulatory  
9 model used for lead risk assessment during childhood (i.e., IEUBK).

10  
11 The presentation in the TSD is easy to follow because it is packaged as a series of “submodels”  
12 for exposure, with equations and parameter values listed in tables.

13  
14 The TSD clearly states that the inputs are intended to represent central tendency estimates, rather  
15 than high-end (reasonable maximum exposure) point estimates or probability distributions. This  
16 greatly reduces the complexity of the model structure and selection of input values, compared  
17 with, for example, a fully probabilistic modeling framework. However, omitting the plausible  
18 ranges and/or distributions in the TSD may constrain options for conducting a robust sensitivity  
19 analysis, since the current model framework requires somewhat ad-hoc changes to combinations  
20 of model inputs.

## 21 Intake Rates

22  
23 The Committee has specific questions and/or recommendations for EPA to consider. Summaries  
24 are presented below, organized by environmental exposure media in the sequence presented in  
25 the TSD (i.e., air, indoor dust, [outdoor] soil, water, food, and other).

### 26 *Air Intake Rate*

27  
28 The Committee noted that EPA uses the term ventilation rate ( $\text{m}^3/\text{d}$ ) as attributed to ICRP  
29 (1994), whereas the term respiration rate (breaths per minute) is preferred in the public health  
30 and clinical/medical fields. The term “ventilation volume rate” may be an improvement over  
31 ventilation rate. Clarifying these terms would be beneficial for a broad model user audience.

32  
33 The TSD (p. 10, lines 2-3, pdf p21) states that ventilation rates in the model can reflect activity  
34 levels and that sources that support the recommended parameter values also observe associations  
35 between water intake and energy expenditure. However, it is unclear how activity levels have  
36 been explicitly considered in the recommended mean parameter values and, therefore, how to  
37 incorporate/characterize these in simulations of populations that exhibit varying activity levels.  
38 The model does not include activity patterns as a user-specified input. Furthermore, it is unclear  
39 if different activity levels may support different assumptions regarding fractional deposition in  
40 and translocation from the respiratory tract of various particle size fractions (e.g., course, fine,  
41 ultra-fine).

42  
43 The ventilation rates throughout the TSD appear to be obtained for healthy individuals. These do  
44 not necessarily apply for individuals with asthma, COPD, or other disease conditions.  
45 Suggesting sources of information or recommended values would further broaden the utility of  
46 the model. Consideration of whether there would be changes in other parameters, such as

1 deposition fractions in regions of the respiratory tract, would be essential for appropriately  
 2 modeling these disease states.

3  
 4 For adults with occupational contact with lead, inhalation may be the most significant route of  
 5 exposure. Greater flexibility is needed with AALM.FOR in order to represent inhalation rate  
 6 scenarios that are more applicable to a range of worker exposure scenarios. For example, the  
 7 user should be afforded the opportunity to adjust the default respiratory rates for the model  
 8 shown in Appendix C (pp. 282-284, pdf pp. 293-295). The model’s default value for adults, 19.9  
 9 m<sup>3</sup>, is apparently intended to represent long-term average daily exposure. Short-term adult  
 10 respiration rates associated with moderate or heavy exertion that may be more applicable to  
 11 occupational lead exposure have been reviewed in Chapter 6 of EPA Exposure Factors  
 12 Handbook (EFH) (U.S. EPA, 2011). The following are specific examples that have been  
 13 proposed by EPA and California Office of Environmental Health Hazard Assessment (OEHHA):  
 14

- 15 • EFH (Table 6-50) suggests that activities requiring physical labor may be associated with  
 16 a median respiration rate of approximately 1.5 m<sup>3</sup> per hour, corresponding to approximately 12  
 17 m<sup>3</sup> for an 8-hour shift.
- 18 • California OEHHA’s Technical Support Document for Exposure Assessment and  
 19 Stochastic Analysis (CalEPA 2012, Chapter 3, Table 3.3b) recommends 12.94 m<sup>3</sup> for adults  
 20 engaged in moderate intensity activities for 8 hours.
- 21 • OEHHA, in the development of the Leggett Plus model for assessment occupational lead  
 22 exposure and dose (CalEPA 2013) used 14.4 m<sup>3</sup> (30 L/min) for 8 hours for moderate workloads.  
 23

24 In addition, certain studies support the use of other values based on sex and body weight, in  
 25 addition to age. The Committee recommends expanding the options for a user to select not only  
 26 the current default daily values, but also values representative of short-term occupational lead  
 27 exposure. The “occupational setting” could assume a value in the range of 12 to 14 m<sup>3</sup> for  
 28 moderate exertion during an 8-hour shift, as an initial recommended range.  
 29

30 AALM.FOR apportions the inhaled lead into four compartments of the respiratory tract, 1)  
 31 extrathoracic (incorrectly termed intrathoracic in the document); 2) bronchiolar; 3) bronchiole;  
 32 and 4) alveolar, by multiplying the average mass of lead inhaled per day (µg Pb/day) by a set of  
 33 deposition fractions (R) (see TSD p. 23, lines 11-20, pdf p. 34). Collectively, the deposition  
 34 fractions sum to 40%, meaning each day, 40% of the total inhaled Pb is initially deposited in the  
 35 respiratory tract, and the balance is exhaled. The estimates of R are summarized in a table  
 36 (copied below from p. 23, pdf p. 34) and attributed to data from five studies conducted from  
 37 1969 through 1980 in which human subjects inhaled submicron Pb-bearing particles:  
 38

Compartment	1	2	3	4
Deposition Fraction (R)	0.08	0.14	0.14	0.04
Rate Coefficient (BR, day <sup>-1</sup> )	16.6	5.4	1.66	0.347
t <sub>1/2</sub> (hour)	1	3	10	40

39  
 40 **Table 1 Respiratory Tract Compartments and Parameter Values** (see TSD p. 23, pdf p. 34)  
 41

1 The table lists the four compartments, but if the numbering sequence (1 through 4) corresponds  
2 with the order of the regions described above (as presented in the TSD), then the 4% value (i.e.,  
3 0.04), assigned to region number 4 in the table, would correspond to the alveolar region, which is  
4 not the region associated with translocation to the GI tract. Rather, the balance (i.e., 36%)  
5 initially deposited in the thoracic and bronchiolar regions would be more likely to translocate to  
6 the GI tract suggesting the parameter CILIAR = 0.36 rather than 0.40.

7  
8 In a more recent study by Lach et (2014), deposition was estimated from lead aerosol particle  
9 size distributions measured in firing ranges. Results showed that 49% of total inhaled Pb would  
10 be deposited in the respiratory tract, of which 37% would be translocated to the GI tract. This  
11 finding is similar to the tabular summary above.

12  
13 It's possible that particle size distribution at the firing ranges is different from that of the  
14 inhalation studies cited in the TSD and attributed to the original Leggett (1993) model. While the  
15 TSD does already include a caveat regarding the sensitivity of the assumption of deposition  
16 fractions to the particle size distribution, the Committee recommends that EPA reconsider the  
17 parameter values and their sources in light of the cited literature noted above.

#### 18 19 *Soil and Dust Intake Rate*

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

25  
26 For parameter estimates for IRsd applied to childhood, the TSD (Appendix C, pp. 280-281, pdf  
27 pp. 291-92) describes two sources of information: 1) USEPA's Exposure Factors Handbook  
28 (EFH), recently updated in 2017 for this exposure variable; and 2) USEPA TRW's estimates as  
29 intended for use in the IEUBK model. In addition, literature sources are cited, but not  
30 summarized or discussed in any manner.

31  
32 The AALM model can be run in one of two modes with respect to transitioning between  
33 consecutive age groups: 1) a step function, or 2) interpolated values between age groups. The  
34 graphics in Exhibit 1 below show the proposed AALM inputs side-by-side with the two key  
35 sources for both run options. During childhood, after approximately age 2 years, the proposed  
36 AALM inputs are systematically higher than the values cited, and no explanation is given to  
37 explain this discrepancy. [Tier 1] The Committee recommends that EPA reconsider the basis for  
38 the recommended parameter values for ages 2 to 15 years to either better align with the materials  
39 cited or explain the rationale for the deviation.

40

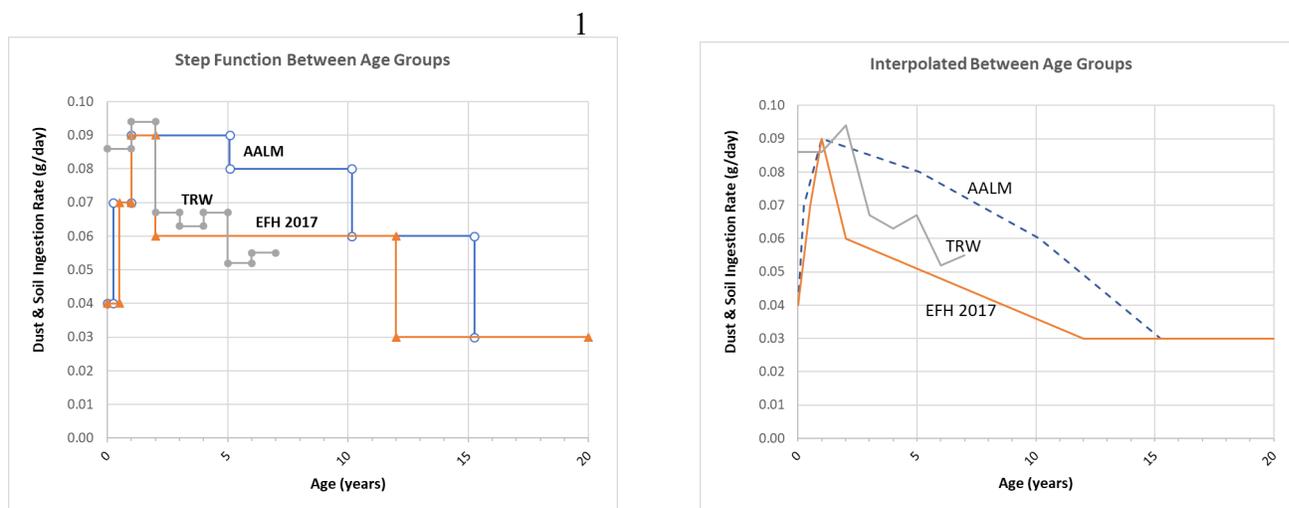


Figure 1 Age-specific parameter values for average soil and dust ingestion rates (g/day) during ages 0 to 20 years, comparing AALM with source information attributed to EPA. Graphic on left corresponds with the step function run option in A

2  
3 Page 12, line 10, states, “Values for IRsoil are interpolated between inputted ages.” Does this  
4 mean that a step-function option is never implemented for this exposure factor? If this is not true,  
5 and a step function is in fact one run option, the Committee recommends that EPA add this  
6 clarification to this section of the TSD.

#### 7 8 *Water Intake Rate*

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

12  
13 a) Describe the populations represented by these study results. Cross referencing EPA’s EFH  
14 (2011), the TSD currently states (p. 281, lines 4-5, pdf p. 292), “Water ingestion rate can be  
15 expected to vary with age, activity level and environmental factors (e.g. temperature, humidity).”  
16 EPA should clarify how (or if) specific activities are reflected in the proposed inputs.

17  
18 b) Presumably the final table values (p. 282, pdf p. 293) reflect a consolidation of the two prior  
19 tables; further explanation is needed. Also, see Editorial Comments (below) for suggestions on  
20 adding an additional column to show the conversion from days to years, which will facilitate  
21 cross-walking between the various tables of source information.

22  
23 In addition, the Committee recommends that EPA include a baseline concentration of lead in  
24 drinking water (e.g., 0.9 µg/L) in the TSD.

25  
26 Like the IRsd discussed above, it is unclear in the TSD how the transition between age-specific  
27 parameters is addressed. The TSD (p. 13, lines 9-10) states, “Values for IRwater are interpolated  
28 between inputted ages.” Does this mean that a step-function option is never implemented for this  
29 exposure factor? If this is not true, and a step function is in fact one run option, the Committee  
30 recommends that EPA add this clarification to this section of the TSD.

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*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  $\mu\text{g Pb/kg-day}$ , which corresponds to an absolute lead intake rate of 10  $\mu\text{g Pb/day}$  for an adult weighing 71.4 kg. The TSD presents age-specific estimates selected by the USEPA 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 Committee 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 Committee recommends a value of 0.128 or 0.13  $\mu\text{g/kg-day}$ , which is better supported by the data cited by EPA, rather than 0.14  $\mu\text{g/kg-day}$ . 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 Committee 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  $\mu\text{g/kg-day}$ . (see the following page – Exhibit 2).
- 3) An error rate of 0% corresponds with a body weight-normalized intake rate of 0.128  $\mu\text{g/kg-day}$ , which corresponds with an absolute intake rate of 9.1  $\mu\text{g/day}$  for a 71.4 kg adult. It is unclear why a parameter value rounded to a whole number (e.g., 9  $\mu\text{g/day}$ ) 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  $\mu\text{g/kg-day}$  corresponds with an absolute intake rate of 9  $\mu\text{g/day}$  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  $\mu\text{g/kg-day}$  (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 Committee 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 Committee 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.

**Science Advisory Board (SAB) Draft Report (April 7, 2020) Preliminary Version-- Do Not Cite or Quote -- This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the chartered SAB and does not represent EPA policy.**

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

Adult BW kg	Dietary Pb Intake		Child (1 to 7 years) % difference
	ug/kg-day	ug/day	
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 years	Multiplier ug/kg-day	Body weights (kg)		Intake (ug/day)				Difference	
		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	<b>1.17</b>	<b>2.26</b>	-1.09	-48%
1 to < 2	0.128	12.3	12.9	1.57	1.65	<b>1.61</b>	<b>1.96</b>	-0.35	-18%
2 to < 3	0.128	14.6	15.3	1.87	1.96	<b>1.91</b>	<b>2.13</b>	-0.22	-10%
3 to < 4	0.128	16.4	17.2	2.10	2.20	<b>2.15</b>	<b>2.04</b>	0.11	5%
4 to < 5	0.128	18.0	18.8	2.30	2.41	<b>2.36</b>	<b>1.95</b>	0.41	21%
5 to < 6	0.128	19.7	20.2	2.52	2.59	<b>2.55</b>	<b>2.05</b>	0.50	25%
6 to < 7	0.128	21.7	21.8	2.78	2.79	<b>2.78</b>	<b>2.22</b>	0.56	25%
<b>average difference</b>									<b>0.0%</b>

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

Figure 2: Comparison of differences between lead intake (ug/day) from food for ages 0 to 7 years, comparing AALM to recommendations by USEPA TRW

**Other Medium Intake Rate**

In general, the Committee finds the use of an “Other” input menu to be straightforward and useful. One of the Committee’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

1 the model as noted in responses to Charge Questions 1 and 7. The Committee recommends  
2 including this “other intake” module in one or more such examples.

3  
4 The TSD refers to the “Other” pathway in the discussion of soil intake (p. 11-12, lines 36-37;  
5 and p. 12, line 1), stating, “The main consideration for including exposures to soil in the soil  
6 pathway rather than simulating the soil exposures in the other pathway is the determination of  
7 whether or not parameter values for soil ingestion rate (IR<sub>soil</sub>, Equation 2.2-14) apply to the soil  
8 exposure.” The Committee finds the wording of this sentence to be confusing because it does  
9 not clarify conditions in which a separate evaluation, using the “other” pathway, would be  
10 warranted. And furthermore, even if there are multiple exposure pathways involving multiple  
11 soil lead concentrations, it is unclear why a different set of age specific IR<sub>sd</sub> values would be  
12 appropriate. Further clarification of these points is needed.

#### 13 14 Parameters for additional exposure variables

15 The Committee also evaluated additional exposure variables, beyond the media-specific intake  
16 rates discussed above.

#### 17 18 *Indoor dust lead*

19 Pb in soil and indoor dust represents the most common source of non-dietary lead exposure in  
20 US children whose blood lead concentration exceeds the CDC reference value of 5 µg/dL  
21 established in 2012, or the value of 3.5 µg/dL proposed by the ATSDR/NCEH Board of  
22 Scientific Counselors in 2016. As such, when AALM.FOR is employed, the user defined value  
23 of lead in soil and indoor dust will be of key importance.

24  
25 In Appendix C (p. 276, pdf p. 287), the TSD recommends a default value for indoor dust of 175  
26 µg/g (ppm). Appendix C further states that a value for indoor Pb dust equal to soil Pb is  
27 recommended where there are no known indoor sources of Pb in dust (e.g. lead paint or hobbies).  
28 However, Appendix C appropriately cautions, “Indoor dust Pb concentrations in residences  
29 impacted by Pb-based paint can be expected to vary considerably within and between residences  
30 and local exposure conditions should be considered to establish a representative estimate.” The  
31 Committee expressed concern that use of 175 µg/g as a default indoor dust Pb concentration may  
32 yield unexpected or unreliable outputs in several situations:

33  
34 First, it may be noted that there is a general consensus that for indoor dust, Pb dust loading (e.g.  
35 µg/ft<sup>2</sup>) rather than Pb dust concentration (µg/g) is a superior predictor of childhood blood lead  
36 (e.g. see Dixon et al., 2009). In a multivariable regression model developed by Dixon et al.,  
37 based on interior Pb dust and child blood Pb measurements from several NHANES surveys (n =  
38 2155), floor Pb dust and windowsill Pb dust loading were significant predictors of blood Pb  
39 (median floor dust loading in that data set was approximately 0.5 µg/ft<sup>2</sup>). In its 2018 Technical  
40 Support Document for Residential Dust-Lead Hazard Standards Rulemaking: Approach taken to  
41 Estimate Blood Lead Levels and Effects from Exposures to Dust-lead EPA, OPPT developed a  
42 nonlinear regression model relating Pb dust loading to Pb dust concentration based on HUD data  
43 collected in the mid-2000s (see U.S. EPA, 2018, section 3.2.4). The extent to which this  
44 relationship might be adapted for the AALM.FOR model merits investigation.

1 Second, selection of a default value of 175 µg/g for Pb concentration of indoor dust  
2 concentration recommended in Appendix C appears to be too high. The calculated median Pb  
3 dust concentration from the aforementioned OPPT document on lead in residential dust (EPA,  
4 2018; Table 3-9) was 101.2 µg/g based on a median background dust loading value of 0.7 µg/ft<sup>2</sup>.  
5 The 175 µg/g default value for indoor Pb dust, when combined with the default value for indoor  
6 dust ingestion of approximately 0.04 g per day (see Appendix C page 281), would yield a lead  
7 intake from this source of 7 µg. Further applying AALM.FOR default dust Pb RBA of 0.6, it  
8 may be seen that Pb ingestion from default indoor dust alone in young children would be 4.2  
9 µg/day. This is approximately equal to estimated dietary lead ingestion for children (Manton et  
10 al., 2005) that has long been considered the major source of background lead exposure for the  
11 general population. Therefore, it may be prudent to use the median value of 101.2 µg/g as a  
12 default if it is necessary to use a concentration term for indoor Pb dust rather than a loading term  
13 in the AALM.FOR model.

14  
15 Third, the recommendation to apply outdoor soil Pb concentration as a surrogate for indoor dust  
16 Pb in situations where no indoor Pb source is known to exist may overestimate indoor dust Pb  
17 concentration. To the extent that outdoor soil Pb is tracked indoors and contributes to indoor Pb  
18 dust it would be subject to dilution by other sources of indoor dust (such as background  
19 exfoliation of skin and dander from humans and pets). The Baseline Human Health Risk  
20 Assessment for the Vasquez Boulevard and I-70 Superfund Site, Denver, CO (EPA Region VIII,  
21 August 2001) reported the correlation between indoor house dust Pb and mean yard soil Pb at 74  
22 properties with a range of soil lead of approximately 80 to 800 ppm. The relationship was  
23 described by  $CPbdust = 0.34 CPbsoil + 150$ , ( $R^2 = 0.18$ ). In this sample, where residential soil  
24 Pb concentration exceeded 227 ppm, indoor house dust Pb was less than soil lead. It may be  
25 useful to examine additional data sets where simultaneous measurements of soil and indoor Pb  
26 dust concentration have been compared.

## 27 28 **Charge Question 3a Recommendations (by exposure routes)**

### 29 30 **Overall and Air Intake Rate**

#### 31 **Tier 1**

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

#### 39 **Tier 2**

- 40 • Provide additional guidance and examples for modeling inhalation exposures for individuals  
41 with occupational exposures. As noted on p 282 of the TSD (pdf p 293) appropriate  
42 interrelationships need to be addressed for particle size, clearance, deposition, and ventilation  
43 volume rates.

44

1 **Tier 3**

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

5

6 **Soil and Dust Intake Rate**

7 **Tier 1**

- 8 • Revisit the basis for the recommended soil and dust intake rate parameter values for ages 2 to  
9 15 years to either better align with the materials cited or explain the rationale for the deviation.

10 **Tier 2**

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

12

13 **Water Intake Rate**

14 **Tier 2**

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

19

20 **Food Intake Rate**

21 **Tier 2**

- 22 • Re-evaluate lead intake rate in food of 0.14  $\mu\text{g Pb/kg-day}$  as the committee recommends a  
23 value of 0.128 or 0.13  $\mu\text{g Pb/kg-day}$  as explained in the above text.  
24 • Add text to documentation about intakes by age compared to TRW recommendations.  
25 • Explain if breast milk is included in the food pathway or not. Assuming it is not, add text to  
26 explain how it would be included in the modeling.  
27 • Clarify the TSD text about soil intake and the “other” pathway.

28

29 **Indoor Dust Lead**

30 **Tier 1**

- 31 • Reevaluate the default value of 175  $\mu\text{g/g}$  for Pb concentration of indoor dust. The median  
32 value of 101.2  $\mu\text{g/g}$  may be more appropriate as a default.

33 **Tier 3**

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

1 **2.3.2. Charge Question 3b. Are the uptake/absorption parameters and parameters**  
2 **requiring modification for specific routes of exposure adequately described?**

3  
4 The AALM is based upon previous modeling, particularly by Leggett (1993) and relies heavily  
5 upon that theoretical approach and the methods used to estimate parameters with some updates  
6 and adjustments to further address changes in kinetics with age. Evaluating the  
7 uptake/absorption parameters is made difficult by the complexity of the documentation and  
8 differences in values reported in different parts of the documentation, e.g., the main text,  
9 Appendix D, and the EXCEL spreadsheet implementing the model.

10  
11 The first issue for users or reviewers of this model may be definitional. Generally, in discussing  
12 absorption and absorption parameters in models integrating exposure, biokinetics,  
13 pharmacokinetics, and adverse health effects; the terms absorption, absorption fraction,  
14 bioavailability, bio-accessibility, relative bioavailability, bioactivity etc. have somewhat different  
15 meanings to various disciplines. The IEUBK Technical Support Documents provided specific  
16 definitions as to how these were applied in the model development and use. The AALM  
17 documents could benefit from more precise definitions and extended discussion of the approach.  
18 It would seem advantageous to EPA to use the same definitions as elsewhere, although there may  
19 be some differences with the original model developers' approaches and use of absorption  
20 terminology.

21  
22 The response to this charge question will address absorption in the respiratory tract followed by  
23 the gastrointestinal tract, consistent with the presentation in the TSD. Relative bioavailability  
24 was implemented and described in the TSD as part of the exposure calculation prior to passing  
25 values to the biokinetic model. However, bioavailability largely reflects differences in the  
26 availability of the lead in different environmental media or diet for absorption, so it will be  
27 discussed following inhalation and oral absorption.

28  
29 The TSD indicates that absorption from dermal exposure to surface dust is simulated (see  
30 Section 2.3.3, document p22, pdf p33), but this was not found in the description of the model.  
31 Clarification is needed for whether dermal absorption is included as a specific pathway in the  
32 model. While there is some description of how hand to mouth behaviors leading to oral  
33 exposure to dust or soil on the skin is addressed, providing examples would clarify and  
34 strengthen this aspect.

35  
36 Uptake/absorption in the respiratory tract (Inhalation)

37  
38 Review of the modeling for the respiratory tract found that the current model and recommended  
39 parameters could be appropriate for specific conditions that are not clearly specified, e.g.,  
40 average individual inhalation of relatively small environmental lead particles, but that different  
41 parameter values would be needed, particularly for occupational exposures, to address varied  
42 activity levels, changes in respiration, and larger particle sizes. Variations in particle size that  
43 affect deposition in the respiratory tract and the fraction subject to mucociliary clearance to the  
44 GI tract for absorption also need to be addressed.

1 Inhalation absorption assumptions appear to be rather undeveloped. In section 2.3.3.1,  
2 Absorption from the Respiratory Tract, (pdf page 34, document page 23), AALM.FOR adopts  
3 the assumptions made by the Leggett model with respect to inhaled Pb aerosols, i.e. 40 percent  
4 of inhaled Pb is retained in the respiratory tract, and of this, only 4 percent is transferred by  
5 mucociliary clearance to the gut (cf. definition of CILIAR, pdf page 311) while the remainder  
6 (96 percent of deposited Pb) is absorbed. These parameter values were based on the clinical  
7 studies cited in section 2.3.3.1 where the inhaled Pb aerosols were soluble submicron particles of  
8 the type released by automotive exhaust in the 1970s. Such assumptions may continue to be  
9 reasonable for the minute amount of lead present in ambient air in the United States today (on  
10 the order of 0.01  $\mu\text{g}/\text{m}^3$ , which is the default value recommended by the TSD for the  
11 AALM.FOR in Appendix C (pdf page 286 document page 275).

12  
13 Significantly, the TSD states "These assumptions would not necessarily apply for exposures to  
14 larger or less soluble airborne particles." (pdf page 34, document page 23) In Appendix C, page  
15 282 lines 10-14 states "Regional deposition and clearance in the RT (will depend on numerous  
16 factors, including age, particle size, as well as various factors that affect ventilation rates  
17 (mg/day) which vary with age and physical activity. The interrelationships between particle size,  
18 clearance, regional deposition and ventilation rate should be considered in assigning values of  
19 these parameters for simulating specific populations and exposure settings, these subjects are  
20 treated in depth in ICRP (1994)."

21  
22 Section 3.4 (pdf page 72, document page 62) "DATA NEEDS FOR FURTHER REFINEMENT  
23 OF THE AALM" indicates the dose of Pb particles deposited in the lung "must be calculated  
24 outside of the AALM.FOR for a given set of assumptions" (lines 40-41). This point should be  
25 made clearer in discussion of uptake/absorption parameters, Section 2.3.3.1.

26  
27 The TSD does not discuss whether or how to utilize well established tools and models designed  
28 to address the impact of particle density, particle size and size distribution on regional deposition  
29 in the lung (and subsequent absorption). The Multiple Path Particle Dosimetry (MPPD) model is  
30 well established for addressing just these concerns (see Asgharian et al., 2001; Miller et al.,  
31 2016; etc.). Exposure modeling of various particle size distributions (i.e. normal distribution  
32 around a mass mean aerodynamic diameter, skewed towards larger or smaller particle sizes, bi-  
33 modal) for a set air concentration of lead (e.g.  $\mu\text{g}/\text{m}^3$ ) indicate the potential for significant  
34 variability in regional deposition in the lung and subsequent absorption (see Petito Boyce et al.  
35 2017). As noted above in the discussion of inhalation intake (Charge Question 3a), the study by  
36 Lach et al. (2014), showed that 49% of total inhaled Pb would be deposited in the respiratory  
37 tract, of which 37% would be translocated to the GI tract in contrast to the 4% based upon  
38 Leggett (1993).

39  
40 There was difficulty understanding the meaning of the relevant respiratory parameters (e.g., R1-  
41 R4, BR1-BR4, CILIAR) and how they might be modified by a user. Inconsistencies in text,  
42 tables, and the EXCEL spreadsheet implementation of the model were noted. Examples include:  
43 P23 (pdf p34) Line 32 defines  $BR_i$  as a fraction when it is a rate  
44 P25 (pdf p36) Line 2  $BR_i$  again described as a fraction when it is a rate

1 P299 (pdf p310) BR1 to BR4 – Half-life values given are rounded and converted to days in  
2 calculations of rates, which are shown as  $0.693/T_{1/2}$  but in the EXCEL spreadsheet, they are  
3 calculated as  $\ln(2)/T_{1/2} * 24$  so the numbers don't match.

4 P302 (pdf p313) R1 – 10% value given in text (line 14), but the calculation shown, and the value  
5 used in the spreadsheet (LUNG tab) is 0.08 or 8%

6 P302 (pdf p313) R3 – 12% value given in text (line 26), but calculation shown, and value used in  
7 spreadsheet (LUNG tab) is 0.14 or 14%

8  
9 Some discussion is recommended of how the R, BR, and CILIAR parameter values were derived  
10 (other than citing the original studies), the assumptions and factors that would need to be  
11 considered in changing these variable values, and whether the values need to be changed  
12 concurrently to not upset material balances in the model.

### 13 14 Occupational inhalation exposures

15  
16 Particles encountered in occupational settings (including those encountered episodically by  
17 outdoor construction and remediation workers who are receptors of interest in EPA risk  
18 assessments) tend to be larger, sometimes less soluble, and present at much higher  
19 concentrations. Several approaches are available for addressing these issues including clearly  
20 specifying for what conditions the current AALM model parameters are appropriate and when  
21 they are not, developing modifications for the model and its parameters to facilitate its utility for  
22 these other settings, or relying on other lead modeling focused on occupational exposures for that  
23 purpose.

24  
25 California OEHHA (CalEPA 2013) developed a modification of the Leggett model to account  
26 for Pb anticipated to be present in workplace air. As detailed in the OEHHA report, (subsection  
27 B.2, pp 71 et seq), it was found practical to use the Multi-Path Particle Dosimetry Model version  
28 2 (MPPD2) to describe size dependent deposition of inhaled particles in various regions of the  
29 airway (Asgharian et al., 2001; Miller et al., 2016). OEHHA conservatively assumed 100  
30 percent absorption of Pb particles from the lung to the blood, which is somewhat higher than the  
31 95% assumed by Leggett and used in AALM.FOR. Interestingly the OEHHA model found that  
32 although particle deposition in the MPPD2 module differed significantly from original Leggett  
33 model assumptions, the overall default inhalation transfer coefficient arrived at by OEHHA,  
34 0.30, was not much different than that yielded by the Leggett model. That's because for very  
35 small size Pb aerosols (e.g. submicron), the minor fraction retained in the body (i.e. not exhaled)  
36 undergoes a high degree of transfer to the blood from deep lung regions; conversely for larger  
37 size Pb particles, a high percentage that are inhaled are retained in the upper airway and cleared  
38 by mucociliary clearance to the gut, where percent absorption is relatively low compared to the  
39 lung. In addition to exploring the utility of MPPD2 as applied by OEHHA, the developers of  
40 AALM.FOR should explore additional modifications of the model that would allow the user to  
41 specifically indicate the RBA of inhaled particles that are cleared to the gut.

42  
43 One specific route of exposure for workers is inhaled particles that are removed by ciliary action  
44 and swallowed during and after meals where absorption efficiency can increase substantially  
45 from the default of 12% oral absorption of lead from the small intestine.

1 A lead pharmacokinetic model designed to address occupational exposures for the Department of  
2 Defense has been under review by a committee for the National Academies of Science,  
3 Engineering, and Medicine (Review of DoD's Proposed Occupational Exposure Limits for Lead,  
4 PIN: DELS-BEST-18-05). In early 2020, the draft of this review has been completed and is  
5 undergoing internal peer review at the National Academies, so it should be made public midyear.  
6 This modeling is based upon the physiologically based pharmacokinetic modeling originally  
7 done by Prof. O'Flaherty, where AALM is derived from the modeling by Dr. Leggett. However,  
8 the availability of a peer reviewed model for at least some occupational exposures could be a  
9 useful option for the EPA to consider for modeling solely occupational exposures, or to provide  
10 insights and parameter values for expanding AALM to address occupational exposures in a  
11 context of prior childhood exposures.

### 12 13 Uptake/absorption in the gastrointestinal tract (Oral)

14  
15 Although gut absorption of lead is exceedingly complex and depends on numerous factors,  
16 absorption from the gut in the AALM approach seems simplified to a first-order fraction of the  
17 contents of the small intestine, based on a single age-dependent coefficient. As a result,  
18 characterization of the absorption parameters for the AALM would reflect the appropriateness of  
19 the original formulae developed earlier as cited in the document. However, the extent to which  
20 the model emulates understanding of the processes and concentration-dependent rate  
21 characteristics bears further discussion.

22  
23 The extent to which overall absorption or the amount of total intake that eventually reaches (or is  
24 accessible to) tissue compartments has long been debated among researchers, practitioners and  
25 the regulatory community. Several alternative explanations have been advanced in application of  
26 these models to health response and regulatory actions, often with considerable impact on  
27 outcomes. The IEUBK model support materials noted some years ago that, in order to more  
28 accurately model lead uptake from the gut at higher intake rates, absorption fractions should be  
29 modified to separate non-saturable and saturable components. That is apparently not considered  
30 in this approach or if non-linear absorption is addressed. The IEUBK Technical Support  
31 Document extensively discusses both bioavailability application and gut absorption, and their  
32 role in applying combined passive/active absorption mechanisms to mimic non-linear uptake. It  
33 is not clear how non-linear uptake is accomplished in the AALM, especially with respect to  
34 which variables and parameter values specify or influence age-dependent and concentration  
35 dependent parameters; or whether there is "double counting" of absorption factors in applying  
36 bioavailability as an intake adjustment.

37  
38 Section 2.3.3.2. Absorption from the Gastrointestinal Tract, indicates that AALM.FOR has  
39 incorporated age dependent gastrointestinal absorption fractions (AF), ranging from 0.39 at birth  
40 to 0.12 that do not otherwise vary based on whether Pb enters the gut without food (e.g. fasting  
41 condition), with liquids, or with food. However, as noted in the cited references (e.g. James et  
42 *al.*, 1985) and several other studies (cf discussion in Maddaloni et *al.*, 2005 and CalEPA 2013 pp  
43 83 et seq and appendix A), the extent of GI Pb absorption varies considerably depending on  
44 whether Pb enters the gut with or without food or liquids. This applies not only to Pb ingested  
45 during meals, but also Pb transported from the respiratory tract by mucociliary clearance (a  
46 relatively continuous process throughout the day). For risk assessment scenarios, there may be a

1 basis to distinguish between Pb ingested with meals (food and water), and that ingested during  
2 outdoor recreation or work when food is not eaten. OEHHA considered this by estimating three  
3 mean gastrointestinal absorption fractions for adults: 50% after several hours of fasting, 19%  
4 with liquid between meals, and 12% during intake with solid food (OEHHA, 2013, page 82). It  
5 further calculated a 24-hour TWA GI absorption of 30% assuming 10 hours fasting (50% AF),  
6 10 hours with liquids between meals (19% AF), two hours intake with solid food (12% AF), and  
7 two hours in which no lead enters the GI tract. The impact of revising the AALM.FOR to  
8 consider this additional variability in GI absorption of Pb based on co-ingestion with food and  
9 liquid should be examined.

10  
11 The new ICRP age-specific and sex-specific model, called the Human Alimentary Tract Model  
12 (HATM) may be appropriate to include in the AALM because it has been vetted and updates the  
13 GI tract model included in the current AALM (Leggett et al., 2007; ICRP 2006). This newer  
14 model should be evaluated for use in future versions of the AALM and discuss the uncertainties  
15 in the data used to parameterize/evaluate the model. It is more complex and might be difficult  
16 and time consuming to implement.

#### 17 Relative bioavailability for ingestion

18  
19  
20 For the INGESTION pathway, the inputs are adjusted by relative bioavailability (RBA) in the  
21 SOIL, DUST, WATER, FOOD and OTHER Exposure Modules. Relative bioavailability is  
22 determined by comparison with availability with lead completely soluble in water. Each of these  
23 reduces the amount of lead entering the biokinetic model. The model user can adjust the RBAs.  
24 Default values are 60% for soil and dust and 100% for food, water and other lead. Because these  
25 adjustments are made to the amount of lead entering the biokinetic model, this results in a  
26 material imbalance under-predicting the fecal lead content. Lead in these media delivers a  
27 combined available Pb to the gut, which is augmented by secretions from other model  
28 components (lung, bile, plasma) for transfer to the plasma by first-order absorption coefficients.  
29 Four compartments are modeled in series, the contents of the stomach, small intestine, upper  
30 large intestine, and lower large intestine (feces) with first-order transfer rate coefficients. All  
31 absorption of Pb from the gastrointestinal tract is assumed to occur in the small intestine, which  
32 is described by an absorption fraction (AF), representing the fraction of Pb mass in the small  
33 intestine that is transferred to the diffusible plasma compartment. The remainder is passed to the  
34 large intestine and eventually excreted in the feces. The absorption fraction, AF, given is age-  
35 dependent, and derived by formulae from historic studies.

36  
37 The fact that RBA is applied to *intake* rather than *uptake* is noted in several places (e.g., Section  
38 2.2.3), and it is stated that this simplification may yield an under prediction of excretion and,  
39 therefore, a negative mass balance with Intake > body burden + excretion. It also appears that by  
40 adopting the same RBA as has been historically used in IEUBK and ALM, the proposed inputs  
41 may tend to over predict *uptake* because the variability in fed/fasted state is not taken into  
42 account.

43  
44 It would be helpful for the developers to explain why for most media, e.g. Pb in soil, Pb in dust,  
45 Pb in water, only a single RBA applies to all intake relative to that medium. For example, in  
46 Section 2.2.3.3. (pdf page 22) the narrative states, “The model accepts a single inputted value for

1 RBA which represents soil from all sources, in all exposure settings.” The same provision for a  
2 single RBA applies to all Pb in indoor dust (Section 2.2.3.2). This seems counter to the model’s  
3 flexibility in allowing for multiple values of Pb intake in soil or dust at different times of the day  
4 (or week). It seems likely that the soil or dust from different sources may have different  
5 solubility, particle size, and chemical composition, and by extension different RBA.

6  
7 With respect to lead intake in water (section 2.2.3.4; pdf page 24), the narrative states:

8  
9 
$$IN_{WATER} = Pb_{WATER} \cdot IR_{WATER} \cdot RBA_{WATER} \quad \text{Eq. (2.2-18)}$$

10  
11 where  $IN_{water}$  is the intake of Pb in water ( $\mu\text{g Pb/day}$ ),  $Pb_{water}$  is the Pb concentration in water  
12 ( $\mu\text{g Pb/L}$ ),  $IR_{water}$  is the rate of ingestion of water (L/day) and  $RBA_{water}$  is the relative  
13 bioavailability of Pb in water and dust, relative to water-soluble Pb. Values for  $IR_{water}$  are  
14 interpolated between inputted ages. The model accepts a single inputted value for RBA which  
15 represents both water [SIC], in all exposure settings. Lead dissolved in water would, by  
16 definition, have  $RBA = 1$ ; however, the RBA parameter could be used in scenarios in which  
17 ingestion exposures include Pb-bearing particulates suspended in water for which the RBA may  
18 be  $<1$ .

19  
20 Here again, the intent of the model to account for intervals of ingestion of water containing  
21 soluble lead (with an  $RBA = 1$ ) as well as intervals of ingestion of suspended lead that may have  
22 a lower RBA is salutary. Notwithstanding that human data pertaining to different bioavailability  
23 of soluble Pb versus suspended fine particulate is sparse, it is conceivable that a receptor could  
24 be simultaneously exposed (during the course of a day) to a given mass of soluble and particulate  
25 lead. How would the model account for the possibility that these two different types of Pb in the  
26 same sample might have quite different RBAs? This scenario is plausible in domestic tap water,  
27 where intermittent releases of particulate Pb may greatly exceed baseline soluble lead. In a  
28 bioaccessibility experiment using simulated gastric fluid to measure the dissolution of lead  
29 particulate collected from home faucets, dissolution at 48 hours was 66% in one instance and  
30 21% in another (Triantafyllidou et al., 2007). In a study examining the observed in vitro  
31 bioaccessibility of a spectrum of lead particulate harvested from field collection of household  
32 water faucet, median estimated relative bioavailability of the lead particulate was 33%  
33 (Deshommes and Prevost, 2012). Pediatric blood lead concentration resulting from chronic or  
34 acute exposure to lead in drinking water has recently been estimated using the IEUBK and  
35 Leggett models (Triantafyllidou et al., 2014). Comparison of AALM.FOR simulations to the  
36 results of Triantafyllidou et al. (2014) may be informative.

37  
38 On the RBA tab of the EXCEL spreadsheet, the GI absorption fraction is called “F1” in the  
39 boxes and “AF1” in the heading on column D where values would be entered. Terminology  
40 should be consistent in sheet and with documentation.

41  
42 The RBA assumptions are not described/justified anywhere until Appendix C (this is true for  
43 many of the parameters). It was difficult to keep going back to that to see what the values and  
44 sources were.

1 On the backside of the “absorption” membrane, the amount of lead transferred to and from the  
2 plasma seems to be dependent on parameters in the blood compartments and particularly the  
3 exchange of Pb from the RBC and plasma components. The discussion related to the influence of  
4 the RBC parameters on childhood blood lead predictions, in comparison to the IEUBK model in  
5 Section 4, suggests that downstream mechanisms may have significant influence on  
6 “absorption”, at least, uptake in the gut. On the other hand, the comparisons alluding to  
7 difference in absolute and relative bioavailability in the IEUBK and AALM is intriguing and  
8 could contribute to the prediction differences. Section 3.3.9. Comparison to IEUBK Model for  
9 Pb in Children states:

10  
11 “Figure 3-19 compares predictions of the AALM and the IEUBK model for a continuous  
12 dust Pb intake of 10 µg/day. In both models, the relative bioavailability (RBA) for Pb in dust  
13 was assumed to be 60%. This corresponds to an absolute bioavailability of approximately  
14 20% at age 2 years in the AALM and 30% in the IEUBK model. At age 2 years the IEUBK  
15 model predicts a blood Pb concentration of 1.18 µg/dL; the AALM predicts 1.25 µg/dL.”  
16

17 It seems there should be no difference in absolute bioavailability as that should be a fixed  
18 characteristic of the substrate, and the RBA is referenced to the absolute bioavailability of lead in  
19 water, which should also have a single value. The statement above indicates that bioavailability  
20 is age-dependent and differs in the two applications. This divergence, perhaps, refers to the  
21 differences in AI assumptions that EPA assigns in the models, as those relate to an absolute  
22 value expressed as an RBA. The age-dependent differences in blood lead predictions could be  
23 related to the apparent “age-related” differences in bioavailability generated by the intake  
24 “adjustments”. It would be best to discuss, if not resolve, these differences as these models are  
25 released.  
26  
27

### 28 **Charge Question 3b Recommendations (General)**

#### 29 **Tier 1**

- 30 • Clarify in model documentation whether dermal absorption is included as a specific pathway  
31 in the model or not.  
32

#### 33 **Tier 3**

- 34 • While there is some description of how hand to mouth behaviors leading to oral exposure to  
35 dust or soil on the skin is addressed, providing examples would clarify and strengthen this  
36 aspect.  
37

### 38 **Charge Question 3b Recommendations (Inhalation)**

#### 39 **Tier 1**

- 40 • Clarify when the current model structure and parameter values would be appropriately used  
41 and when they would need to be modified (e.g., occupational inhalation exposures to larger  
42 particles) to guide users to appropriately use the model and avoid inappropriate uses.  
43

#### 44 **Tier 2**

- 1 • Clarify that MPPD deposition fraction and fraction of total lead are very different for  
2 different air sampling methods and size of particles and how this should be addressed in  
3 modeling.
- 4 • Add a discussion about the time to stomach and conditions in the stomach (fasting, water-  
5 only, with meal) for swallowed particles.

### 7 **Charge Question 3b Recommendations (GI and RBA)**

#### 9 **Tier 1**

- 10 • Change the model to quantify the total elimination in feces (e.g. fate of non-absorbed lead in  
11 soil and dust) and maintain mass balance.

#### 13 **Tier 2**

- 14 • Provide model users with guidance to address differences in lead bioavailability of different  
15 media from multiple sources.

#### 17 **Tier 3**

- 18 • Add more discussion about active and passive absorption.
- 19 • Gut absorption needs further discussion and potentially update the model (see Leggett et al.  
20 2007 intro to new ICRP GI model)
- 21 • Add discussion on bioavailability of suspended particle versus water soluble lead

### 22 **2.3.3. Charge Question 3c. Are the biokinetic parameters describing lead distribution and 23 elimination adequately described?**

24  
25 In general, the biokinetic parameters described in Tables 2-3 and 3-2 of the Technical Support  
26 Document (TSD) were adopted from the Leggett model and are generally well accepted.

#### 28 Parameter Inconsistencies and Uncertainties

29  
30 However, in order to recode the All Ages Lead Model (AALM) to run in MATLAB (adult  
31 parameters only) and reproduce the output from the AALM in Figure 3-10, several errors and  
32 omissions were discovered. The FORTRAN input file named POUNDS\_GUI.DAT listing input  
33 values for ICRPversion8 provided the following information that is missing from or inconsistent  
34 with Tables 2-3 and 3-2 of the TSD:

- 36 • The value for total transfer rate from exchange bone volume is 0.02311. The fraction of total  
37 transfer from the exchangeable bone directed to non-exchangeable bone is 60% of 0.02311 or  
38 0.01387 not 0.02311 as listed in Table 2-3. The transfer of lead from "Exch Vol" to "Surf  
39 bone" is 40% of 0.02311 or 0.0092 not 0.0185 as listed in Table 2-3. (Note that in Appendix  
40 D p303, the calculation of RDIFF from  $\ln 2$ /half-life has a typo, 0.00231.)
- 41 • Regarding the deposition fraction from Plasma-D to Kidney 2, Table 2-3 indicates a change  
42 from the original value of 0.4 to 0.8. However, in Table 3-2 the change in the Kidney 2  
43 deposition fraction from ICRPv4 or ICRPv5 to AALM.FOR is missing.

1 • Changes made to the deposition fraction from Plasma-D remove the mass balance originally  
2 present in the ICRP (Leggett) model. Specifically, the deposition from Plasma-D to all  
3 destinations should add up to 2000  $\mu\text{g}$  of lead. Instead it adds up to 1980.36. This mass  
4 imbalance has resulted from three changes in the fractional transfer of lead from Plasma-D to  
5 urine from 30 to 0, to kidney-1 from 40 to 50, and to kidney-2 from 0.4 to 0.8. These  
6 changes drop about 20  $\mu\text{g}$ . Maintaining mass balance is essential for insuring correct model  
7 behavior.

8  
9 Other changes made to the model that had to be obtained from the FORTRAN input file before  
10 Figure 3-10 could be reproduced include changes in:

- 11  
12 • Blood volume (dL) from  $0.726 \times \text{body weight}$  to  $0.67 \times \text{body weight}$   
13 • Default adult Hematocrit was changed from 0.45 to 0.46  
14

15 Findings from this limited exercise indicate that a more complete check for errors and omissions  
16 in Tables 2-3 and 3-2 describing the parameters for the entire model is needed. Nomenclature  
17 throughout the document (e.g., Table 2-3 and Appendix D) needs to be consistent so readers are  
18 certain what is being referred to. Parameter values and sources listed in documentation and  
19 model files (e.g., EXCEL spreadsheet) need to be cross-checked with the current ICRP version 8  
20 code file. If errors are only in documentation, then documentation readily can be corrected, but it  
21 is also possible that errors have been introduced in the modeling that need to be corrected.  
22

### 23 Red Blood Cell Binding

24

25 The assumption that saturation of binding in RBCs begins increasing the proportion of unbound  
26 lead at about 60  $\mu\text{g}/\text{dL}$  RBC (25  $\mu\text{g}/\text{dL}$  whole blood levels) was introduced by Chamberlain  
27 (1985) based on research published by Manton and Cook (1984) and subsequently adopted by  
28 Leggett. Leggett's equation depicting this nonlinear increase predicted plasma lead levels in-line  
29 with Manton and Cook data at whole blood lead up to about 90  $\mu\text{g}/\text{dL}$  and remained below the  
30 curve fit to data from DeSilva (1981) at levels above 90  $\mu\text{g}/\text{dL}$ . If the alternate assumption were  
31 made that there is a nonlinear increase in the proportion of lead in plasma relative to whole blood  
32 at any level of lead in whole blood, then the threshold constant would be set to zero and the  
33 saturation constant would be reduced from the current value of 350  $\mu\text{g}/\text{dL}$  to 290  $\mu\text{g}/\text{dL}$  RBCs.  
34 The latter assumption (RBC binding would begin to saturate at any level of lead in whole blood)  
35 was adopted by others (O'Flaherty and OEHHA). The description of RBC binding in the AALM  
36 should be re-evaluated for possible updating in a future version of the AALM.  
37

38 Biokinetics associated with changes in hematocrit, especially at highly elevated lead levels (e.g.  
39 lead induced anemia) should also be considered, or perhaps noted as an additional area of  
40 uncertainty. Leggett (1993) suggested that RBC maximum capacity binding constants would be  
41 much lower for acute high exposures based upon data on urine clearance of lead from such  
42 exposures in adults. Data in Kochen et al., (1973) also could be useful to consider.  
43  
44  
45  
46

### 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 hyperactive (e.g., athletes) or hypoactive (e.g., couch potatoes) 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 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 US 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 EFH 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 EFH 2011 ranges. 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 EFH.

### 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 US 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

1 study of perimenopausal and postmenopausal women (n=1225), linear multivariate models  
2 demonstrated that biomarkers of bone turnover (N-telopeptide cross-linked collagen type I,  
3 bone-specific alkaline phosphates, and osteocalcin) were significant predictors of blood lead  
4 concentration (Machida *et al.*, 2009).

5  
6 In a cross-sectional study of bone lead concentration by non-invasive K x-ray fluorescence in  
7 101 subjects age 11 to 78 with background environmental lead exposure, a significant age•sex  
8 interaction accounted for higher tibial bone lead concentrations in men over the age of 55 years  
9 (Kosnett *et al.*, 1994). Similar findings of an age•sex interaction in the relationship of age to  
10 tibial bone lead was observed in a more recent study conducted in subjects (n=263) from the  
11 general population of Ontario (Behinaein *et al.*, 2017). Popovic *et al.* (2005) examined blood and  
12 bone concentration study in a cohort of women with a history of occupational lead exposure to  
13 unexposed referents (n=207). Among the women with past occupational lead exposure, the ratio  
14 of blood to bone lead was substantially higher after menopause. The authors noted, “The results  
15 suggest that the endogenous release rate (micrograms Pb per deciliter blood ÷ micrograms Pb per  
16 gram bone) in postmenopausal women is double the rate found in premenopausal women”  
17 (Popovic *et al.*, 2005). Bone Pb was significantly greater in postmenopausal referent women  
18 treated with estrogen (Popovic *et al.*, 2005). Related findings were observed in a longitudinal  
19 study of bone lead concentration in postmenopausal women, in which hormone replacement  
20 therapy (HRT) was associated with higher bone lead concentration compared to women not on  
21 HRT (Webber *et al.*, 1995). Overall, the available research strongly suggests that the  
22 AALM.FOR would benefit by refinements that account for sex-related differences in bone lead  
23 accretion and release associated with changes related to menopause (O’Flaherty 2000).

#### 24 25 Elimination pathways

26  
27 The relevance of the sweat elimination pathway and its inclusion in the model should be clarified  
28 or at least qualified as a relatively minor pathway. Leggett (1993) indicates this only accounts  
29 for a small percentage of elimination.

### 30 31 **Charge Question 3c Recommendations**

#### 32 33 **Tier 1**

- 34 • Errors identified in Tables 2-3 and 3-2 raised uncertainty in our evaluation and indicate a  
35 more complete check of biokinetic parameters is necessary. If errors are only in the  
36 documentation, text editing is necessary, but if there are errors in the modeling then these need to  
37 be corrected and the documentation updated accordingly.
- 38 • Nomenclature needs to be made consistent in the documentation and the EXCEL  
39 implementation of the model (and any other computer files).
- 40 • TSD text needs to make clear that the biokinetic parameters reflect standard tendencies for an  
41 “average” individual.

1 **Tier 2**

- 2 • Assumptions regarding saturation of binding to red blood cells (RBCs) need to be re-  
3 evaluated and the implications for the modeling better described. Changes in hematocrit with  
4 lead exposure should also be discussed in more detail.  
5 • Default sex specific body weight values should be reconsidered considering recent data for  
6 the US population, as they hold implications for blood and organ mass and perfusion, and  
7 ultimately biokinetics. Consider whether BW or BMI or both should be applied in the modeling  
8 and explain options and choices in documentation.  
9

10 **Tier 3**

- 11 • Revise AALM to account for postmenopausal changes in bone turnover and age-sex  
12 interactions in bone lead and release of lead from bone.  
13 • Evaluate whether to retain the plasma-D to bladder and sweat elimination pathways in the  
14 model.  
15

16 **2.3.4. Charge Question 3 continued. Additionally, please comment on any strengths or**  
17 **weaknesses in the justification provided for model assumptions (data inputs,**  
18 **methodology, etc.) and the quantitative impact of those assumptions on the model and**  
19 **its results.**

20  
21 While the committee found that the justifications for model assumptions were sound, we think it  
22 should be a matter of concern that both the Leggett and O’Flaherty models are highly sensitive to  
23 two parameters:  
24

- 25 - parameters C1 and C2 in the calculation of urinary clearance in AALM-OF.CSL  
26 - parameters TEVF and TORBC in the plasma compartment of AALM-LG.CSL  
27

28 These results need to be investigated and for all sensitivity analyses the direction of change  
29 needs to be indicated, that is, positive for a direct dependence and negative for an inverse  
30 dependence. For the four parameters noted above, there appears to be unusually high sensitivity,  
31 i.e., the ratio of percent change in blood concentration to percent change in parameter is much  
32 greater than 1 in absolute value, indicating significant amplification of error from the input  
33 parameter to the model output. For example, a 10% variation in one of the parameters would  
34 produce a 50% to 90% change in the predicted blood lead level. The discussion of these results  
35 does not provide a satisfactory explanation for such a significant impact by these parameters.  
36

37 **Charge Question 3 continued Recommendations**

38  
39 **Tier 1**

- 40  
41 • The sensitivity analysis should include the direction of the sensitivity; that is, positive for a  
42 direct dependence and negative for an inverse dependence.  
43 • Each of the two models underlying the AALM appear to be overly sensitive to two of their  
44 parameters. This dependence needs to be investigated.

1 **2.4. Charge Question Four: What are the Panel’s views of Chapter 3: Evaluation and**  
2 **Development of AALM.FOR) with regard to:**

3  
4 **2.4.1. Charge Question 4a. The predictive accuracy and reliability of the AALM based on**  
5 **comparisons to available data sets.**

6  
7 The Committee discussed how to interpret the terms “predictive accuracy and reliability” used in  
8 this charge question. In both Chapter 3 (regarding AALM.FOR) and Chapter 4 (regarding  
9 AALM.CLS [sic]), the term “prediction” refers to the model output (e.g., p. 54, lines 2-6, pdf p.  
10 65), primarily for blood and bone lead concentrations. This leads to confusion because the TSD  
11 does not distinguish between predictions based upon an established model and parameter values  
12 and outputs from simulations that were used to optimize parameters during a model calibration  
13 step. This is relevant because one outcome of model calibration is expected to be close  
14 correspondence between model output (predictions) and data. While calibration of parameter  
15 values may have been done using the ACSL version of the model, rather than the Fortran  
16 version, these two models should be considered similar enough that using the Fortran version to  
17 simulate the data should not be considered a *de novo* prediction. The comments herein include  
18 observations about model performance with respect to AALM.FOR.

19  
20 As described in the response to Charge Question 3c, re-implementing adult modeling in  
21 MATLAB identified a series of issues about parameter values that appeared necessary to  
22 reproduce some Figures in the TSD. That has raised additional uncertainties in the review of the  
23 model results in comparison with the data as discussed here in response to Charge Question 4a.

24  
25 Many of the simulation results, whether pure predictions or fits by adjusting parameters, are  
26 quite good. The following are notable exceptions with respect to model performance:

- 27
- Figure 3-14. Based on comparisons to data reported by Ryu *et al.* (1983), the model shows a  
28 much more rapid increase following the change in formula at age 112 days as compared to the  
29 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  
30 by Sherlock and Quinn (1986), not only because of the difference in slope, but also the intercept,  
31 which would be an indication of a baseline blood Pb in the absence of the additional Pb intake.  
32 Also, note that the y-axis is incorrectly labeled “Blood Pb intake” when it is “Blood Pb  
33 concentration”.
- 34  
35

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

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

1

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

4 a. The capacity limit of 350  $\mu\text{g}/\text{dL}$  RBCs may be too high.

5 Step 2 (plasma/RBC ratio) lists six studies that support estimates of this ratio. With respect to  
6 RBC binding capacity, the Committee recommends referring to Figure 14 in Leggett (1993) and  
7 Figure 1 in Bergdahl et al. (1998). Bergdahl et al. (1998) reported an RBC capacity limit of  
8 300  $\mu\text{g}/\text{dL}$  – similar to previous findings by this group and others. In Figure 1 of Bergdahl et al.  
9 (1998), the modeled line representing the three observed lead-binding components is closer to  
10 the line representing the DeSilva data shown in Figure 14 in Leggett (1993) and in O’Flaherty  
11 (1993). Based on the conclusions stated by these authors, perhaps the capacity limit of 350  
12  $\mu\text{g}/\text{dL}$  RBCs is too high. The issue of how to describe RBC binding also has been raised in  
13 charge question 3c.

14 b. Urine clearances reported in the literature are quite variable – how was this addressed in the  
15 proposed plasma-to-urine clearance estimates (Step 3)?

16 Step 3 lists five studies that support plasma (blood) to urine clearance. Figure 13 in Leggett  
17 (1993) shows that short term and chronic exposure scenarios can yield vastly different urine  
18 clearances relative to blood lead levels. Were exposure scenarios from all five studies similar?  
19 EPA should consider examining this variability and discussing implications for these findings on  
20 the input parameter selected for AALM.

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

22 Step 4 lists four studies that support soft tissue/bone Pb ratios. When a 20-yr simulation with the  
23 AALM of the lead distributed to compartments representing bone, blood, liver, kidney, brain  
24 other tissue was conducted as described in Leggett (1993), results for kidney and liver were  
25 substantially higher than those estimated from autopsy data summarized in Table 3 of Leggett  
26 (1993). EPA may wish to revisit this optimization step using summaries of tissue lead  
27 distribution.

28 d. AALM appears to underestimate the ratio of trabecular bone Pb:cortical bone Pb.

29 Step 5 lists two studies that support estimates of blood/bone Pb ratios. Figure 4-18 of the TSD  
30 shows a range of plasma/bone Pb ratios. Additional data combined from reports in studies by  
31 Fleming et al., Brito et al., and Nie et al. (see bibliography in response to Charge Question 4c)  
32 provide additional information about bone lead elimination. Currently, the AALM ratio of  
33 trabecular to cortical bone lead ( $\mu\text{g}/\text{g}$  bone mineral basis) is much lower than observed in Nie et  
34 al., Hernandez-Avila et al. and Cake et al.

35 e. AALM appears to overestimate peak blood Pb.

36 Step 7 lists one study (Rabinowitz, 1976) as a source of data on blood elimination kinetics in  
37 adults. Some of these data are displayed in Figure 3-10 of the TSD, which shows strong  
38 correspondence between observed and predicted blood 207Pb concentrations, after gut  
39 absorption fractions were adjusted to match values reported in Rabinowitz. Figure 7 of Leggett  
40 (1993) shows simulations results using absorption fractions from the Rabinowitz study, as  
41 reanalyzed by Chamberlain. When the modified absorption fractions were applied using the  
42 AALM, peak blood leads were higher than previously modeled for three out of four subjects.

1 The elimination kinetics did not change but perhaps the body weight-based blood volume is too  
2 low.

3 f. Calibration of the model to historic empirical data may introduce a high bias in predicted  
4 blood lead concentrations for current day occupational exposure scenarios.  
5 In terms of model performance for occupational exposure scenarios, the Committee notes that  
6 most of the available data used for calibrating the model is for studies published more than 20  
7 years ago. Modern exposure controls and hygiene practices may reduce the actual inhalation and  
8 incidental oral exposures for a given air concentration, as compared with older occupational  
9 settings. For example, hygiene or other exposure control mechanisms employed in newer  
10 facilities may reduce average daily exposures, including ingestion of particles that may  
11 accumulate on worker hands during smoke breaks or lunch breaks. Furthermore, exposure  
12 control mechanisms may impact particle size distributions, with subsequent impacts on particle  
13 deposition in the lung and impacts on blood lead. Model calibration and evaluation of model  
14 performance using older studies could, therefore, appear to provide strong correspondence  
15 between predicted and observed blood lead concentrations, when in fact, applications of the  
16 model to current day exposure scenarios, using air Pb concentrations alone, may result in  
17 overestimates of blood lead levels. The Committee encourages EPA to discuss this potential  
18 source of uncertainty in the TSD.

## 19 **Charge Question 4a Recommendations**

### 20 **Tier 1**

21 • Use prediction in the documentation to mean a *de novo* prediction from an established set  
22 model and parameter values. Otherwise, describe the output of the model as simulations, results,  
23 or model outputs.  
24

### 25 **Tier 2**

- 26 • Re-evaluate simulations shown in Figures 3-14 and 3-15. Determine if adjustments to the  
27 model can improve the fits or provide text in the documentation to assist the user in  
28 understanding implications of these fits for using the model in specific contexts.  
29 • Review whether any additional data for females is available that could inform model  
30 parameters.  
31 • Re-evaluate the calibration steps described in Table 4-16 considering the comments provided  
32 above. Make adjustments as deemed appropriate to the model and add explanations to the  
33 documentation for adjusting or not.  
34 • Discuss the potential uncertainties associated with model calibration and evaluation from  
35 historical data as compared to likely contemporary exposures.  
36  
37

### 38 **2.4.2. Charge Question 4b: The extent to which the computer code implementing the** 39 **model has been adequately verified and is operating as expected, based on the results** 40 **comparing model predictions between applications of the AALM implemented in** 41 **distinctly differing platforms.** 42

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

5  
6 The AALM has been successfully executed with proprietary software such as ACSL extreme,  
7 MATLAB and Excel on Windows operating systems. It has not yet been successfully executed  
8 on Apple or Linux operating systems.

## 10 **Charge Question 4b Recommendations**

### 12 **Tier 1**

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

### 16 **2.4.3. Charge Question 4c. The availability of other datasets that may be useful for further 17 model evaluation.**

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

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

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

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

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

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

3  
4 **Comment** Hryhorczuk et al.: Slow phase blood lead elimination half-lives in patients chronic  
5 occupational lead intoxication followed for more than 5 years after removal from exposure  
6 ranged from 1,658 to 7,189 days.

7  
8 • Manton WI, Angle CR, Stanek KL et al. Acquisition and retention of lead by young  
9 children. Environ Research. Section A. 82:60-80; 2000

10  
11 **Comment** Manton et al.: Data on children with relatively long T1/2 of lead in bone after earlier  
12 life exposure prolonged lead exposure.

13  
14 • O'Flaherty EJ, Hammond PB, Lerner SI. Dependence of apparent blood lead half-life on the  
15 length of previous lead exposure in humans. Fund Appl Toxicol 2:49-54; 1982

16  
17 **Comment** O'Flaherty et al.: Decline in blood lead after cessation of exposure is markedly longer  
18 in adult males with long history of exposure, consistent with strong effect of slow release of lead  
19 in bone.

20  
21 • Brito, J. A., McNeill F.E., Stronach I., Webber C.E., Wells S., Norbert R., Chettle D.R.,  
22 2001. Longitudinal changes in bone lead concentration: Implications for modelling of human  
23 bone lead metabolism. J Environ Monit 3:343-351. DOI: 10.1039/b101493p PMID: 11523432

24 • Brito, J. A., F. E. McNeill, D. R. Chettle, C. E. Webber, C. Vaillancourt. 2000. Study of the  
25 relationships between bone lead levels and its variation with time and the cumulative blood lead  
26 index, in a repeated bone lead survey. J Environ Monit 2:271-276. DOI: 10.1039/b002855j  
27 PMID: 11256712

28 • Fleming, D. E., D. Boulay, N. S. Richard, J. P. Robin, C. L. Gordon, C. E. Webber, D. R.  
29 Chettle. 1997. Accumulated body burden and endogenous release of lead in employees of a lead  
30 smelter. Environ Health Perspect 105:224-233. DOI: 10.1289/ehp.97105224 PMID: 9105798

31 • Fleming, D. E., D. R. Chettle, J. G. Wetmur, R. J. Desnick, J. P. Robin, D. Boulay, N. S.  
32 Richard, C. L. Gordon, C. E. Webber. 1998b. Effect of the delta-aminolevulinatase  
33 polymorphism on the accumulation of lead in bone and blood in lead smelter workers. Environ  
34 Res 77:49-61. doi: S0013-9351(97)93818-4 [pii]10.1006/enrs.1997.3818.

35 • Fleming, D. E., D. R. Chettle, C. E. Webber, E. J. O'Flaherty. 1999. The O'Flaherty model of  
36 lead kinetics: An evaluation using data from a lead smelter population. Toxicol Appl Pharmacol  
37 161:100-109. doi: 10.1006/taap.1999.8790 S0041-008X(99)98790-2 [pii].

38 • Nie, H., D. R. Chettle, C. E. Webber, J. A. Brito, J. M. O'Meara, F. E. McNeill. 2005. The  
39 study of age influence on human bone lead metabolism by using a simplified model and x-ray  
40 fluorescence data. Journal of environmental monitoring: JEM 7:1069-1073. doi:  
41 10.1039/b507749d.

42  
43 **Comment** In Chapter 3 section 3.3, authors stated that they were able to obtain blood and bone  
44 lead measurements along with dates of hire and birth dates for 209 smelter workers. However,  
45 authors concluded that the data was not suitable for model evaluation. The authors state:

1  
2       *“Data that were available from the Nie study consisted of three longitudinal blood and bone*  
3 *XRF measurements for 209 adult Pb workers. The measurements were made in 1991, 1999*  
4 *and 2008. This period included a nine-month strike (July 1990 to May 1991), during which*  
5 *exposures at the plant were interrupted. The available data also included birth dates and*  
6 *dates of hire. There were no data on actual exposures at the plant. Although attempts were*  
7 *made to reconstruct exposures so that blood and bone Pb concentrations could be predicted*  
8 *and compared to observations, ultimately, it was concluded that the data were not suitable*  
9 *for model evaluations because of the uncertainty in the exposures that preceded the blood*  
10 *and bone Pb measurements and that occurred during the measurement period. Exposures*  
11 *prior to 1991, including the period of the strike, had to be reconstructed with no basis for*  
12 *verification other than the observed blood and bone Pb measurements.”*  
13

14 This dataset appears to have as much or more detail as those datasets that appear in Figures 4-18  
15 and 4-19 (pages 177-178 TSD 2019). The exposure history of the cohort from 1968 – 1995  
16 appears in Brito et al. 2000 and 2001 and in Fleming et al. 1997. It appears that this group level  
17 blood lead data – by absence of these references – was not considered. An initial assessment of  
18 the 9 retired workers in Nie et al. 2005 by a committee member indicates that lead in trabecular  
19 bone on a ug lead/g bone mineral basis, remains higher than in cortical bone for four or more  
20 years after removal from occupational exposure. However, predictions from the current AALM  
21 inverts this relationship.  
22

## 23 **Charge Question 4c Recommendations**

### 24 **Tier 1**

- 25 • Compare AALM simulation results with the data sets provided to further assess the  
26 capabilities of the model. Particular attention should be paid to the comments provided with  
27 each reference or the group of references associated with Nie et al., 2005 for evaluating whether  
28 the model captures the behaviors described.  
29  
30  
31

## 32 **2.5. Charge Question Five: Is the AALM Fortran Users Guide sufficiently clear and useful** 33 **in providing “user friendly” instructions for carrying out model runs for AALM** 34 **applications? How might the AALM user’s manual be improved?**

### 35 **2.5.1 General Comments Responding to Question Five**

37 The Committee found that the AALM is functional, but not particularly user-friendly. User-  
38 friendly in this context refers to the Excel software interface and whether it is easy to use, and  
39 not difficult to learn or understand. User-friendly interfaces should be simple, well-organized,  
40 intuitive and reliable; should provide a positive experience; and not cause undue frustration for  
41 the user. User-friendly model interfaces are typically more successful and widely used than those  
42 with complex, convoluted difficult interfaces.

1 Several Committee members noted throughout the review that the perception of user-  
2 friendliness, and indeed the effectiveness of the model predictions, depend on the intended use of  
3 the model and the experience level of the user. There seemed to be a consensus that the interface  
4 is sufficiently functional for skilled modelers, but nevertheless requires internet searches to  
5 overcome Excel and operations systems glitches. However, as an Application Guide for broader  
6 range of potential users (e.g., state or local public health official or risk assessors, medical  
7 doctors.); the User's Guide probably discourages those who might otherwise find the model a  
8 useful tool.

9 An illustrative measure of "User Friendly" is a comparison of time expended (and frustrations  
10 vented), by Committee members before and during the open meeting, on making the model run  
11 versus running the model and assessing its effectiveness in blood lead predictions. Only a  
12 minority of members were able to implement and use the model. A disproportionate amount of  
13 time, although useful and instructive, was spent during the meeting toward making the AALM  
14 operational. The Committee requested a tutorial session on how to implement the model to  
15 develop a better understanding of model capabilities and the types of output that can be  
16 produced. The live demonstrations by EPA Staff were immensely helpful. EPA should consider  
17 developing a companion video if releasing the User's Guide in its current format. Additionally,  
18 an appendix could be added to the User's Guide that uses screen shots to provide several  
19 examples of typical uses of the AALM including exposure pathways beyond drinking water and  
20 the user entries that would be required. Training videos for different aspects of the model, such  
21 as each exposure pathway, would be valuable.

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

28 EPA Staff indicated that Question 5 refers to the internal technical specifications stated on page  
29 4 of the User's Guide:

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

36  
37 In that context (its purpose being to implement a FORTRAN Program using an Excel Interface);  
38 the User's Guide is functional, assuming the User has substantial knowledge and familiarity with  
39 similar models. Uninitiated Users would have considerable difficulty and frustration in making  
40 the model operational, making informed modifications, and storing and interpreting the results.  
41 There is little guidance provided, in either of the documents, regarding how to save, connect and  
42 interpret the input and output summaries.

1  
2 There is also confusion as to how and what would be released by EPA should AALM be  
3 endorsed for use by the Agency. It is unclear whether the earlier support documents and previous  
4 "... the more extensive AALM.CSL documentation ..." part of the package, as item 3 above  
5 would suggest. There were references to Batch Mode simulations and other options available in  
6 the ACSL edition not available in the FORTRAN version and indications that there were  
7 additional compartments in some of the biokinetic modules.

8  
9 As these materials were not provided to the Committee, it was difficult to assess the adequacy of  
10 the User's Manual in this context.

## 11 12 **2.5.2 Specific Comments and Suggestions by Section**

13  
14 **Front Material:** The Cover Page does not include Authors, Project Officers, responsible Agency  
15 Division, Contract References or Contact information. There is no link to an "Assistance or  
16 Help" resource. The Table of Contents is minimal and does not contain a Preface, List of Tables,  
17 Figures, Screens, or a Glossary. These are ostensibly available in the Technical Support  
18 Document and were provided in the Draft 2005 Guidance Manual. However, in some cases the  
19 descriptions in the Technical Support Document are insufficient to aid in implementing the  
20 model, and it is cumbersome to move between two documents that are seemingly connected, but  
21 not referenced to each other. Numbering the figures and tables would help users quickly find the  
22 correct one without searching through the text.

23  
24 **Section I.** Introduction is brief and, for an uninitiated reader, provides minimal information as to  
25 the background, purpose, development, informative descriptions, historical evolution, intended  
26 or potential uses, biological and physical plausibility, computational accuracy, validation,  
27 empirical comparisons. Summary descriptions of these attributes would typically be expected in  
28 a User's Guide with specific reference to the Technical Support Documents. In this case, the  
29 User must refer to the Technical Support Document without references or refer to documents  
30 from earlier versions of the AALM. The Committee suggests adding a sub-section to the  
31 Introduction describing Model Limitations, identifying where data are missing or weak, and  
32 where simplifying assumptions are made.

33  
34 It is unclear if the final sentence in this section applies to the original Leggett model, or to this  
35 document:

36 *This approach was designed to provide maximum flexibility and versatility rather than user-*  
37 *friendliness.*

38  
39 **Section II.** Overview of the Excel User Interface discusses the Excel user interface file, an input  
40 file template, the Leggett executable, and supplemental files (User's Guide and Leggett model  
41 text file). The explanation of the "pieces" is confusing. There are other Tabs in the interface file  
42 that are not discussed. It is not clear that that the "input file template" are some of the Tabs in the  
43 interface file. There is a second Excel file called the Intermediate Exposure Time Series file that  
44 is not referenced or explained. Committee members were not able to locate the "Leggett text  
45 files" indicated. The executable file is problematic in that it gives no other indication it is  
46 functional other than a "blink" of a black rectangle on the screen.

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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 don’t work, 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 if 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” although there are two Excel files provided and the instructions apply alternatively to both. Nowhere in the Guide does it describe the purpose and function of the Intermediate File, except as a summary of the lead input to the biokinetic module, although it does suggest this file is vital to execute the model. The instructions to add a runtime library to this Excel file are confusing. Several committee 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.

1  
2 A caution should be added to enable Macros in all Excel files after enabling editing. This should  
3 be mentioned before trying to implement the VB Editor. A screen shot indicating the yellow bar  
4 etc. would be helpful.

5  
6 The reviewed document's Subsection 2 addresses completing the **Simulation Control Tab**.  
7 EXPAGE, NDELTA, TSTOP should be defined in the text. The entire concept of Simulation Time  
8 and Time Steps is sometimes confusing in both the User's Guide and Support Document. A  
9 clarification of both the rationale for time steps in modeling and the mechanics of implementing  
10 time steps to make the model perform accordingly would help uninitiated users.

11  
12 Several committee members endorsed USEPA internalizing the entire Time Step procedure and  
13 with an appropriate algorithm that would allow the User to simply select the simulation Time  
14 Step for the model and the frequency of the output. This would avoid having to include  
15 confusing statements such as:

16  
17 *One final nuance: TSTOP and the total number of cycles may not actually match each other*  
18 *based on user input, and the FORTRAN code will use whichever is shorter. If TSTOP = 80, the*  
19 *actual simulation period will be 80 days. On the other hand, if TSTOP = 180, the actual*  
20 *simulation period will be 137.5 days (the number of cycles specified in the time step input table).*

21  
22 The historic note regarding computer capacity in the Leggett era is interesting but perhaps better  
23 in a footnote or Appendix, as the recommendation for current use is the important message here.  
24 There are several "asides" throughout the document referring to nuances and notes regarding  
25 situations the programmers encountered in converting the codes that might be moved to a Notes  
26 section in the Appendices.

27  
28 Some description of the considerations for TSTOP would be advisable. Discussion regarding  
29 changing the NDELTA is confusing. The reference to entering the value of DELTA in cell H20 is  
30 somewhat confusing as the DELTA value is entered in cell I20. Also, the text indicates that Time  
31 Steps 2, 3 etc. should be entered in H21, H22 etc., but these are not colored yellow to indicate  
32 allowable input. Should the user do the Step numbers in these cells? The example on page 11  
33 indicates NDELTA=3 (two different time steps). Should this not be 3 total time steps or 2  
34 additional time steps? Shouldn't there be a warning issued regarding the "one final nuance"?

35  
36 The variable CINT should be defined including units if any. The cell defining CINT (D35)  
37 defaults to the inverse of cell I20 after each run. This results in the output being produced for  
38 each inverse of the DELTA value (which was highly recommended to be a fraction of a day)  
39 resulting in cumbersome output. Obtaining a reasonable output frequency seems to require  
40 overriding the default and entering some fraction of the ICYC. Additionally, program errors have  
41 occurred on some runs referencing the CINT value as division by 0, if an actual number is not  
42 entered.

43  
44 Saving the Intermediate Exposure Time Series.csv file does summarize the inputs to the Leggett  
45 biokinetic modules. However, there is no apparent way to save a Table indicating inputs to the

1 Simulation Control Tab and Exposure Tabs, and Model Run Parameters corresponding to the  
2 output file as opposed to summarizing the calculated inputs to the biokinetic model.

3  
4 In the discussion of interpolated versus stepwise exposure time series, the term “time stamps” is  
5 used but never defined. When selecting either stepwise or interpolated exposures and it is unclear  
6 if the selection applies to all exposures.

7  
8 The reviewed document’s Subsection 3. Exposure Input Tabs describes the inputs for the  
9 exposure modules. Each of these Tabs is relatively straight forward. There is confusion related  
10 to the discrete and pulse fractions concerning whether the combination of these must total one  
11 or if a pulse can overlap a discrete exposure. It is unclear how the discrete component relates to  
12 the Baseline in the Pulse exposure? Step 2 is not intuitive, though logically it makes sense that  
13 pulse trains need to be specified for some period of time, with some intervening interval. The  
14 Guide would greatly benefit from more examples of screen shots with various entries, followed  
15 by a summary table.

16  
17 The text indicates that, presumably internal, programming to translate exposure profiles into the  
18 Leggett model is intricate and refers to a “tool” that accomplishes this translation. It is unclear  
19 why this is of interest to the user or what tool this references.

20  
21 The reference to the “tool” also discusses the application of the RBA tab. The text indicates that  
22 the user should specify a “generic” bioavailability for (e.g., food) and then relative  
23 bioavailability for the other media compared to food. This description could be at odds with the  
24 use of the term relative bioavailability in other USEPA applications, usually related to particular  
25 lead salts dissolved in water. The discussion here should be amended to reflect bioavailability  
26 determinations consistent with other EPA models and Programs.

27  
28 The discussions regarding nuances of the AALM.CSL verse AALM.FOR are likely of concern  
29 to the programmers doing the conversion but inclusion of the notes in a User’s Guide is not  
30 necessary, e.g.:

31 *The user interface has to translate these profiles into the format used by the Leggett model.*  
32 *Again, this process is seamless in AALM.CSL but is fairly intricate in AALM.FOR.*

33  
34 Section 4. Necessary Changes to the Biokinetic Input Tabs briefly notes the location of  
35 biokinetic parameters but provides little information regarding these variables. Any  
36 considerations for changing these values would be referred to the Support Documentation which,  
37 in some instances, is insufficient to support any changes. This Section references the Pounds.dat  
38 output file that has never been described throughout the document.

## 39 40 **Charge Question 5 Recommendations**

### 41 42 **Tier 1**

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

1

2 **Tier 2**

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

12 **Tier 3**

- 13 • EPA develop a more “modern dashboard” interface if the model goes forward in a  
14 substantially modernized format.  
15

16 **2.6. Charge Question Six: How could specific features of the AALM be further refined to**  
17 **improve its predictive accuracy?**

18 Throughout its responses to previous charge questions, the committee has noted features that  
19 could be improve the predictive accuracy of the model.  
20

21 Fecal Excretion and Mass Balance

22  
23 While it would only impact matching fecal data and calculating mass balance, it appears that  
24 correcting for the RBA (p8 lines 2-4, pdf p 19) would not be difficult. The exposure model  
25 currently passes the RBA adjusted intake to the biokinetic model, so presumably the remainder  
26 (1-RBA adjusted intake) would be added to fecal excretion to obtain the output. Similarly,  
27 corrections would be made to the mass balance equations. This was not an issue in AALM.CSL  
28 but arose in AALM.FOR (Table 3-3 p 72, pdf p83) and the functionality/output affected.  
29

30 Addressing Particle Size

31  
32 The absence of airborne Pb aerodynamic particle diameter is a limitation as noted previously  
33 especially in Charge Question 3b. Pb from engine exhaust is sub-micrometer in diameter, so it  
34 has high deposition in the alveoli (and access to macrophage degradation, and proximity to a rich  
35 blood supply), while Pb from other sources (paint sanding and removal, metal grinding,  
36 resuspended dirt, Pb paint spray, and Pb powder dispersion) will be well above 1 micrometer  
37 and well above 10 um mass median aerodynamic diameter (MMAD) and have high bronchial  
38 deposition (with little blood access), and in many cases no deposition in alveoli (Petito Boyce et.  
39 *al.*, 2017). Adding particle size categories (e.g., ultrafine, fine and coarse) would improve  
40 accuracy and applicability to realistic exposures. It will also tie into EPA's air monitoring  
41 network.

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### Integration Algorithm

Add a variable-step predictor-corrector algorithm such as the Adams method or the Gear implicit method. These methods specify the acceptable error in the simulation or further explain the approach used for controlling numerical integration error during the model simulations, as described in section 2.3.1. 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.

### 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 BLL 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 p92), 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 as expected (i.e. on average a near zero difference in slope of the BLL relative to days of workplace exposure).

Consider using Hattis's method for examining model performance relative to length of job tenure (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 BLLs after a 273-day strike that are too low on average for workers with shorter job tenures with a trend toward predicting higher BLLs on average for workers with longer tenures. The goal is to have no trend across the range of job tenures and predicted BLLs. 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.

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## Pregnancy, Fetal and Infant Exposures

Add a gestation model for the fetus. 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, but 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 should be changed. This functionality (or lack thereof) needs to be further explained at least, but preferably would be made active in the model.

## **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.

## **2.7. Charge Question Seven: How could specific features of the AALM be further refined to make it more user-friendly?**

The Committee discussed a wide range of ideas to improve the model’s overall functionality as well as applicability for a broader range of scenarios. Many Committee members found it challenging to navigate the user interface. The Committee 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

1 example of EPA’s Benchmark Dose Software (BMDS) – presumably referring to earlier -  
2 versions, given that the current version utilizes an Excel workbook interface.

3 The committee felt that it would be beneficial for the broad range of stakeholders to be able to  
4 use this model. It is highly likely that it could have quite valuable roles in public health practice  
5 and research, as well as in risk assessment and risk management. For the model to be broadly  
6 accessible and user friendly, it needs to be structured to readily accept the kinds of information  
7 that are available to public health professionals (e.g., dust lead loading, as reported by public  
8 health agencies in mcg/ft<sup>2</sup>), and researchers as well as risk assessors.

9 In addition, as noted in charge question 5, well-developed training materials would be beneficial  
10 to anyone trying to learn to use a model of this complexity. The tutorial provided the Committee  
11 was very helpful and availability of such presentations as pdfs as well as videos of tutorials  
12 would be useful. Such materials would help guide users toward appropriately applying and  
13 using good modeling practices given the complexity of this model.

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

## 16 **Charge Question 7 Recommendations**

17

### 18 **Tier 1**

19 • Create a library of input files (or example Excel workbooks) that correspond with example  
20 scenarios. Then use those scenarios as part of the User’s Guide and other training materials to  
21 coach new users on various common scenarios, and how to populate the dialogue boxes. The  
22 current User’s Guide gives an example for water intake. The Committee recommends providing  
23 at least one example for each exposure pathway and environmental medium.

24 • Improve the consistency in naming conventions for model input variables between the user  
25 interface (Excel file) and the accompanying documentation.

26

### 27 **Tier 2**

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

31

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

33

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

36

37 • Create a single worksheet for risk characterization. It might apply an assumed lognormal  
38 distribution model and generate a plot is automatically (also see response for charge question 9  
39 on approaches to addressing variability and uncertainty). Include a short set of entries at the top  
40 of the page that are dynamic (i.e., change the plots when the entries are changed). Incorporate  
41 user-specified GSD and age ranges to display. Include a tabular summary of common risk

1 metrics: 1) probability of exceedance of user-specified threshold; 2) predicted blood lead  
2 concentration at user-specified percentile.

3  
4 • As part of the Simulation Control worksheet, include an option (toggle) for the user to enter a  
5 constant media concentration for each of the common exposure media (e.g., soil, dust, air, water,  
6 etc.), as an alternative to populating the age-specific concentrations in each separate worksheet.  
7 This should allow entry in units that arise in a range of different settings, including for example  
8 amount of Pb per square foot for dust ug/ft<sup>2</sup> in addition to the currently entered ug/g. Similarly,  
9 enhance the model to allow for user entered Blood Lead Levels (BLL) rather than having to  
10 “create” an exposure to obtain a given BLL.

11  
12 • Consider including the Adult Lead Model directly in the current workbook such that entries  
13 are automatically populated (linked) to the entries specified by the user when running AALM.  
14 As a research tool, this will facilitate the understanding of AALM’s application in a risk  
15 assessment context, including features that have been enhanced and/or changed.

16  
17 • Create additional user options to specify parameters for the relative bioavailability (RBA)  
18 term. Currently, a single RBA applies to all intakes for a specific exposure medium as previously  
19 noted in charge question 3b. This seems counter to the model’s flexibility in allowing for  
20 multiple values of Pb intake in soil or dust at different times of the day (or week). It seems likely  
21 that the soil or dust in different occupational, residential, and public setting may have different  
22 solubility, particle size, and chemical composition, and by extension different RBA.

23  
24 • How to effectively implement age-related changes in food intake needs to be clarified in the  
25 model documentation and examples created. EPA should consider including an appendix to the  
26 model documentation of suggested sources or values for age specific intake rates or other  
27 parameters needed for implementing this pathway?

28  
29  
30 • Since this is a life-stage model and simulations can be started from birth, accounting for  
31 breast milk exposure would be essential. Add text to explain how it can be done.

### 32 33 **Tier 3**

34 • Consider a module that allows for exposure or kinetics parameters to be modified to account  
35 for co-exposures to other chemicals. Exposure to lead typically occurs in conjunction with  
36 simultaneous exposures to other heavy metals of concern to human environmental health,  
37 especially susceptible populations. AALM may sufficiently model Pb exposures in most  
38 scenarios, although it seems monolithic in that it cannot model exposures to real-life exposures  
39 to multiple metals. This should be viewed as a limitation of the model, possibly significant,  
40 especially when one considers the weight of evidence in the published scientific literature that  
41 Pb, Mn, Hg and other metals may converge on absorption, transport, metabolic, and  
42 neurotoxicity pathways.

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**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 Panel agreed that the model documentation and development processes for the AALM have generally been consistent with the EPA 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 another 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 controlled studies and designed experiments. The Panel 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, Panel members were able to find it at: [https://www.epa.gov/sites/production/files/2015-04/documents/cred\\_guidance\\_0309.pdf](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 present version of Technical Support Document 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, is needed. 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 final part of Charge Question 3, the Panel 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:

1  
2 Tables of key uncertainties of inputs and outputs: These tables should make key uncertainties  
3 clear to model users and risk assessors.  
4

5 It should be clearly conveyed to users that uncertainty in model outputs will vary. For example,  
6 there are simply more data sets available with measured blood lead versus brain lead levels and  
7 there is thus more uncertainty around the prediction of brain lead.  
8

9 The WHO/IPCS PBPK Guidance (WHO/IPCS 2010) contains tables for characterizing  
10 uncertainty and variability could be useful in uncertainty evaluation for the AALM. It is  
11 recommended that the Agency evaluate this document and include similar tables in the  
12 documentation for the AALM.  
13

14 Specification of uncertainties should then focus future research efforts to address those needs.  
15

16 Bayesian statistical analysis using Markov Chain Monte Carlo methods incorporates parameter  
17 correlations and should be performed on at the very least, blood lead, in order to obtain  
18 uncertainty estimates in kinetic parameters. Separate analyses should be performed for  
19 biokinetics and for the exposure module in order to obtain uncertainty estimates for the two  
20 separate parts of the model. MCSim, which is free software, can be used to perform Bayesian  
21 analyses and can be found at: <https://www.gnu.org/software/mcsim/> (accessed March 12, 2020).  
22

23 There are numerous parameter values included in this model, and many of the variable value  
24 selections should not be made in isolation. In addition to uncertainty analyses, additional  
25 sensitivity analyses might be conducted that examine the effects of multiple variable interactions.  
26 These findings might lead to additional guidance cautions about the appropriate ranges and other  
27 parameter settings that might be considered in altering input values.  
28

29 An understated strength of this model is that it can be applied across a large range of biological  
30 effects, age and exposure/dose considerations. There is an unfortunate tendency in Agency  
31 efforts to focus modeling and research efforts on current US exposure levels. This model is also  
32 applicable to the higher levels of lead intoxication observed globally in vulnerable populations. It  
33 could be of immense service to international institutions implementing health and environmental  
34 responses. The calibration and verification efforts should continue to be across the full range of  
35 lead intoxication levels previously observed in the US.  
36

37 It may be useful to compare the data used in Leggett's original model and the updated AALM to  
38 develop and/or update parameters values with criteria listed in the CREM guidance on study  
39 quality. Attributes of study quality are also addressed in a series of articles on this subject  
40 written by Leggett and colleagues; these articles should be evaluated by the Agency. In addition,  
41 comments about the quality of data used to calibrate and test model parameters from the original  
42 Leggett (1993) publication should be extracted and commented on in the technical guidance.  
43 The assumptions, rationale, and limitations of parameter values listed in the original Leggett  
44 model should also be checked and commented on.  
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## 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).<sup>1</sup> 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 90<sup>th</sup> 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

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<sup>1</sup> 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).

1 2009). For each of the foregoing assumptions, OEHHA entered various default values in the  
2 respective models for parameters such as exposure frequency, soil intake rate, and geometric  
3 standard deviation. Intake of lead from other pathways was considered to be zero. For the adult  
4 worker scenario, the geometric mean background blood lead concentration was assumed to be  
5 0.6 µg/dL.  
6

7 It may be envisioned that the AALM could be utilized to address questions of a similar nature  
8 relating soil exposure to estimated increment in blood lead. The design of the AALM requires  
9 assumptions about prior lifetime lead exposure history and the corresponding lead content of  
10 various tissue compartments. This could be addressed by developing certain generic datasets or  
11 libraries of past lead exposure depicting representative lifetime lead exposure patterns for various  
12 receptors, such as a two-year-old child, or a 25-year-old male or female adult. When used in  
13 conjunction with the AALM, these datasets could be used as a point of departure to solve for a  
14 certain concentration and pattern of soil lead exposure (e.g. exposure to X ppm of lead in soil for  
15 90 consecutive calendar days, or 250 consecutive work days) that would be associated with a  
16 benchmark increment in blood lead concentration (e.g. 1 µg/dL). As currently structured, the  
17 AALM would yield an exposure that would apply to a benchmark blood lead increment at the  
18 central tendency, or median. Application of methods to estimate variability around the central  
19 tendency, e.g. by use of an assumed GSD or Monte Carlo modeling, could be added to the  
20 AALM to yield medium-specific lead values that would yield a benchmark change in blood lead  
21 to the 95<sup>th</sup> percentile receptor.  
22

### 23 **2.9.2. Population variability in AALM outputs to facilitate use in risk assessment and risk** 24 **management**

25  
26 As noted above, the current construction of the AALM.FOR yields outputs for tissue  
27 compartments, such as blood lead, that represent central tendency estimates derived from the  
28 selected exposure inputs and biokinetic settings. While these central tendency estimates are  
29 informative, risk managers often require outputs that also present tissue concentration such as  
30 blood lead at the upper end of a population distribution, e.g. the 95<sup>th</sup> percentile. For example, the  
31 IEUBK model is used in risk assessment to calculate the geometric mean blood lead  
32 concentration, the 95-percentile confidence interval about the geometric mean, and the 95<sup>th</sup>  
33 percentile of the lognormal distribution. The latter value represents the blood lead concentration  
34 that will be exceeded by no more than 5% of children subject to the exposure inputs (e.g. soil  
35 lead concentration) of the modeled situation. IEUBK calculates the 95<sup>th</sup> percentile using a  
36 geometric standard deviation (GSD) that is intended to capture the variability in everything  
37 except the concentration term. Specifically, the GSD incorporates variability inherent in behavior  
38 that contributes to the exposure (such as hand to mouth activity), relative bioavailability of lead  
39 in soil, and biokinetics. EPA has long recommended the default GSD of 1.6, although use of  
40 site-specific GSD is permissible.  
41

42 Several approaches would be possible to depict variability around central tendency estimates  
43 generated by AALM.FOR. As with the IEUBK, it would be possible to assume that the  
44 population distribution is lognormal and can be calculated using an assigned GSD. Some  
45 panelists cautioned that unlike the long term experience with IEUBK that has validated the use

1 of a default GSD of 1.6 for childhood blood lead, there is insufficient data and experience with  
2 the AALM.FOR to identify a default GSD valid for the myriad of settings and age ranges for  
3 which the model is intended.

4  
5 Probabilistic methods, incorporating Monte Carlo simulations for exposure and biokinetic  
6 parameters, would represent an alternative approach to estimation of variability in AALM.FOR.  
7 Monte Carlo modules have been developed for use with IEUBK (Goodrum *et al.*, 1996), for the  
8 O’Flaherty model applied to childhood blood lead (Beck *et al.*, 2001), and for the O’Flaherty  
9 model applied to adults with occupational lead exposure (Sweeney, 2019). Panelists suggested  
10 that variability in the AALM.FOR outputs could be generated using either conventional (random  
11 seed) Monte Carlo methods, or Markov chain methods, applied to both exposure and biokinetic  
12 parameters.

### 14 **2.9.3. Multiple user-friendly model outputs**

15  
16 A key area of research is to develop a better understanding of what measures of lead in the body  
17 best relate to neurotoxicological outcomes. Since AALM calculates lead levels in blood and  
18 different tissues, it could assist in research on such questions. What measures of lead in blood  
19 (e.g., circulating unbound lead levels, average daily lifetime blood lead level, area under the  
20 curve for blood concentration, cumulative blood lead levels), brain, or bone would be most  
21 informative about health outcomes? Would expansion of the brain model beyond a single  
22 compartment be useful? Is there an “ideal” bone for measuring lead deposits, what contributes to  
23 the differences, and what role does bone injury play in re-exposure to deposited lead?

24  
25 Pb in bone, as measured by non-invasive K x-ray fluorescence (KXRF) has been shown in  
26 various studies to be a biomarker of an individual’s blood lead level over time (cumulative blood  
27 lead index, or CBLI). As reported in several publications from the Normative Aging Study, a  
28 person’s bone lead concentration at mid to late life, or an increment bone lead concentration  
29 across a given age strata, are better predictors than blood lead (or change in blood lead) of  
30 significant health endpoints such as cardiovascular morbidity and mortality and cognitive  
31 function. The ability of the AALM to include bone lead concentration as an output is likely to be  
32 helpful for risk assessment. By reference to investigations such as the Normative Aging Study,  
33 this information may facilitate assessment of the health risks associated with cumulative lead  
34 exposure.

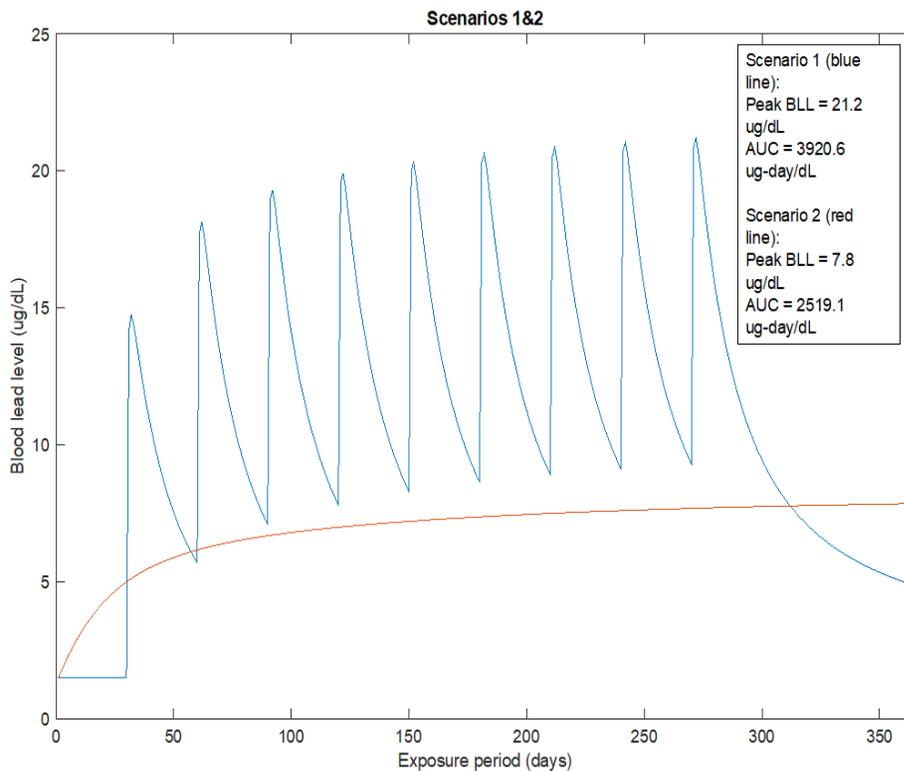
35  
36 The validity of KXRF as a biomarker of cumulative lead has primarily been established by  
37 favorable comparison of a single KXRF measurement to long term blood Pb biomonitoring in  
38 occupational cohorts. In most cases, the Pb exposure of these cohorts has been relatively stable  
39 for many years, (sometimes with a gradual decline over time). Based on this data, Person A with  
40 a cumulative blood lead index (CBLI) of 300  $\mu\text{g}/\text{dL}\cdot\text{years}$  will predictably have a higher KXRF  
41 bone lead concentration than person B with a CBLI of 200  $\mu\text{g}/\text{dL}\cdot\text{years}$  where Person A  
42 sustained 20 years of blood lead of 15  $\mu\text{g}/\text{dL}$  and person B sustained 20 years of blood lead of 10  
43  $\mu\text{g}/\text{dL}$ . However, it’s not clear how the KXRF bone lead measurements would compare if Person  
44 B’s CBLI of 200  $\mu\text{g}/\text{dL}\cdot\text{years}$  were instead accrued through 15 years of blood lead of 5  $\mu\text{g}/\text{dL}$

1 followed by 5 years of blood lead of 25  $\mu\text{g}/\text{dL}$ . Outputs from the AALM that include estimated  
2 bone lead burden is likely to facilitate research into the utility of KXRF as a biomarker.

3  
4 In like manner, a few epidemiological studies have found that CBLI is a significant predictor of  
5 adverse health effects. This metric may grow in use in the future. It would be useful for  
6 AALM.FOR to calculate CBLI (essentially the area under the curve of blood lead by time plot)  
7 as an output. For example, this may be helpful in illustrating how infrequent exposure to high  
8 levels of lead in air, e.g. during infrequent maintenance work, might result in considerably more  
9 cumulative lead exposure than regular daily exposure at lower levels.

10  
11 For example, the consider two scenarios evaluated by the OEHHA Leggett+ model. The area  
12 under the curve (AUC) in the model represents CBLI for this time interval.

13  
14 Scenario I. A 25 year old worker who starts work with a BLL of 1.5, and whose only lead  
15 exposure for the next year is one 8 hour day, once a month for 9 months, engaged in heavy work  
16 (breathing rate of  $8.67 \text{ m}^3/8 \text{ hour}$ ) where the airborne lead is  $500 \text{ ug}/\text{m}^3$ . The second scenario is  
17 the same worker, but this time he begins work characterized by moderate exertion, 5 days a  
18 week, for 12 months, at an air lead concentration of  $10 \text{ ug}/\text{m}^3$ . Over the course of one year, AUC  
19 for scenario 1 =  $3075 \text{ ug}\cdot\text{day}/\text{dL}$ , for scenario 2 it is  $2477 \text{ ug}\cdot\text{day}/\text{dL}$ . This illustration depicts the  
20 pitfall of exempting workers with only infrequent lead exposure from medical surveillance.



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

#### 5 **2.9.4. Comparison of multiple model simulations**

6  
7 Users will likely want to compare blood lead (and other tissue lead) levels across multiple  
8 exposure scenarios simultaneously (*e.g.* varying the exposure terms, varying exposure frequency  
9 or periodicity, varying exposure cessation). To the extent possible, the panel recommends that  
10 this functionality be made available and easy to use. For example, the option to run multiple  
11 exposure scenarios with blood or tissue lead levels reported on a single graph would enhance  
12 efficient communication of results. Capabilities for batch runs and plotting the results could also  
13 be valuable.

#### 14 **2.9.5. Assessing exposure due to paint**

15  
16 Guidance on how to estimate and assess lead exposure from lead-based paint would be useful  
17 (maybe in the context of presenting some examples with real-world exposures/exposure  
18 patterns). Estimates of how much paint children might ingest at different ages and examples that  
19 estimate lead intake based on the lead content of paint from XRF measurements would be much  
20 appreciated. There is probably a lot of uncertainty around these types of data but even some  
21 guidance on recommended values would be helpful. Any guidance on how to evaluate cases  
22 with paint exposures or lead from other sources (pottery, dishes, etc.) would be helpful.  
23

### 24 **Charge Question 9 Recommendations**

#### 25 **Tier 1**

26  
27 • Augment the current model outputs to include metrics that are under active research  
28 investigation, such as cumulative blood lead index (CBLI) and concentration of lead in cortical  
29 and trabecular bone (ppm), and evaluate whether model outputs of values or graphs can be made  
30 more user-friendly.  
31

#### 32 **Tier 2**

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

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This draft is a work in progress, does not reflect consensus advice or recommendations, has not been  
reviewed or approved by the chartered SAB and does not represent EPA policy.**

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**Tier 3**

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

### 3. REFERENCES

- 1  
2  
3  
4 Asgharian, WH; Hofmann, W; Bergmann, R. (2001) "Particle deposition in a multiple-path  
5 model of the human lung." *Aerosol Sci. Technol.* 34(4):332-339  
6  
7 Beck BD, Mattuck RL, Bowers TS, Cohen JT, O'Flaherty E. (2001) The development of a  
8 stochastic physiologically-based pharmacokinetic model for lead. *Sci Total Environ.* 274(1-  
9 3):15-19. PMID: 11453291  
10  
11 Behinaein S, Chettle DR, Fisher M et al. (2017) Age and sex influence on bone and blood lead  
12 concentrations in a cohort of the general population living in Toronto. *Physiol Meas.* 38:431 -  
13 451  
14  
15 Bergdahl, IA; Sheveleva, M; Schutz, A; Artamonova, VG; Skerfving, S. (1998). Plasma and  
16 blood lead in humans: Capacity-limited binding to delta-aminolevulinic acid dehydratase and  
17 other lead-binding components. *Toxicol Sci* 46: 247-253.  
18 <http://dx.doi.org/10.1093/toxsci/46.2.247>  
19  
20 Brito, J. A., McNeill F.E., Stronach I., Webber C.E., Wells S., Norbert R., Chettle D.R., (2001)  
21 Longitudinal changes in bone lead concentration: Implications for modelling of human bone lead  
22 metabolism. *J Environ Monit* 3:343-351. DOI: 10.1039/b101493p PMID: 11523432  
23  
24 Brito, J. A., F. E. McNeill, D. R. Chettle, C. E. Webber, C. Vaillancourt. (2000) Study of the  
25 relationships between bone lead levels and its variation with time and the cumulative blood lead  
26 index, in a repeated bone lead survey. *J Environ Monit* 2:271-276. DOI: 10.1039/b002855j  
27 PMID: 11256712  
28  
29 CalEPA (California Environmental Protection Agency). (2009). Revised California human  
30 health screening levels for lead. Office of Environmental Health Hazard Assessment: California  
31 Environmental Protection Agency. September 2009b.  
32 <https://oehha.ca.gov/media/downloads/crn/leadchhsl091709.pdf>  
33  
34 CalEPA (California Environmental Protection Agency). (2012). Technical Support Document  
35 for Exposure Assessment and Stochastic Analysis. [https://oehha.ca.gov/air/crn/notice-adoption-](https://oehha.ca.gov/air/crn/notice-adoption-technical-support-document-exposure-assessment-and-stochastic-analysis-aug)  
36 [technical-support-document-exposure-assessment-and-stochastic-analysis-aug](https://oehha.ca.gov/air/crn/notice-adoption-technical-support-document-exposure-assessment-and-stochastic-analysis-aug)  
37  
38 CalEPA (California Environmental Protection Agency). (2013). Estimating workplace air and  
39 worker blood lead concentration using an updated Physiologically-based Pharmacokinetics  
40 (PBPK) model. [https://oehha.ca.gov/air/document/estimating-workplace-air-and-worker-blood-](https://oehha.ca.gov/air/document/estimating-workplace-air-and-worker-blood-lead-concentration-using-updated-pbpk-model)  
41 [lead-concentration-using-updated-pbpk-model](https://oehha.ca.gov/air/document/estimating-workplace-air-and-worker-blood-lead-concentration-using-updated-pbpk-model)  
42

- 1 Carlisle JC, Dowling KC, Siegel DM, Alexeeff GV. (2009) A blood lead benchmark for  
2 assessing risks from childhood lead exposure. *J Environ Sci Health A Tox Hazard Subst Environ*  
3 *Eng. Oct;44(12):1200-8.* doi: 10.1080/10934520903139829 PMID: 19847706  
4
- 5 Chamberlain, AC. (1985) Prediction of response of blood lead to airborne and dietary lead from  
6 volunteer experiments with lead isotopes. *Proc R Soc Lond B Biol Sci.* 224 (1235): 149-182.  
7
- 8 Christoffersson JO, Ahlgren L, Schutz A, Skerfving S, Mattson S. (1986) Decrease of skeletal  
9 lead levels in man after end of occupational exposure. *Arch Environ Health* 41:312-318.  
10
- 11 Deshommes E, Prévost M. (2012) Pb particles from tap water: bioaccessibility and contribution  
12 to child exposure. *Environ Sci Technol.* Jun 5;46(11):6269-77. doi: 10.1021/es2045585. Epub  
13 2012 May 11. Erratum in: *Environ Sci Technol.* 2012 Dec 18;46(24):13559-60. PMID:22540891  
14
- 15 DeSilva, PE. (1981). Determination of lead in plasma and studies on its relationship to lead in  
16 erythrocytes. *Br J Ind Med* 38: 209-217.  
17
- 18 Dixon SL, Gaitens JM, Jacobs DE, Strauss W, Nagaraja J, Pivetz T, Wilson JW, Ashley PJ.  
19 (2009) Exposure of U.S. children to residential dust lead, 1999-2004: II. The contribution of  
20 lead-contaminated dust to children's blood lead levels. *Environ Health Perspect.* 117(3):468-74.  
21 doi: 10.1289/ehp.11918. Epub 2008 Nov 14. PMID: 19337524  
22
- 23 Fleming, D. E., D. Boulay, N. S. Richard, J. P. Robin, C. L. Gordon, C. E. Webber, D. R.  
24 Chettle. (1997) Accumulated body burden and endogenous release of lead in employees of a lead  
25 smelter. *Environ Health Perspect* 105:224-233. DOI: 10.1289/ehp.97105224 PMID: 9105798  
26
- 27 Fleming, D. E., D. R. Chettle, J. G. Wetmur, R. J. Desnick, J. P. Robin, D. Boulay, N. S.  
28 Richard, C. L. Gordon, C. E. Webber. (1998b) Effect of the delta-aminolevulinate dehydratase  
29 polymorphism on the accumulation of lead in bone and blood in lead smelter workers. *Environ*  
30 *Res* 77:49-61. doi: S0013-9351(97)93818-4 [pii]10.1006/enrs.1997.3818.  
31
- 32 Fleming, D. E., D. R. Chettle, C. E. Webber, E. J. O'Flaherty. (1999). The O'Flaherty model of  
33 lead kinetics: An evaluation using data from a lead smelter population. *Toxicol Appl Pharmacol*  
34 161:100-109. doi: 10.1006/taap.1999.8790 S0041-008X(99)98790-2 [pii].  
35
- 36 Garza A, Vega R, Soto E. Cellular mechanisms of lead neurotoxicity. *Med Sci Monit.* 2006  
37 Mar;12(3):RA57-65. Epub 2006 Feb 23. Review. PMID: 16501435  
38
- 39 Goodrum PE, Diamond GL, Hassett JM, Johnson DL. (1996). Monte Carlo modeling of  
40 childhood lead exposure: Development of a probabilistic methodology for use with the USEPA  
41 IEUBK Model for Lead in Children. *Human and Ecological Risk Assessment.* 2. 681-708.  
42 Doi:10.1080/10807039609383648.  
43
- 44 Hattis, D. (1981). Dynamics of medical removal protection for lead--A reappraisal. (CPA-81-  
45 25). Cambridge, MA: Massachusetts Institute of Technology, Center for Policy Alternatives.  
46

- 1 Hodgkins DG, Hinkamp DL, Robins TG, Schork MA, Krebs WH. (1991) Influence of high past  
2 lead-in-air exposures on the lead-in-blood levels of lead-acid battery workers with continuing  
3 exposure. *J Occup Med* 33:797-803.  
4
- 5 Hryhorczuk DO, Rabinowitz MB, Hessel SM et al.. (1985) Elimination kinetics of blood lead in  
6 workers with chronic lead intoxication. *Am J Indust Med* 8:33-42.  
7
- 8 ICRP (International Commission on Radiological Protection). (1994). Human respiratory tract  
9 model for radiological protection: A report of a task group of the International Commission on  
10 Radiological Protection. ICRP Publication 66. New York, NY: Pergamon Press.  
11
- 12 ICRP (2006) Human alimentary tract model for radiological protection. (ICRP Pub 100) *Annals*  
13 *of the ICRP* 36:i-i. doi: 10.1016/j.icrp.2006.03.001.  
14
- 15 James, HM; Hilburn, ME; Blair, JA. (1985). Effects of meals and meal times on uptake of lead  
16 from the gastrointestinal tract of humans. *Hum Exp Toxicol* 4: 401-407.  
17
- 18 Kochen JA, Greener Y (1973) Levels of Lead in Blood and Hematocrit: Implications for the  
19 Evaluation of the Newborn and Anemic Patient. *Pediatr. Res.* 7:937-944  
20
- 21 Kosnett MJ, Becker CE, Osterloh JD, et al.. (1994) Factors influencing bone lead concentration  
22 in a suburban community assessed by noninvasive K x-ray fluorescence. *JAMA* 1994; 271:197-  
23 203  
24
- 25 Lach, S., B. Steer, G. Gorbunov, V. Micka, R. Muir. (2014) Evaluation of exposure to airborne  
26 heavy metals at gun shooting ranges. *The Annals of Occupational Hygiene*, 59:307-323.  
27 <https://doi.org/10.1093/annhg/meu097>.  
28
- 29 Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich  
30 KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G,  
31 Graziano J, Roberts R. Low-level environmental lead exposure and children's intellectual  
32 function: an international pooled analysis. *Environ Health Perspect.* 2005 Jul;113(7):894-9.  
33 Erratum in: *Environ Health Perspect.* 2019 Sep;127(9):99001. PMID: 16002379  
34
- 35 Leggett, RW. (1993). An age-specific kinetic model of lead metabolism in humans [Review].  
36 *Environ Health Perspect* 101: 598-616. <http://dx.doi.org/10.1289/ehp.93101598>  
37
- 38 Leggett R, Harrison J, Phipps A. (2007) Reliability of the ICRP's dose coefficients for members  
39 of the public: IV. Basis of the human alimentary tract model and uncertainties in model  
40 predictions. *Radiat Prot Dosimetry* 123:156-170. doi: 10.1093/rpd/ncl104.  
41
- 42 Machida M, Sun SHJ, Oguma E at al.. (2009) High bone matrix turnover predicts levels of lead  
43 among perimenopausal women. *Environ Res* 109:880-886  
44
- 45 Maddaloni, M; Ballew, M; Diamond, G; Follansbee, M; Gefell, D; Goodrum, P; Johnson, M;  
46 Koporec, K; Khoury, G; Luey, J; Odin, M; Troast, R; Van Leeuwen, P; Zaragoza, L. (2005).

- 1 Assessing lead risks at non-residential hazardous waste sites. *Hum Ecol Risk Assess* 11: 967-  
2 1003. <http://dx.doi.org/10.1080/10807030500257838>  
3
- 4 Manton, WI; Cook, JD. (1984). High accuracy (stable isotope dilution) measurements of lead in  
5 serum and cerebrospinal fluid. *Occup Environ Med* 41: 313-319.  
6 <http://dx.doi.org/10.1136/oem.41.3.313>  
7
- 8 Manton WI, Angle CR, Stanek KL et al.. (2000) Acquisition and retention of lead by young  
9 children. *Environ Research. Section A.* 82:60-80.  
10
- 11 Manton WI, Angle CR, Krogstrand KL. (2005) Origin of lead in the United States diet. *Environ*  
12 *Sci Technol.* 39(22):8995-9000. PMID: 16329199  
13
- 14 Miller, FJ; Asgharian, B; Schroeter, JD; Price, O. (2016) "Improvements and additions to the  
15 Multiple Path Particle Dosimetry model." *J. Aerosol Sci.* 99:14-26.  
16 doi:10.1016/j.jaerosci.2016.01.018.)  
17
- 18 Moel DI, Sachs HK, Drayton MA. (1986) Slow, natural reduction in blood lead level after  
19 chelation therapy for lead poisoning in childhood. *AJDC* 140:905-908.  
20
- 21 Nash D, Magder LS, Sherwin R et al.. (2004) Bone density-related predictors of blood lead  
22 among peri- and postmenopausal women in the United States. *Am J Epid* 160:901-911  
23
- 24 Nie, H., D. R. Chettle, C. E. Webber, J. A. Brito, J. M. O'Meara, F. E. McNeill. (2005) The study  
25 of age influence on human bone lead metabolism by using a simplified model and x-ray  
26 fluorescence data. *Journal of environmental monitoring: JEM* 7:1069-1073. doi:  
27 10.1039/b507749d.  
28
- 29 O'Flaherty EJ, Hammond PB, Lerner SI. (1982) Dependence of apparent blood lead half-life on  
30 the length of previous lead exposure in humans. *Fund Appl Toxicol* 2:49-54.  
31
- 32 O'Flaherty, EJ. (1993). Physiologically based models for bone-seeking elements: IV. Kinetics of  
33 lead disposition in humans. *Toxicol Appl Pharmacol* 118; 16-29.  
34 <http://dx.doi.org/10.1006/taap.1993.1004>  
35
- 36 O'Flaherty, EJ. (2000). Modeling normal aging bone loss, with consideration of bone loss in  
37 osteoporosis. *Toxicol Sci* 55: 171-188.  
38
- 39 Petitoyce, C; Sax, SN; Cohen, JM. (2017) "Particle size distributions of lead measured in  
40 battery manufacturing and secondary smelter facilities and implications in setting workplace lead  
41 exposure limits." *J. Occup. Environ. Hyg.* 14(8):594-608. doi: 10.1080/15459624.2017.1309046  
42
- 43 Popovic M, McNeill FE, Chettle DR et al.. (2005) Impact of occupational lead exposure on lead  
44 levels in women. *Environ Health Perspect*; 113:478-484  
45

- 1 Rabinowitz, MB; Wetherill, GW; Kopple, JD. (1976). Kinetic analysis of lead metabolism in  
2 healthy humans. *J Clin Invest* 58: 260-270. <http://dx.doi.org/10.1172/JCI108467>  
3
- 4 Ryu, JE; Ziegler, EE; Nelson, SE; Fomon, SJ. (1983). Dietary intake of lead and blood lead  
5 concentration in early infancy. *Am J Dis Child* 137: 886-891.  
6
- 7 Schutz A, Skerfving S, Christoffersson JO, Ahlgren L, Mattson S. (1987) Lead in vertebral bone  
8 biopsies from active and retired lead workers. *Arch Environ Health*. 42(6): 340-6.  
9
- 10 Schütz A, Skerfving S, Ranstom J, Christoffersson JO. (1987) Kinetics of lead in blood after the  
11 end of occupational exposure. *Scand J Work Environ Health*. 13(6):221-31. PMID: 3616551  
12
- 13 Sherlock, JC; Quinn, MJ. (1986) Relationship between blood and lead concentrations and dietary  
14 lead intake in infants: The Glasgow Duplicate Diet Study 1979-1980. *Food Addit Contam* 3:  
15 167-176. <http://dx.doi.org/10.1080/02652038609373579>  
16
- 17 Silbergeld EK, Schwartz J, Mahaffey K. (1988) Lead and osteoporosis: mobilization of lead  
18 from bone in postmenopausal women. *Environ Res* 47:79-94  
19
- 20 Steuerwald AJ, Blaisdell FS, Geraghty CM, Parsons PJ. (2014) Regional distribution and  
21 accumulation of lead in caprine brain tissues following a long-term oral dosing regimen. *J*  
22 *Toxicol Environ Health A*. 77(12):663-78. doi: 10.1080/15287394.2014.880328. PMID:  
23 24786674  
24
- 25 Symanski E, Hertz-Picciotto I. (1995) Blood lead levels in relation to menopause, smoking and  
26 pregnancy history. *Am J Epidemiol*. 141:1047 – 1058  
27
- 28 Sweeney LM (2015) Evaluation of pharmacokinetic models for the disposition of lead (Pb) in  
29 humans, in support of application to occupational exposure limit derivation Final Technical  
30 Report for the  
31
- 32 Department of Defense, Naval Medical Research Unit. Report No. NAMRU-D-16-11  
33 <https://apps.dtic.mil/dtic/tr/fulltext/u2/1000455.pdf>  
34
- 35 Sweeney, L.M. (2019) Physiologically Based Pharmacokinetic Modeling of Airborne Lead in  
36 Support of Development of an Occupational Exposure Limit for Department of Defense  
37 Workers. AFRL-SA-WP-TR-2019-0003. Available at <http://www.dtic.mil>  
38
- 39 Triantafyllidou S, Parks J, Edwards M (2007) Lead Particles in Potable Water *AWWA Journal*  
40 99(6):107-117 [https://awwa.onlinelibrary.wiley.com/doi/abs/10.1002/j.1551-](https://awwa.onlinelibrary.wiley.com/doi/abs/10.1002/j.1551-8833.2007.tb07959.x)  
41 [8833.2007.tb07959.x](https://awwa.onlinelibrary.wiley.com/doi/abs/10.1002/j.1551-8833.2007.tb07959.x)  
42
- 43 Triantafyllidou S, Gallagher D, Edwards M. (2014) Assessing risk with increasingly stringent  
44 public health goals: the case of water lead and blood lead in children. *J Water Health*. 12(1):57-  
45 68. doi: 10.2166/wh.2013.067. PMID: 24642433  
46

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reviewed or approved by the chartered SAB and does not represent EPA policy.**

- 1 U.S. EPA (U.S. Environmental Protection Agency). (2005) U.S. EPA Technical Review  
2 Workgroup for Lead, Adult Lead Committee Version date 05/19/05.  
3
- 4 U.S. EPA (U.S. Environmental Protection Agency). (2011) Exposure factors handbook: 2011  
5 edition (final) [EPA Report]. (EPA/600/R-090/052F). Washington, DC: U.S. Environmental  
6 Protection Agency, Office of Research and Development, National Center for Environmental  
7 Assessment. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252>  
8
- 9 U.S. EPA (U.S. Environmental Protection Agency). (2013) Integrated science assessment for  
10 lead [EPA Report]. (EPA/600/R-10/075F). Research Triangle Park, NC: U.S. Environmental  
11 Protection Agency, National Center for Environmental Assessment.  
12 <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=255721>  
13
- 14 US. EPA (U.S. Environmental Protection Agency). (2018) Approach taken to Estimate Blood  
15 Lead Levels and Effects from Exposures to Dust-lead EPA, (EPA, June 2018; available at:  
16 <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0166-0571>)  
17
- 18 Vork KL and Carlisle JC (2020) Evaluation and Updates to the Leggett model for  
19 Pharmacokinetic Modeling of exposure to lead in the workplace – Part I adjustments to the adult  
20 systemic model. Journal of Occupational and Environmental Hygiene. In press.  
21
- 22 Webber CE, Chettle DR, Bowins RJ, et al.. (1995) Hormone replacement therapy may reduce the  
23 return of endogenous lead from bone to the circulation. Environ Health Perspect 103: 1150–3.  
24
- 25 WHO/IPCS (2010) Characterization and Application of Physiologically Based Pharmacokinetic  
26 Models in Risk Assessment.  
27 <http://www.inchem.org/documents/harmproj/harmproj/harmproj9.pdf> (accessed March 12, 2020)  
28  
29

## 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 32: BRi is a rate not a fraction

P 27 line 20: Delete “of binding”

P 31 line 35: Change “form” to “from”

P 32 line 12: Delete “up”?

P 32 line 23: Delete “in”

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

P 57 line 26: make “period” plural

P 59 line 33: make “Figures” singular

P 61 line 13: fix “were parameters were”

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

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

P 279 line 8: “TRW” undefined and unreferenced

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

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  $\ln 2$ /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

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

1  
2  
3

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

Exposure	Other	For each discrete age: $Other_{Total_{discrete}} = Other1 + Other_2 + Other_3$
----------	-------	--

4  
5  
6

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: $BRETH = IN_{air_{total}}$
Exposure	Ingested	For combined ingestion pathways: $IN_{ingestion_{total}} = IN_{water} + IN_{dust} + IN_{food} + IN_{other}$
Exposure	Ingested	For input to biokinetics: $EAT = IN_{ingestion_{total}}$

7  
8  
9

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

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

10  
11

Suggest the following:

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

12  
13  
14

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

$$YPLS_0 = \left( YPLS_0 - \left( \frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE * DELT)} + \frac{INRATE}{OUTRATE}$$

15  
16  
17

2. Table B-1.

a. Explanation column for “Sex”: change to “Female or male”

IR_water	unitless	C	S	Female or male
----------	----------	---	---	----------------

18  
19

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
----------	-------	---	---	--

20

- 1 c. Confirm that term “indoor soil” is intentional – is it better defined as simply “soil”?  
 2 p. 257

Age_soil_IR	day	A	F	Age for indoor soil ingestion rate
-------------	-----	---	---	------------------------------------

- 4 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
------------------	-----	---	---	---

8 3. Appendix C

- 9 a. p. 276, table at Line 4: following the units in the footnote, explain the statistics given in the table  
 10 (e.g., mean ± SD; or mean ± SE). Also, missing close parenthesis on header, Floors, sample size.

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

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

5 Units:  $\mu\text{g}/\text{ft}^2$

- 11  
 12  
 13 b. p. 276, line 13: delete the word “of” in the phrase “A value of equal to...”; line 14: add hyphen for  
 14 “soil-derived”; line 15: comma after “e.g.”

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

16 Furthermore, modify the sentence to explain how the corresponding soil Pb concentration is 25  $\mu\text{g}/\text{g}$ , 50  
 17  $\mu\text{g}/\text{g}$ , or 250  $\mu\text{g}/\text{g}$  depending on proximity to historical emission sources and the age of the housing  
 18 stock. In total, suggest the following revision:

19 “A value equal to the soil Pb concentration (i.e., 25, 50, or 250  $\mu\text{g}/\text{g}$ , depending on proximity to  
 20 historical emission sources and age of housing stock – see section on *Soil Lead Concentration* below) is  
 21 recommended for *Dust\_baseline* for simulating residences where soil-derived dust is the major source of  
 22 indoor dust Pb (e.g., no other significant indoor sources such as paint or hobbies).”

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

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Full Transect (n = 4841)	Statewide Average (n = 48)
25 (8, 44) <sup>a</sup>	30 (14, 68) <sup>b</sup>

Units:  $\mu\text{g/g}$ .  
 Statewide average is the average of state means.  
<sup>a</sup>5<sup>th</sup>-95<sup>th</sup> percentile range  
<sup>b</sup>range

- 1  
2 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,  $\mu\text{g/g}$ ; GSD, geometric standard deviation

- 3  
4 Suggest the following notes:  
5 units (GM, median, mean):  $\mu\text{g/g}$   
6 GM, geometric mean; GSD, geometric standard deviation

- 7 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,  $\mu\text{g/g}$ ; GSD, geometric standard deviation

- 8  
9 f. p. 281, line 8, delete extra “e” at end of line  
10 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:

- 11  
12 h. p. 282, table after line 3 – include a second column for Age that provides equivalent years

Age (days)	Water Intake (L/day)	Age (days)	Age (years)	Water Intake (L/day)
0	0.20	0	0	0.20
90	0.30	90	0.25	0.30
365	0.35	365	1	0.35
1825	0.35	1,825	5	0.35
3650	0.45	3,650	10	0.45
5475	0.55	5,475	15	0.55
9125	0.70	9,125	25	0.70
$\geq 18250$	1.04	$\geq 18,250$	50	1.04



1 The same comment applies to the following summary tables:

2 • p. 281, dust and soil ingestion rates

3 • p. 284, ventilation rates

4

5 i. p. 282 line 7 Appendix D does not have B1-B4, presumably this should be BR1-BR4

6 j. p. 282, line 10, delete the extra “(“after RT

7 10 were based on experimental studies conducted indoors who inhaled suspension particles from automobile exhausts while they were sedentary. However, regional deposition and clearance in the RT (will depend

8 k. p. 284, line 15, reword “for from”

9 15 few exceptions, these have not used IVBA methods for from which RBA can be reliably predicted

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

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

16 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.

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

18 p. 291

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

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## APPENDIX B TABLE OF PANEL 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
<b>Model users and applications</b>														
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 algorithm											Tier 2			
Modernized interface										Tier 3				
<b>Editorial</b>														
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													

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**Inhalation**

Ventilation rates and activity	Tier 1		
Particle size		Tier 2	Tier 2
Particles to GI (fraction deposited)	Tier 1		
Inhalation parameters for disease states	Tier 3		

**Oral**

GI absorption - various aspects		Tier 2&3	
RBA	Tier 2	Tier 2	Tier 2
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		
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**Distribution/Elimination**

Brain lead description	Tier 1		
Bone kinetics and post-exposure blood kinetics	Tier 2		Tier 1
Inhalation & nasal olfactory uptake	Tier 3		Tier 1
Fecal elimination & mass balance		Tier 1	Tier 1
Cortical-trabecular bone levels			Tier 2a*
RBC parameters		Tier 2	Tier 1
Kidney & liver distribution		Tier 3	Tier 2a

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Growth curves	Tier 1				
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
<b>Exposures</b>					
Additional exposure examples					Tier 1
Constant media concentration & background or baseline exposures		Tier 1&3-dust,soil			
Soil and dust		Tier 2 - water		Tier 2	Tier 2
Lead in paint modeling		Tier 3	Tier 2		Tier 3
Occupational Exposure		Tier 2		Tier 2a	
Chelation					Tier 3
<b>Sex, life stage, &amp; health</b>					
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 3		
Inhalation and respiratory diseases		Tier 3			
<b>Model Evaluation</b>					
Model reproducibility uncertainty			Tier 1		
Model sensitivity				Tier 1	

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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

Co-exposures or mixtures

Tier 3

\*Tier 2a: Single recommendation covers these topics