

June 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 makes 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 to provide an updated version available to the public to replace the AALM 2.0 reviewed by the Panel.

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1 The Panel recommends that the Agency develop and implement a plan to expand the utility of the
2 AALM 2.0 for use in risk assessments and public health assessments. These recommendations are
3 largely described in the Panel's Tier 2 recommendations and in some Tier 3 recommendations.
4

5 EPA should have an ongoing commitment to continued maintenance of the AALM, including its
6 parameter values and model documentation. EPA should provide support and training to the broad
7 range of likely users of the model. This support should include continued updates to the model and
8 to its recommended parameters as new data become available. It should also include extending the
9 model to address aspects of exposure or pharmacokinetic biological processes that require more
10 effort and longer time frames (included in the report's discussion of Tier 3 recommendations).
11

12 As the EPA finalizes its External Review Draft AALM Draft 2.0, the SAB encourages the Agency to
13 address the panel's concerns raised in the enclosed report and consider their advice and
14 recommendations. The SAB appreciates this opportunity to review EPA's AALM 2.0 and looks
15 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

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18 Enclosure:
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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	Centers 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 (U.S. EPA)
ICRP	International Commission on Radiological Protection
IEUBK	Integrated Exposure Uptake Biokinetic (lead exposure model; U.S. EPA)
MATLAB	Matrix Laboratory – proprietary programming language developed by Mathworks
MPPD	Multi-Path Particle Dosimetry
NTIS	National Technical Information Service
OEHHA	Office of Environmental Health Hazard Assessment
OPPT	Office of Pollution Prevention and Toxics
Pb	chemical symbol for lead
RBA	relative bioavailability
TRW	Technical Review Workgroup
TSD	Technical Support Document for AALM
SAB	Science Advisory Board
U.S. EPA	United States Environmental Protection Agency
WHO/IPCS	World Health Organization/International Programme on Chemical Safety

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

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 B. All materials and comments related to this report are available at:
6 [https://yosemite.epa.gov/sab/sabproduct.nsf//LookupWebProjectsCurrentBOARD/9B019D11EF](https://yosemite.epa.gov/sab/sabproduct.nsf//LookupWebProjectsCurrentBOARD/9B019D11EF07A3FA8525831A006275A4?OpenDocument)
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 adult lead models and to provide additional assessment capability for older children and adolescent subpopulations. This is a major step forward from both technical and public policy perspectives for conducting human health risk assessments. Overall, the 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 Technical Support Document (TSD) has extensive
4 discussion of the different models EPA developed leading to the AALM.FOR version under
5 review, it is a challenge to fully evaluate the many aspects involved. Many of the O’Flaherty
6 equations and parameter values have replaced Leggett’s values, and in some cases altered the
7 structure of the model (e.g. removing one of the pathways of lead elimination via urine). Hence,
8 the AALM is not really a newer version of the Leggett (or ICRP) model. This change from
9 version 5 of the ICRP model to a hybrid of model is significant. The evolution from the original
10 ICRP model (ICRP 1993 pub 67) to the structurally altered age-specific kinetic model of lead
11 metabolism in humans (Leggett 1993) has been difficult to convey and has remained unclear for
12 some. The switch from a method explained in Leggett’s paper of interpolating lead mass transfer
13 values between specific ages to a method for establishing tissue growth and volumes based
14 mostly on scaling and other equations from the O’Flaherty model needs to be clear. Many of
15 O’Flaherty’s equations appeared in the TSD, being the growth equations used in AALM. For the
16 childhood and adolescent part of the model, Leggett has a significant discussion about the
17 uncertainty of his lead mass transfer values in childhood and adolescence due to limited data
18 available to calibrate such values. In addition, given this switch from mass transfer to tissue
19 concentrations of lead based on age and body weight scaling, it would be important to revisit
20 O’Flaherty’s check on age- and body weight-related concentrations of lead with data as well as
21 Leggett’s check on age-related distributions of lead mass compared to estimates published in
22 Leggett (1993) of lead 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. The model is also potentially applicable for public
32 health and clinical purposes to describe impacts of interventions, but chelation therapy is turned
33 off and modifications like inputting dust lead loading are needed. These and other examples of
34 exposure scenarios for which the model is not parameterized or cannot account should be clearly
35 stated. In addition, Section 2.3.3 of the guidance states that that the model simulates lead
36 absorption from inhalation, ingestion, and dermal contact with dust. No dermal contact with soil
37 or dust is discussed in the document; thus, the fact that dermal exposure is not accounted for
38 should be stated as a limitation. Similarly, the current strengths of the AALM and examples of
39 exposure scenarios that it can simulate should be clearly outlined/stated.

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

1 altered by removing the transfer of lead from diffusible plasma to bladder contents (i.e., the
2 transfer rate is now zero).

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

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

21 **Charge Question 1 Recommendations**

23 **Tier 1**

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

38 **Tier 2**

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

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

3 4 **Tier 3**

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

7 8 9 **2.2. Charge Question Two: are the model features supported by available research** 10 **findings in published peer-reviewed literature or by reasonable extrapolations from** 11 **such findings?**

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

15 16 **Relative bioavailability**

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

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

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

1 **Post-exposure lead kinetics**

2 In AALM, when long term exogenous lead exposure is terminated, the blood Pb concentration
3 declines rapidly. For example, see Figure 3-2 B (p. 76, pdf page 87). This output appears to fit
4 well with the empiric data shown in Figure 3-6 for a lead worker whose exposure was interrupted
5 during a strike. However, there is concern, based on other observations, that the decline in blood
6 lead is not as rapid as predicted by the model in other cases.

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

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

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

42
43 **Brain and olfactory uptake modeling**

44 The model has a simple description of a single brain compartment. This is understandable in that
45 brain Pb concentrations are simply not available from which more extensive modeling can be
46 undertaken. Consequently, they are not available for use in risk assessment scenarios. However,

1 it is critical to remember that brain Pb is the basis of the neurodevelopmental toxicity in children
2 and could contribute to the increasing effects of Pb described in relation to neurodegenerative
3 diseases. For that reason, statements about brain Pb and appropriate references should be
4 included or clarified in text related to brain Pb (e.g., Section 2.3.8). For example, p. 31 (pdf p.
5 42) makes the statement of ‘non-uniform distribution of Pb in brain tissues. It is not clear where
6 this assertion comes from. If it was based on studies done in rodents, it is critical to recognize
7 that studies citing greater accumulation of Pb in hippocampus suffer from the fact that
8 concentrations in different regions were based on regional dry weights, which artifactually
9 increases levels in some regions, and when based on wet weights, as appropriate, there is a
10 uniformity of concentrations across regions.

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

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

34 35 **Charge Question 2 Recommendations**

36 37 **Tier 1**

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

1 **Tier 2**

- 2 • Obtain additional datasets that document the decline in blood lead concentration following
3 abrupt cessation of long-term elevated lead exposure. Evaluate AALM.FOR model
4 predictions for blood lead decline after extended intervals of moderate to high lead exposure
5 to characterize the accuracy of the model.
6 • Any uncertainties or limitations regarding the most appropriate elimination assumptions for
7 different types of exposure scenarios should be detailed in the documentation.
8

9 **Tier 3**

- 10 • Enhance treatment of age-related food Pb intake by offering known or established age-
11 dependent food intake rates (e.g. adopted from the EPA Exposure Factors handbook) or
12 obtain new data that can be applied to various types of food ingested by a receptor at
13 different times and locations.
14 • EPA should acquire more data regarding total amounts of lead in the brain from various
15 exposure routes, such as directly through inhalation across the blood brain barrier.
16
17

18 **2.3. Charge Question Three: In general, is the theoretical basis for the model adequately**
19 **described in Chapter 2: Theoretical Framework, Parameters, and Equations?**

20 Overall, the theoretical model is well explained. This is discussed further in response to the
21 subparts of this charge question. Please comment on the discussion of the following specifics
22 regarding AALM:
23

24 **2.3.1. Charge Question 3a. Are the values specified for the intake rates as a function of age**
25 **for different media adequately described?**

26
27 The Committee finds that the TSD provides mostly adequate and clear descriptions of how
28 AALM is parameterized with respect to intake rates (i.e., what parameter values have been
29 selected as a function of age for different exposure media), and why EPA selected these
30 parameter values (i.e., the theoretical basis and justification for the choices). The TSD presents
31 the parameters in the following specific sections and tables:
32

- 33 • Chapter 2.2 - Exposure Model
34 ○ Table 2-1. Exposure Equations of AALM.FOR
35 • Appendix A, Table A-1. Equations of AALM.FOR
36 • Appendix C, AALM Exposure Parameter Values
37 ○ Appendix C, Table C-1. List of Parameters that are Assigned Constants or are
38 Represented by Age Arrays
39

40 The following aspects of the summaries in the TSD are well done:
41
42
43

1 The meaning of the term Intake rate is clearly presented.

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

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

19
20 The presentation in the TSD is easy to follow because it is packaged as a series of “submodels”
21 for exposure, with equations and parameter values listed in tables.

22
23 The TSD clearly states that the inputs are intended to represent central tendency estimates, rather
24 than high-end (reasonable maximum exposure) point estimates or probability distributions. This
25 greatly reduces the complexity of the model structure and selection of input values, compared
26 with, for example, a fully probabilistic modeling framework. However, omitting the plausible
27 ranges and/or distributions in the TSD may constrain options for conducting a robust sensitivity
28 analysis, since the current model framework requires somewhat ad-hoc changes to combinations
29 of model inputs.

30 Intake Rates

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

34 *Air Intake Rate*

35
36 The Committee noted that EPA uses the term ventilation rate (m^3/d) as attributed to ICRP
37 (1994), whereas the term respiration rate (breaths per minute) is preferred in the public health
38 and clinical/medical fields. The term “ventilation volume rate” may be an improvement over
39 ventilation rate. Clarifying these terms would be beneficial for a broad model user audience.

40
41
42 The TSD (p. 10, lines 2-3, pdf p 21) states that ventilation rates in the model can reflect activity
43 levels and that sources that support the recommended parameter values also observe associations
44 between water intake and energy expenditure. However, it is unclear how activity levels have
45 been explicitly considered in the recommended mean parameter values and, therefore, how to
46 incorporate/characterize these in simulations of populations that exhibit varying activity levels.

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

5
6 The ventilation rates throughout the TSD appear to be obtained from healthy individuals. These
7 do not necessarily apply for individuals with asthma, COPD, or other disease conditions.
8 Suggesting sources of information or recommended values would further broaden the utility of
9 the model. Consideration of whether there would be changes in other parameters, such as
10 deposition fractions in regions of the respiratory tract, would be essential for appropriately
11 modeling these disease states.

12
13 For adults with occupational contact with lead, inhalation may be the most significant route of
14 exposure. Greater flexibility is needed with AALM.FOR in order to represent inhalation rate
15 scenarios that are more applicable to a range of worker exposure scenarios. For example, the
16 user should be afforded the opportunity to adjust the default respiratory rates for the model
17 shown in Appendix C (pp. 282-284, pdf pp. 293-295). The model's default value for adults, 19.9
18 m³, is apparently intended to represent long-term average daily exposure. Short-term adult
19 respiration rates associated with moderate or heavy exertion that may be more applicable to
20 occupational lead exposure have been reviewed in Chapter 6 of EPA Exposure Factors
21 Handbook (EFH) (U.S. EPA, 2011). The following are specific examples that have been
22 proposed by EPA and California Office of Environmental Health Hazard Assessment (OEHHA):
23

- 24 • EFH (Table 6-50) suggests that activities requiring physical labor may be associated with
25 a median respiration rate of approximately 1.5 m³ per hour, corresponding to
26 approximately 12 m³ for an 8-hour shift.
- 27 • California OEHHA's Technical Support Document for Exposure Assessment and
28 Stochastic Analysis (CalEPA 2012, Chapter 3, Table 3.3b) recommends 12.94 m³ for
29 adults engaged in moderate intensity activities for 8 hours.
- 30 • OEHHA, in the development of the Leggett Plus model for assessment occupational lead
31 exposure and dose (CalEPA 2013), used 14.4 m³ (30 L/min) for 8 hours for moderate
32 workloads.

33
34 In addition, certain studies support the use of other values based on sex and body weight, in
35 addition to age. The Committee recommends expanding the options for a user to select not only
36 the current default daily values, but also values representative of short-term occupational lead
37 exposure. The "occupational setting" could assume a value in the range of 12 to 14 m³ for
38 moderate exertion during an 8-hour shift, as an initial recommended range.

39
40 AALM.FOR apportions the inhaled lead into four compartments of the respiratory tract, 1)
41 extrathoracic (incorrectly termed intrathoracic in the document); 2) bronchial; 3) bronchiolar;
42 and 4) alveolar, by multiplying the average mass of lead inhaled per day (µg Pb/day) by a set of
43 deposition fractions (R) (see TSD p. 23, lines 11-20, pdf p. 34). Collectively, the deposition
44 fractions sum to 40%, meaning each day, 40% of the total inhaled Pb is initially deposited in the
45 respiratory tract, and the balance is exhaled. The estimates of R are summarized in a table

(copied below from p. 23, pdf p. 34) and attributed to data from five studies conducted from 1969 through 1980 in which human subjects inhaled submicron Pb-bearing particles:

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

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

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

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

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

Soil and Dust Intake Rate

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

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

The AALM model can be run in one of two modes with respect to transitioning between consecutive age groups: 1) a step function, or 2) interpolated values between age groups. The graphics in Exhibit 1 below show the proposed AALM inputs side-by-side with the two key sources for both run options. During childhood, after approximately age 2 years, the proposed AALM inputs are systematically higher than the values cited, and no explanation is given to

1 explain this discrepancy. [Tier 1] The Committee recommends that EPA reconsider the basis for
2 the recommended parameter values for ages 2 to 15 years to either better align with the materials
3 cited or explain the rationale for the deviation.
4

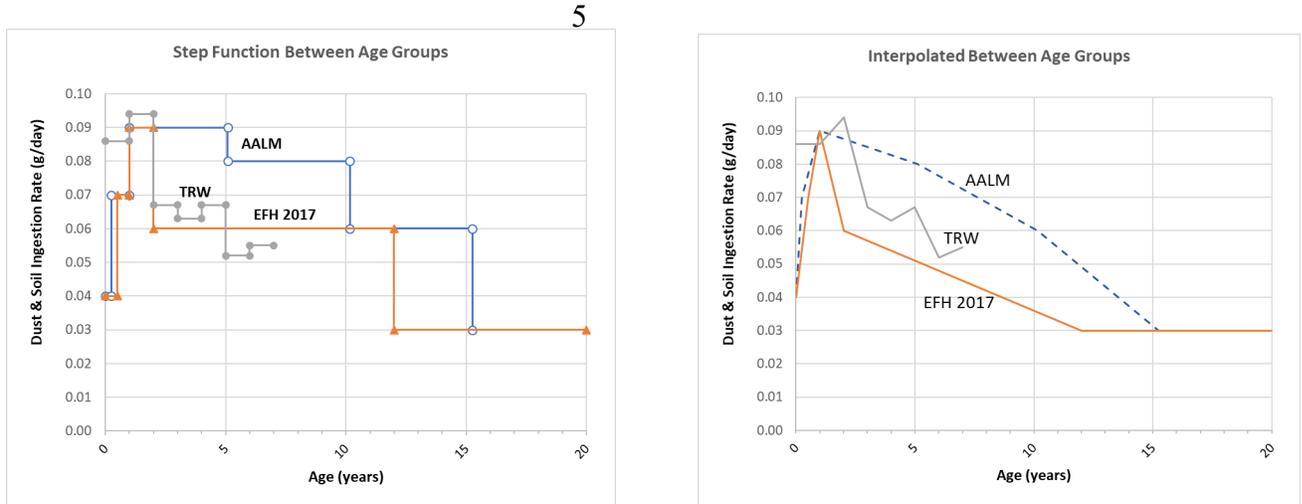


Figure 1 Age-specific parameter values for average soil and dust ingestion rates (g/day) during ages 0 to 20 years, comparing AALM with source information attributed to EPA. Graphic on left corresponds with the step function run option in A

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

11
12 *Water Intake Rate*

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

16
17 a) Describe the populations represented by these study results. Cross referencing EPA’s EFH
18 (2011), the TSD currently states (p. 281, lines 4-5, pdf p. 292), “Water ingestion rate can be
19 expected to vary with age, activity level and environmental factors (e.g. temperature, humidity).”
20 EPA should clarify how (or if) specific activities are reflected in the proposed inputs.

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

26
27 In addition, the Committee recommends that EPA include a baseline concentration of lead in
28 drinking water (e.g., 0.9 µg/L) in the TSD.
29

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

6 7 *Food Intake Rate*

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

13
14 The Committee notes that the decision to simplify the input parameter to a single bodyweight-
15 normalized value makes good sense from both a model implementation perspective (i.e., it is
16 very straightforward to calculate this intake term from age-specific body weight). However, the
17 Committee recommends a value of 0.128 or 0.13 µg/kg-day, which is better supported by the
18 data cited by EPA, rather than 0.14 µg/kg-day. The basis for this statement is as follows:

- 19
20 1) The AALM model yields estimates of food Pb intake for children that, on average
21 (considering each 1-year age group separately from ages 1 to 7 years, inclusive) differs
22 from the input parameters recommend by the TRW by 9.4%. This considers the age-
23 specific body weights for male and female children, as presented in the TSD.
24 2) The Committee conducted a simple sensitivity analysis to illustrate how this
25 error/deviation from TRW inputs changes as a function of changes in intake rates ranging
26 from 0.120 to 0.150 µg/kg-day. (see the following page – Exhibit 2).
27 3) An error rate of 0% corresponds with a body weight-normalized intake rate of 0.128
28 µg/kg-day, which corresponds with an absolute intake rate of 9.1 µg/day for a 71.4 kg
29 adult. It is unclear why a parameter value rounded to a whole number (e.g., 9 µg/day)
30 would be preferable, given the number of significant figures EPA has historically applied
31 to estimates of food lead intake intakes in the IEUBK model. A slightly lower lead
32 intake rate of 0.126 µg/kg-day corresponds with an absolute intake rate of 9 µg/day for a
33 71.4 kg adult. While the error/discrepancy is quite low (-1.5% on average for children
34 ages 1-7 years), it implies a slight underestimation may occur during childhood.

35
36 It would be helpful to explain that even though an intake rate of 9.1 µg/kg-day (or similar value)
37 reproduces the TRW values quite well on average, there is a systematic discrepancy on a year-
38 by-year basis. Specifically, this approach for AALM will consistently underestimate food Pb
39 intakes (compared with TRW’s recommended inputs) during birth to 3 years, and overestimate
40 intakes during 3 to 7 years.

41
42 Also, several Committee members noted that the current model structure does not appear to
43 accommodate a nursing infant exposure scenario, whereby lead levels in breast milk may be
44 elevated if the adult body burden of lead is elevated. While such a scenario could be evaluated
45 using the option for the “Other” exposure pathway, the Committee recommends that EPA add a

Science Advisory Board (SAB) Draft Report (June 2, 2020) for Quality Review-- Do Not Cite or Quote --This draft has not been reviewed or approved by the chartered SAB and does not represent EPA policy.

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

3
 4

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	1.17	2.26	-1.09	-48%
1 to < 2	0.128	12.3	12.9	1.57	1.65	1.61	1.96	-0.35	-18%
2 to < 3	0.128	14.6	15.3	1.87	1.96	1.91	2.13	-0.22	-10%
3 to < 4	0.128	16.4	17.2	2.10	2.20	2.15	2.04	0.11	5%
4 to < 5	0.128	18.0	18.8	2.30	2.41	2.36	1.95	0.41	21%
5 to < 6	0.128	19.7	20.2	2.52	2.59	2.55	2.05	0.50	25%
6 to < 7	0.128	21.7	21.8	2.78	2.79	2.78	2.22	0.56	25%
								average difference	0.0%

Intake (all ages):

0.140 ug/kg-day

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

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

5
 6
 7

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

8
 9

Other Medium Intake Rate

1 In general, the Committee finds the use of an “Other” input menu to be straightforward and
2 useful. One of the Committee’s broader recommendations is that EPA include more working
3 examples of applications of the model so that users can more quickly understand how to apply
4 the model as noted in responses to Charge Questions 1 and 7. The Committee recommends
5 including this “other intake” module in one or more such examples.
6

7 The TSD refers to the “Other” pathway in the discussion of soil intake (p. 11-12, lines 36-37;
8 and p. 12, line 1), stating, “The main consideration for including exposures to soil in the soil
9 pathway rather than simulating the soil exposures in the other pathway is the determination of
10 whether or not parameter values for soil ingestion rate (IR_{soil}, Equation 2.2-14) apply to the soil
11 exposure.” The Committee finds the wording of this sentence to be confusing because it does
12 not clarify conditions in which a separate evaluation, using the “other” pathway, would be
13 warranted. And furthermore, even if there are multiple exposure pathways involving multiple
14 soil lead concentrations, it is unclear why a different set of age specific IR_{sd} values would be
15 appropriate. Further clarification of these points is needed.
16

17 Parameters for additional exposure variables

18 The Committee also evaluated additional exposure variables, beyond the media-specific intake
19 rates discussed above.
20

21 *Indoor dust lead*

22 Pb in soil and indoor dust represents the most common source of non-dietary lead exposure in
23 U.S. children whose blood lead concentration exceeds the CDC reference value of 5 µg/dL
24 established in 2012, or the value of 3.5 µg/dL proposed by the ATSDR/NCEH Board of
25 Scientific Counselors in 2016. As such, when AALM.FOR is employed, the user defined value
26 of lead in soil and indoor dust will be of key importance.
27

28 In Appendix C (p. 276, pdf p. 287), the TSD recommends a default value for indoor dust of 175
29 µg/g (ppm). Appendix C further states that a value for indoor Pb dust equal to soil Pb is
30 recommended where there are no known indoor sources of Pb in dust (e.g. lead paint or hobbies).
31 However, Appendix C appropriately cautions, “Indoor dust Pb concentrations in residences
32 impacted by Pb-based paint can be expected to vary considerably within and between residences
33 and local exposure conditions should be considered to establish a representative estimate.” The
34 Committee expressed concern that use of 175 µg/g as a default indoor dust Pb concentration may
35 yield unexpected or unreliable outputs in several situations:
36

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

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

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

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

30 31 **Charge Question 3a Recommendations (by exposure routes)**

32 33 **Overall and Air Intake Rate**

34 **Tier 1**

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

42 **Tier 2**

- 43 • Provide additional guidance and examples for modeling inhalation exposures for individuals
44 with occupational exposures. As noted on p 282 of the TSD (pdf p 293) lines 12-15

1 appropriate interrelationships need to be addressed for particle size, clearance, deposition,
2 and ventilation volume rates.

3
4 **Tier 3**

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

8
9 **Soil and Dust Intake Rate**

10 **Tier 1**

- 11 • Revisit the basis for the recommended soil and dust intake rate parameter values for ages 2 to
12 15 years to either better align with the materials cited or explain the rationale for the
13 deviation.

14 **Tier 2**

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

16
17 **Water Intake Rate**

18 **Tier 2**

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

23
24 **Food Intake Rate**

25 **Tier 2**

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

32
33 **Indoor Dust Lead**

34 **Tier 1**

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

37 **Tier 2**

- 38 • Evaluate relationships between indoor dust loading and indoor dust Pb concentration for
39 application in AALM.

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

4 **2.3.2. Charge Question 3b. Are the uptake/absorption parameters and parameters**
5 **requiring modification for specific routes of exposure adequately described?**

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

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

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

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

38
39 Uptake/absorption in the respiratory tract (Inhalation)

40
41 Review of the modeling for the respiratory tract found that the current model and recommended
42 parameters could be appropriate for specific conditions that are not clearly specified, e.g.,
43 average individual inhalation of relatively small environmental lead particles, but that different
44 parameter values would be needed, particularly for occupational exposures, to address varied

1 activity levels, changes in respiration, and larger particle sizes. Variations in particle size that
2 affect deposition in the respiratory tract and the fraction subject to mucociliary clearance to the
3 GI tract for absorption also need to be addressed.

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

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

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

30
31 The TSD does not discuss whether or how to utilize well established tools and models designed
32 to address the impact of particle density, particle size and size distribution on regional deposition
33 in the lung (and subsequent absorption). The Multiple Path Particle Dosimetry (MPPD) model is
34 well established for addressing just these concerns (see Asgharian *et al.*, 2001; Miller *et al.*,
35 2016; *etc.*). Exposure modeling of various particle size distributions (*i.e.* lognormal distribution
36 around a mass mean aerodynamic diameter, skewed towards larger or smaller particle sizes, bi-
37 modal) for a set air concentration of lead (*e.g.* $\mu\text{g}/\text{m}^3$) indicate the potential for significant
38 variability in regional deposition in the lung and subsequent absorption (see Petito Boyce *et al.*
39 2017). As noted above in the discussion of inhalation intake (Charge Question 3a), the study by
40 Lach *et al.* (2014), showed that 49% of total inhaled Pb would be deposited in the respiratory
41 tract, of which 37% would be translocated to the GI tract in contrast to the 4% based upon
42 Leggett (1993).

43
44 There was difficulty understanding the meaning of the relevant respiratory parameters (*e.g.*, R1-
45 R4, BR1-BR4, CILIAR) and how they might be modified by a user. Inconsistencies in text,
46 tables, and the EXCEL spreadsheet implementation of the model were noted. Examples include:

1 P23 (pdf p34) Line 32 defines BR_i as a fraction when it is a rate
2 P25 (pdf p36) Line 2 BR_i again described as a fraction when it is a rate
3 P299 (pdf p310) BR_1 to BR_4 – Half-life values given are rounded and converted to days in
4 calculations of rates, which are shown as $0.693/T_{1/2}$ but in the EXCEL spreadsheet, they are
5 calculated as $LN(2)/T_{1/2} * 24$ so the numbers don't match.
6 P302 (pdf p313) R_1 – 10% value given in text (line 14), but the calculation shown, and the value
7 used in the spreadsheet (LUNG tab) is 0.08 or 8%
8 P302 (pdf p313) R_3 – 12% value given in text (line 26), but calculation shown, and value used in
9 spreadsheet (LUNG tab) is 0.14 or 14%

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

15 16 Occupational inhalation exposures

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

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

44

1 One specific route of exposure for workers is inhaled particles that are removed by ciliary action
2 and swallowed during and after meals where absorption efficiency can increase substantially
3 from the default of 12% oral absorption of lead from the small intestine.
4

5 A lead pharmacokinetic model designed to address occupational exposures for the Department of
6 Defense was recently reviewed by a committee for the National Academies of Science,
7 Engineering, and Medicine (Review of DoD's Proposed Occupational Exposure Limits for Lead,
8 PIN: DELS-BEST-18-05). The report is available online (NASEM 2020). This modeling is
9 based upon the physiologically based pharmacokinetic modeling originally done by Prof.
10 O'Flaherty, whereas AALM is derived from the modeling by Dr. Leggett. However, the
11 availability of a peer reviewed model for at least some occupational exposures could be a useful
12 option for the EPA to consider for modeling solely occupational exposures, or to provide insights
13 and parameter values for expanding AALM to address occupational exposures in a context of
14 prior childhood exposures.
15

16 Uptake/absorption in the gastrointestinal tract (Oral) 17

18 Although gut absorption of lead is complex and depends on numerous factors, absorption from
19 the gut in the AALM approach seems simplified to a first-order fraction of the contents of the
20 small intestine, based on a single age-dependent coefficient. As a result, characterization of the
21 absorption parameters for the AALM would reflect the appropriateness of the original formulae
22 developed earlier, as cited in the document. However, the extent to which the model emulates
23 understanding of the processes and concentration-dependent rate characteristics bears further
24 discussion.
25

26 The extent to which overall absorption or the amount of total intake that eventually reaches (or is
27 accessible to) tissue compartments has long been debated among researchers, practitioners, and
28 the regulatory community. Several alternative explanations have been advanced in application of
29 these models to health response and regulatory actions, often with considerable impact on
30 outcomes. The IEUBK model support materials noted some years ago that, in order to more
31 accurately model lead uptake from the gut at higher intake rates, absorption fractions should be
32 modified to separate non-saturable and saturable components. It is not clear to what extent the
33 AALM has considered dual components or other nonlinear approaches to modeling
34 gastrointestinal absorption. The IEUBK Technical Support Document extensively discusses both
35 bioavailability application and gut absorption, and their role in applying combined passive/active
36 absorption mechanisms to mimic non-linear uptake. It is not clear how non-linear uptake is
37 accomplished in the AALM, especially with respect to which variables and parameter values
38 specify or influence age-dependent and concentration dependent parameters, or whether there is
39 "double counting" of absorption factors in applying bioavailability as an intake adjustment.
40

41 Section 2.3.3.2. Absorption from the Gastrointestinal Tract, indicates that AALM.FOR has
42 incorporated age dependent gastrointestinal absorption fractions (AF), ranging from 0.39 at birth
43 to 0.12 that do not otherwise vary based on whether Pb enters the gut without food (e.g., fasting
44 condition), with liquids, or with food. However, as noted in the cited references (e.g., James et
45 *al.*, 1985) and several other studies (cf. discussion in Maddaloni *et al.*, 2005 and CalEPA 2013
46 pp 83 et seq. and appendix A), the extent of GI Pb absorption varies considerably depending on

1 whether Pb enters the gut with or without food or liquids. This applies not only to Pb ingested
2 during meals, but also Pb transported from the respiratory tract by mucociliary clearance (a
3 relatively continuous process throughout the day). For risk assessment scenarios, there may be a
4 basis to distinguish between Pb ingested with meals (food and water), and that ingested during
5 outdoor recreation or work when food is not eaten. OEHHA considered this by estimating three
6 mean gastrointestinal absorption fractions for adults: 50% after several hours of fasting, 19%
7 with liquid between meals, and 12% during intake with solid food (CalEPA, 2013, page 82). It
8 further calculated a 24-hour TWA GI absorption of 30% assuming 10 hours fasting (50% AF),
9 10 hours with liquids between meals (19% AF), two hours intake with solid food (12% AF), and
10 two hours in which no lead enters the GI tract. The impact of revising the AALM.FOR to
11 consider this additional variability in GI absorption of Pb based on co-ingestion with food and
12 liquid should be examined.

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

20 21 Relative bioavailability for ingestion

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

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

1 It would be helpful for the developers to explain why for most media (e.g., Pb in soil, Pb in dust,
2 Pb in water) only a single RBA applies to all intake relative to that medium. For example, in
3 Section 2.2.3.3. (pdf page 22) the narrative states, “The model accepts a single inputted value for
4 RBA which represents soil from all sources, in all exposure settings.” The same provision for a
5 single RBA applies to all Pb in indoor dust (Section 2.2.3.2). This seems counter to the model’s
6 flexibility in allowing for multiple values of Pb intake in soil or dust at different times of the day
7 (or week). It seems likely that the soil or dust from different sources may have different
8 solubility, particle size, and chemical composition, and by extension, different RBA.

9
10 With respect to lead intake in water (section 2.2.3.4; pdf page 24), the narrative states:

$$11 \quad \text{“}IN_{\text{WATER}} = Pb_{\text{WATER}} \cdot IR_{\text{WATER}} \cdot RBA_{\text{WATER}} \quad \text{Eq. (2.2-18)} \quad 12$$

13
14 where IN_{water} is the intake of Pb in water ($\mu\text{g Pb/day}$), Pb_{water} is the Pb
15 concentration in water ($\mu\text{g Pb/L}$), IR_{water} is the rate of ingestion of water (L/day)
16 and RBA_{water} is the relative bioavailability of Pb in water and dust, relative to
17 water-soluble Pb. Values for IR_{water} are interpolated between inputted ages. The
18 model accepts a single inputted value for RBA which represents both water [SIC],
19 in all exposure settings. Lead dissolved in water would, by definition, have RBA
20 = 1; however, the RBA parameter could be used in scenarios in which ingestion
21 exposures include Pb-bearing particulates suspended in water for which the RBA
22 may be <1 .”
23

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

41
42 On the RBA tab of the EXCEL spreadsheet, the GI absorption fraction is called “F1” in the
43 boxes and “AF1” in the heading on column D where values would be entered. Terminology
44 should be consistent in the spreadsheet and with documentation.
45

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

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

14
15 “Figure 3-19 compares predictions of the AALM and the IEUBK model for a continuous
16 dust Pb intake of 10 µg/day. In both models, the relative bioavailability (RBA) for Pb in dust
17 was assumed to be 60%. This corresponds to an absolute bioavailability of approximately
18 20% at age 2 years in the AALM and 30% in the IEUBK model. At age 2 years the IEUBK
19 model predicts a blood Pb concentration of 1.18 µg/dL; the AALM predicts 1.25 µg/dL.”
20

21 It seems there should be no difference in absolute bioavailability as that should be a fixed
22 characteristic of the substrate, and the RBA is referenced to the absolute bioavailability of lead in
23 water, which should also have a single value. The statement above indicates that bioavailability
24 is age-dependent and differs in the two applications. This divergence, perhaps, refers to the
25 differences in assumptions that EPA assigns in the models, as those relate to an absolute value
26 expressed as an RBA. The age-dependent differences in blood lead predictions could be related
27 to the apparent “age-related” differences in bioavailability generated by the intake “adjustments.”
28 It would be best to discuss, if not resolve, these differences as these models are released.
29
30

31 **Charge Question 3b Recommendations (General)**

32 **Tier 1**

- 33 • Clarify in model documentation whether dermal absorption is included as a specific
34 pathway in the model or not.
35
36

37 **Tier 3**

- 38 • While there is some description of how hand to mouth behaviors leading to oral exposure
39 to dust or soil on the skin is addressed, providing examples would clarify and strengthen
40 this aspect.
41

42 **Charge Question 3b Recommendations (Inhalation)**

43 **Tier 1**

- 44 • Clarify when the current model structure and parameter values would be appropriately
45 used and when they would need to be modified (e.g., occupational inhalation exposures
46

1 to larger particles) to guide users to appropriately use the model and avoid inappropriate
2 uses.
3

4 Tier 2

- 5 • The TSD should acknowledge that the current default modeling approach of the
6 AALM.FOR for absorption of lead in the respiratory tract may be best suited to scenarios
7 associated with exposure to low concentrations of soluble submicron lead particulate. Use
8 of the model for scenarios with exposure to higher concentrations of larger, sometimes
9 less soluble lead particles (e.g. at outdoor remediation sites or other occupational settings)
10 is also desirable, and future development of the AALM should examine the utility of
11 adapting the Multi-Path Particle Dosimetry Model (MPPD2 or subsequent iterations) to
12 revise the respiratory tract model.
- 13 • Add a discussion about the time to stomach and conditions in the stomach (fasting, water-
14 only, with meal) for swallowed particles.
15

16 Charge Question 3b Recommendations (GI and RBA)

17 Tier 1

- 18 • Change the model to quantify the total elimination in feces (e.g. fate of non-absorbed lead
19 in soil and dust) and maintain mass balance.
- 20 • Revise the model to allow different user defined relative bioavailability (RBA) values for
21 each source of ingested medium containing Pb encountered by a receptor at different
22 times and locations (e.g. multiple sources of soil, dust, water). Currently a single RBA
23 applies to all intake of a specific medium.
24
25

26 Tier 2

- 27 • Provide model users with guidance to address differences in lead bioavailability of
28 different media from multiple sources.
- 29 • Future revisions of the AALM should address non-linear aspects of gastrointestinal lead
30 absorption that account for active and passive absorption mechanisms, the impact of food
31 in the gastrointestinal tract (i.e. fasting vs. non-fasting states), the absorption of
32 particulate lead in water compared to soluble lead in water, and lead concentration in the
33 gut on lead absorption fraction.
34

35 Tier 3

- 36 • Gut absorption needs further discussion and potentially update the model (see Leggett et
37 al. 2007 intro to new ICRP GI model)
38
39

40 2.3.3. Charge Question 3c. Are the biokinetic parameters describing lead distribution and 41 elimination adequately described?

42
43 In general, the biokinetic parameters described in Tables 2-3 and 3-2 of the TSD were adopted
44 from the Leggett model and are generally well accepted.

1
2 Parameter Inconsistencies and Uncertainties
3

4 However, in order to recode the All Ages Lead Model (AALM) to run in MATLAB (adult
5 parameters only) and reproduce the output from the AALM in Figure 3-10, several errors and
6 omissions were discovered. The FORTRAN input file named POUNDS_GUI.DAT listing input
7 values for ICRPversion8 provided the following information that is missing from or inconsistent
8 with Tables 2-3 and 3-2 of the TSD:
9

- 10
- 11 • The value for total transfer rate from exchange bone volume is 0.02311. The fraction of total
12 transfer from the exchangeable bone directed to non-exchangeable bone is 60% of 0.02311 or
13 0.01387 not 0.02311 as listed in Table 2-3. The transfer of lead from "Exch Vol" to "Surf
14 bone" is 40% of 0.02311 or 0.0092 not 0.0185 as listed in Table 2-3. (Note that in Appendix
15 D, p. 303, the calculation of RDIFF from $\ln 2$ /half-life has a typo, 0.00231.)
 - 16 • Regarding the deposition fraction from Plasma-D to Kidney 2, Table 2-3 indicates a change
17 from the original value of 0.4 to 0.8. However, in Table 3-2 the change in the Kidney 2
18 deposition fraction from ICRPv4 or ICRPv5 to AALM.FOR is missing.
 - 19 • Changes made to the deposition fraction from Plasma-D remove the mass balance originally
20 present in the ICRP (Leggett) model. Specifically, the deposition from Plasma-D to all
21 destinations should add up to 2000 μg of lead. Instead it adds up to 1980.36. This mass
22 imbalance has resulted from three changes in the fractional transfer of lead from Plasma-D to
23 urine from 30 to 0, to kidney-1 from 40 to 50, and to kidney-2 from 0.4 to 0.8. These
24 changes drop about 20 μg . Maintaining mass balance is essential for insuring correct model
25 behavior.

26 Other changes made to the model that had to be obtained from the FORTRAN input file before
27 Figure 3-10 could be reproduced include changes in:
28

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

31
32 Findings from this limited exercise indicate that a more complete check for errors and omissions
33 in Tables 2-3 and 3-2 describing the parameters for the entire model is needed. Nomenclature
34 throughout the document (e.g., Table 2-3 and Appendix D) needs to be consistent so readers are
35 certain what is being referred to. Parameter values and sources listed in documentation and
36 model files (e.g., EXCEL spreadsheet) need to be cross-checked with the current ICRPversion8
37 code file. If errors are only in documentation, then documentation readily can be corrected, but it
38 is also possible that errors have been introduced in the modeling that need to be corrected.
39

40 The AALM appears to have three adjustments to Pb mass leaving diffusible plasma
41 (TSUM=2000) in which mass balance needs to be checked: 1) due to changing some deposition
42 fractions (DFs) between versions of the model (Table 3-2), 2) due to adding an age-scaling
43 equation to the model, and 3) due to changes in RBC binding rate once Pb concentration exceeds
44 20 $\mu\text{g}/\text{dLrbc}$. Mass balance needs to be checked and maintained after changing DFs between
45 versions of the model and across a range of ages and levels of Pb in whole blood.

1
2 Changes were made in several deposition fractions for Pb leaving diffusible plasma such as those
3 to urinary bladder and kidney and bone during multiple updates to the ICRP version 4 (Leggett
4 1993) and AALM. Given these changes, mass Pb leaving diffusible plasma could easily go out
5 of balance. For example, TSUM is achieved when the adult Pb transfer from diffusible plasma
6 to RBCs (TORBC) of 480 per day is increased to 500 per day in the AALM.FOR. This change
7 is consistent with changes made to AALM.LG listed in Table 4-22 for the deposition fraction of
8 Pb leaving diffusible plasma to RBCs, where $0.24/\text{day} = (480/2000)/\text{day}$ and $0.25/\text{day} =$
9 $(500/2000)/\text{day}$. As noted elsewhere, applying the correct TORBC across ages and levels of
10 blood lead is important. In addition, during multiple updates to the ICRP version 4 (Leggett
11 1993) and AALM, the equation for AGESCL appears in the TSD in multiple places and contains
12 slightly different definitions for the value of Pb transferred from diffusible plasma to bone
13 surfaces in the form of TBONE(t), TBONEL and ATBONE.

14
15 $\text{AGESCL} = (1-\text{TEVF}-\text{TBONE})/(1-\text{TEVF}-\text{TBONEL})$ (equation 2.3-12)
16 $\text{AGESCL} = (1-\text{TEVF}-\text{TBONE}(t))/(1-\text{TEVF}-\text{TBONEL})$ (equation 4-5)
17 $\text{AGESCL} = (1-\text{TEVF}-\text{TBONE})/(1-\text{TEVF}-\text{ATBONE})$ (equation in Table A-1, page 199)

18
19 On page 20 of the TSD, TBONEL is the limiting adult value for the bone deposition fraction.
20 On page 102 of the TSD, TBONEL is defined as the terminal value for TBONE on the last day
21 of simulation.

22 On pages 262 and 298 of the TSD, ATBONE is defined as the age-specific deposition fraction
23 from diffusible plasma to surface bone-age array.

24
25 Age-scaling may turn out differently depending on which definition is applied in the model. In
26 addition, the age-specific deposition fractions in Leggett (1993) were derived based on the
27 assumption that increases in Pb transferred during the growth period are proportional to increases
28 in calcium deposition with age in childhood. Additional age-scaling seems redundant. For
29 clarity, further explain why additional age-scaling is needed and its impact on the model.

30
31 An order of adjustment (e.g. age-scale then adjust for changes in binding rate in RBCs) is
32 implied based on the text in Chapter 2 of the TSD. For children, and for blood lead levels
33 exceeding 8 ug/dL whole blood (20 ug/dLrbc), adjustments are applied to the transfer of Pb
34 leaving diffusible plasma to RBCs (TORBC) according to the equation for TOORBC in Table 2-
35 $2:\text{TOORBC} = \text{TRBC} \times [1 - ((\text{RBCCONC}-\text{RBCNL})/(\text{SATRAT}-\text{RBCNL}))]^{1.5}$

36
37 For example, TORBC listed in Table 2-3 becomes TRBC after it has been age adjusted and all
38 other deposition fractions are adjusted based on equation 2.3-13. Also, TOORBC is TORBC
39 adjusted downward when RBC concentrations exceed 20 ug/dLrbc. All other deposition fractions
40 are adjusted upward based on $\text{CF} = (1-\text{TOORBC})/(1-\text{TRBC})$ (Eq. (2.3-14, Table 2-2 E7) when
41 RBC concentrations exceed 20 ug/dLrbc.

42
43 If this order is correct, state in the TSD the order of adjustment, for the sake of clarity, and to
44 make sure future adjustments to the model preserve this order.

45
46

Red Blood Cell Binding

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

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

Applicability of Biokinetic Parameters

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

Blood Lead Declines Following Exposure Cessation

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

1 Default Sex-Specific Body Weight

2
3 The default sex-specific body weight (technically body mass, but commonly referred to as body
4 weight) values used by AALM.FOR (Figure 2-2) were based on O’Flaherty. These values,
5 particularly for adults, now are somewhat lower than those observed in the latest NHANES
6 surveys for the U.S. population. For example, based on earlier NHANES studies cited in the
7 EPA Exposure Factors Handbook (2011), the mean body weight for males and female adults
8 combined is 80 kg; sex-specific median adult body weights in EFH vary by decade of age but
9 range from 75.1 to 87.8 kg for males and from 62.8 to 73.9 kg for females. These are
10 approximately 10 kg higher than the AALM.FOR defaults. Body weight is a key parameter in
11 biokinetic models, because it influences blood and organ mass and perfusion. Accordingly, the
12 default values for body weight should be updated to include the EFH 2011 ranges. The same
13 recommendation may apply to other biometric defaults in AALM.FOR that differ substantively
14 from those found in recent iterations of NHANES or the EFH.
15

16 Postmenopausal Changes and Age-Sex Interactions in Bone and Lead

17
18 As currently formulated, the biokinetic features of the AALM.FOR incorporate age-related
19 changes in the uptake and release of lead from bone. However, the model does not account for
20 significant sex-related differences in the relevant biokinetics that have been demonstrated in
21 studies of lead in blood and bone. Numerous reports have observed that increased bone turnover
22 and subsequent changes in bone density in perimenopausal and postmenopausal women are
23 associated in part with age-related decline in estrogen. Several studies have found that this has a
24 notable impact on the biokinetics of lead in blood and bone. Three large cross-sectional studies
25 of U.S. women based on NHANES cohorts have documented that postmenopausal women have
26 significantly higher blood lead concentration than premenopausal women, controlling for age
27 and other factors related to exogenous lead exposure, particularly in the years soon after the
28 onset of menopause (Silbergeld *et al.*, 1988; Symanski and Hertz, 1995; Nash *et al.*, 2005). In a
29 large study of perimenopausal and postmenopausal women (n=1225), linear multivariate models
30 demonstrated that biomarkers of bone turnover (N-telopeptide cross-linked collagen type I,
31 bone-specific alkaline phosphates, and osteocalcin) were significant predictors of blood lead
32 concentration (Machida *et al.*, 2009).
33

34 In a cross-sectional study of bone lead concentration by non-invasive K x-ray fluorescence in
35 101 subjects age 11 to 78 with background environmental lead exposure, a significant age•sex
36 interaction accounted for higher tibial bone lead concentrations in men over the age of 55 years
37 (Kosnett *et al.*, 1994). Similar findings of an age•sex interaction in the relationship of age to
38 tibial bone lead was observed in a more recent study conducted in subjects (n=263) from the
39 general population of Ontario (Behinaein *et al.*, 2017). Popovic *et al.* (2005) compared blood and
40 bone concentration study in a cohort of women with a history of occupational lead exposure to
41 unexposed referents (n=207). Among the women with past occupational lead exposure, the ratio
42 of blood to bone lead was substantially higher after menopause. The authors noted, “The results
43 suggest that the endogenous release rate (micrograms Pb per deciliter blood ÷ micrograms Pb per
44 gram bone) in postmenopausal women is double the rate found in premenopausal women”
45 (Popovic *et al.*, 2005). Bone Pb was significantly greater in postmenopausal referent women
46 treated with estrogen (Popovic *et al.*, 2005). Related findings were observed in a longitudinal

1 study of bone lead concentration in postmenopausal women, in which hormone replacement
2 therapy (HRT) was associated with higher bone lead concentration compared to women not on
3 HRT (Webber et al., 1995). Overall, the available research strongly suggests that the
4 AALM.FOR would benefit by refinements that account for sex-related differences in bone lead
5 accretion and release associated with changes related to menopause (O’Flaherty 2000).

6 7 Elimination pathways

8
9 The relevance of the sweat elimination pathway and its inclusion in the model should be clarified
10 or at least qualified as a relatively minor pathway. Leggett (1993) indicates this only accounts
11 for a small percentage of elimination.

12 13 **Charge Question 3c Recommendations**

14 15 **Tier 1**

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

32 33 **Tier 2**

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

1 **Tier 3**

- 2 • Evaluate whether to retain the plasma-D to bladder and sweat elimination pathways in the
3 model.
4

5 **2.3.4. Evaluate whether to retain the plasma-D to bladder and sweat elimination pathways**
6 **in the model.Charge Question 3 continued. Additionally, please comment on any**
7 **strengths or weaknesses in the justification provided for model assumptions (data**
8 **inputs, methodology, etc.) and the quantitative impact of those assumptions on the**
9 **model and its results.**

10
11 While the committee found that the justifications for model assumptions were sound, we think it
12 should be a matter of concern that both the Leggett and O’Flaherty models are highly sensitive to
13 two parameters:

- 14
15 - parameters C1 and C2 in the calculation of urinary clearance in AALM-OF.CSL
16 - parameters TEVF and TORBC in the plasma compartment of AALM-LG.CSL
17

18 These results need to be investigated and for all sensitivity analyses the direction of change
19 needs to be indicated, that is, positive for a direct dependence and negative for an inverse
20 dependence. For the four parameters noted above, there appears to be unusually high sensitivity,
21 i.e., the ratio of percent change in blood concentration to percent change in parameter is much
22 greater than 1 in absolute value, indicating significant amplification of error from the input
23 parameter to the model output. For example, a 10% variation in one of the parameters would
24 produce a 50% to 90% change in the predicted blood lead level. The parameters being in
25 different compartments in the two models is unexpected. The discussion of these results does not
26 provide a satisfactory explanation for such a significant impact by these parameters.
27

28 **Charge Question 3 continued Recommendations**

29
30 **Tier 1**

- 31
32 • The sensitivity analysis should include the direction of the sensitivity; that is, positive for
33 a direct dependence and negative for an inverse dependence.
34 • Each of the two models underlying the AALM appear to be unusually sensitive to two of
35 their parameters. This dependence needs to be investigated and fully explained in the
36 TSD or corrected if there are errors in the sensitivity analysis or the model.
37

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 in addition to the topics discussed here in response to
24 Charge Question 4a.

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

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

36
37 New equations for bone weight and bone volume have been added to the AALM. Given these
38 additions, the adjustment for bone Pb based on bone mineral does not provide the expected
39 answer. However, $ASHwt = WBONE \times 0.6$ based upon information provided in ICRP (2002)
40 for bone ash density and bone volume does. This indicates values on p 63 line 10 of the TSD
41 based upon ICRP 1981 should be reconsidered.

- 1 The description of the modeling of the Hattis data appears to have an error (p. 56, line 37, pdf p.
2 67) indicating “(20 years + duration of strike)”, when presumably it is (20 years + duration of
3 *prestrike* employment).
- 4 The empirical data that are used to evaluate model performance appear to be more heavily
5 weighted to representing males than females. Concerns about modeling breastfeeding and post-
6 menopausal changes in bone have been noted elsewhere and suggestions made about potential
7 data sets to use.
8

- 1 Table 4-16 of the TSD presents a strategy for the sequential parameter optimization of the model
2 using eight steps. The following observations are notable:
- 3 a. The capacity limit of 350 $\mu\text{g}/\text{dL}$ RBCs may be too high.
4 Step 2 (plasma/RBC ratio) lists six studies that support estimates of this ratio. With respect to
5 RBC binding capacity, the Committee recommends referring to Figure 14 in Leggett (1993) and
6 Figure 1 in Bergdahl et al., (1998). Bergdahl et al., (1998) reported an RBC capacity limit of
7 300 $\mu\text{g}/\text{dL}$ – similar to previous findings by this group and others. In Figure 1 of Bergdahl et al.,
8 (1998), the modeled line representing the three observed lead-binding components is closer to
9 the line representing the DeSilva data shown in Figure 14 in Leggett (1993) and in O’Flaherty
10 (1993). Based on the conclusions stated by these authors, perhaps the capacity limit of 350
11 $\mu\text{g}/\text{dL}$ RBCs is too high. The issue of how to describe RBC binding also has been raised in
12 charge question 3c.
- 13 b. Urine clearances reported in the literature are quite variable – how was this addressed in the
14 proposed plasma-to-urine clearance estimates (Step 3)?
15 Step 3 lists five studies that support plasma (blood) to urine clearance. Figure 13 in Leggett
16 (1993) shows that short term and chronic exposure scenarios can yield vastly different urine
17 clearances relative to blood lead levels. Were exposure scenarios from all five studies similar?
18 EPA should consider examining this variability and discussing implications for these findings on
19 the input parameter selected for AALM.
- 20 c. AALM appears to exaggerate Pb concentrations in kidney and liver.
21 Step 4 lists four studies that support soft tissue/bone Pb ratios. When a 20-yr simulation with the
22 AALM of the lead distributed to compartments representing bone, blood, liver, kidney, brain
23 other tissue was conducted as described in Leggett (1993), results for kidney and liver were
24 substantially higher than those estimated from autopsy data summarized in Table 3 of Leggett
25 (1993). EPA may wish to revisit this optimization step using summaries of tissue lead
26 distribution.
- 27 d. It seems possible that AALM.FOR may yield a more rapid decline in trabecular bone relative
28 to cortical bone in adult lead workers following termination of long-term exposure. Data from
29 Nie et al., 2009 presenting KXRF measurement of trabecular and cortical bone lead in retired
30 lead smelter workers indicated that years after exposure ended trabecular bone Pb concentration
31 exceeded cortical bone lead concentration. However, when pre- and post- retirement blood lead
32 presented on one worker in Figure 3 of Nie et al., 2005 were extracted and used by one
33 committee member to model trabecular and cortical bone lead in a MATLAB version AALM,
34 trabecular bone lead declined to less than cortical bone lead beginning approximately 5 years
35 post-retirement. The TSD (page 55 and page 66) noted that published and unpublished blood and
36 bone lead data from the studies by Nie and colleagues had been made available to EPA. The
37 TSD concluded that uncertainty regarding certain aspects of the subjects’ lead exposure
38 constrained the utility of the dataset for evaluation of the model’s biokinetic parameters.
39 Notwithstanding these limitations, future revisions of the AALM may be informed by qualitative
40 patterns of decline in trabecular and cortical bone lead in the Nie datasets, as well as additional
41 data on human bone lead measurements that may become available.

42
43

1 e. AALM appears to overestimate peak blood Pb.
2 Step 7 lists one study (Rabinowitz, 1976) as a source of data on blood elimination kinetics in
3 adults. Some of these data are displayed in Figure 3-10 of the TSD, which shows strong
4 correspondence between observed and predicted blood 207Pb concentrations, after gut
5 absorption fractions were adjusted to match values reported in Rabinowitz. Figure 7 of Leggett
6 (1993) shows simulations results using absorption fractions from the Rabinowitz study, as
7 reanalyzed by Chamberlain. When the modified absorption fractions were applied using the
8 AALM, peak blood leads were higher than previously modeled for three out of four subjects.
9 The elimination kinetics did not change but perhaps, the body weight-based blood volume is too
10 low.

11 **Charge Question 4a Recommendations**

12 **Tier 1**

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

16 **Tier 2**

- 17 • Re-evaluate simulations shown in Figures 3-14 and 3-15. Determine if adjustments to the
18 model can improve the fits or provide text in the documentation to assist the user in
19 understanding implications of these fits for using the model in specific contexts.
- 20 • Review whether any additional data for females are available that could inform model
21 parameters.
- 22 • Re-evaluate the calibration steps described in Table 4-16 considering the comments
23 provided above. Make adjustments as deemed appropriate to the model and add
24 explanations to the documentation for adjusting or not.
- 25 • Discuss the potential uncertainties associated with model calibration and evaluation from
26 historical data as compared to likely contemporary exposures.

27 **2.4.2. Charge Question 4b: The extent to which the computer code implementing the 28 model has been adequately verified and is operating as expected, based on the results 29 comparing model predictions between applications of the AALM implemented in 30 distinctly differing platforms.**

31
32 The similarity of results obtained with the model coded in ACSL and Fortran is a strong
33 verification that the current Fortran version of the model is operating as expected. However, as
34 described in Q3c, an effort to reimplement the adult model in MATLAB identified issues with
35 parameter values.

36
37 The AALM has been successfully executed with proprietary software such as ACSL extreme,
38 MATLAB and Excel on Windows operating systems. It has not yet been successfully executed
39 on Apple or Linux operating systems.

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Charge Question 4b Recommendations

Tier 1

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

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

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

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

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

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

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

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

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

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

3 • Roberts JR, Reigart JR, Ebeling M, Hulsey TC. Time required for blood lead levels to
4 decline in nonchelated children. J Toxicol Clin Toxicol. 2001;39(2):153-60.
5

6 **Comment** Manton et al., and Roberts et al.: Data on children with relatively long T1/2 of lead
7 in bone after earlier life prolonged lead exposure.
8

9 • O’Flaherty EJ, Hammond PB, Lerner SI. Dependence of apparent blood lead half-life on the
10 length of previous lead exposure in humans. Fund Appl Toxicol 2:49-54; 1982.
11

12 **Comment** O’Flaherty et al.: Decline in blood lead after cessation of exposure is markedly longer
13 in adult males with long history of exposure, consistent with strong effect of slow release of lead
14 in bone.
15

16 • Brito, J. A., McNeill F.E., Stronach I., Webber C.E., Wells S., Norbert R., Chettle D.R.,
17 2001. Longitudinal changes in bone lead concentration: Implications for modelling of human
18 bone lead metabolism. J Environ Monit 3:343-351. DOI: 10.1039/b101493p PMID: 11523432

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

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

30 • Fleming, D. E., D. R. Chettle, C. E. Webber, E. J. O’Flaherty. 1999. The O’Flaherty model of
31 lead kinetics: An evaluation using data from a lead smelter population. Toxicol Appl Pharmacol
32 161:100-109. doi: 10.1006/taap.1999.8790 S0041-008X(99)98790-2 [pii].

33 • Nie, H., D. R. Chettle, C. E. Webber, J. A. Brito, J. M. O’Meara, F. E. McNeill. 2005. The
34 study of age influence on human bone lead metabolism by using a simplified model and x-ray
35 fluorescence data. Journal of environmental monitoring: JEM 7:1069-1073. doi:
36 10.1039/b507749d.
37

38 **Comment** In Chapter 3 section 3.3, authors stated that they were able to obtain blood and bone
39 lead measurements along with dates of hire and birth dates for 209 smelter workers. However,
40 authors concluded that the data was not suitable for model evaluation. The authors state:
41

42 *“Data that were available from the Nie study consisted of three longitudinal blood and bone*
43 *XRF measurements for 209 adult Pb workers. The measurements were made in 1991, 1999*
44 *and 2008. This period included a nine-month strike (July 1990 to May 1991), during which*
45 *exposures at the plant were interrupted. The available data also included birth dates and*

1 *dates of hire. There were no data on actual exposures at the plant. Although attempts were*
2 *made to reconstruct exposures so that blood and bone Pb concentrations could be predicted*
3 *and compared to observations, ultimately, it was concluded that the data were not suitable*
4 *for model evaluations because of the uncertainty in the exposures that preceded the blood*
5 *and bone Pb measurements and that occurred during the measurement period. Exposures*
6 *prior to 1991, including the period of the strike, had to be reconstructed with no basis for*
7 *verification other than the observed blood and bone Pb measurements.”*
8

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

17 **Charge Question 4c Recommendations**

18 **Tier 1**

- 19 • Compare AALM simulation results with the data sets provided to further assess the
20 capabilities of the model. Particular attention should be paid to the comments provided
21 with each reference or the group of references associated with Nie et al., 2005 for
22 evaluating whether the model captures the behaviors described.
23
24
25
26

27 **2.5. Charge Question Five: Is the AALM Fortran Users Guide sufficiently clear and useful** 28 **in providing “user friendly” instructions for carrying out model runs for AALM** 29 **applications? How might the AALM user’s manual be improved?**

30 **2.5.1 General Comments Responding to Question Five**

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

38 Several Committee members noted throughout the review that the perception of user-
39 friendliness, and indeed the effectiveness of the model predictions, depend on the intended use of
40 the model and the experience level of the user. There seemed to be a consensus that the interface
41 is sufficiently functional for skilled modelers, but nevertheless requires internet searches to
42 overcome Excel and operations systems glitches. However, as an Application Guide for a

1 broader range of potential users (e.g., state or local public health official or risk assessors,
2 medical doctors.), the User's Guide probably discourages those who might otherwise find the
3 model a useful tool.

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

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

23 EPA Staff indicated that Question 5 refers to the internal technical specifications stated on page
24 4 of the User's Guide:

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

31
32 In that context (its purpose being to implement a FORTRAN Program using an Excel Interface);
33 the User's Guide is functional, assuming the User has substantial knowledge and familiarity with
34 similar models. Uninitiated Users would have considerable difficulty and frustration in making
35 the model operational, making informed modifications, and storing and interpreting the results.
36 There is little guidance provided, in either of the documents, regarding how to save, connect and
37 interpret the input and output summaries.

38
39 There is also confusion as to how and what would be released by EPA should AALM be
40 endorsed for use by the Agency. It is unclear whether the earlier support documents and previous
41 "... the more extensive AALM.CSL documentation ..." part of the package, as item 3 above
42 would suggest. There were references to Batch Mode simulations and other options available in

1 the ACSL edition not available in the FORTRAN version and indications that there were
2 additional compartments in some of the biokinetic modules.

3
4 As these materials were not provided to the Committee, it was difficult to assess the adequacy of
5 the User's Manual in this context.

6 7 **2.5.2 Specific Comments and Suggestions by Section**

8
9 **Front Material:** The Cover Page does not include Authors, Project Officers, responsible Agency
10 Division, Contract References or Contact information. There is no link to an "Assistance or
11 Help" resource. The Table of Contents is minimal and does not contain a Preface, List of Tables,
12 Figures, Screens, or a Glossary. These are ostensibly available in the Technical Support
13 Document and were provided in the Draft 2005 Guidance Manual. However, in some cases the
14 descriptions in the Technical Support Document are insufficient to aid in implementing the
15 model, and it is cumbersome to move between two documents that are seemingly connected, but
16 not referenced to each other. Numbering the figures and tables would help users quickly find the
17 correct one without searching through the text.

18
19 **Section I.** Introduction is brief and, for an uninitiated reader, provides minimal information as to
20 the background, purpose, development, informative descriptions, historical evolution, intended
21 or potential uses, biological and physical plausibility, computational accuracy, validation,
22 empirical comparisons. Summary descriptions of these attributes would typically be expected in
23 a User's Guide with specific reference to the Technical Support Document. In this case, the User
24 must refer to the Technical Support Document without references or refer to documents from
25 earlier versions of the AALM. The Committee suggests adding a sub-section to the Introduction
26 describing Model Limitations, identifying where data are missing or weak, and where
27 simplifying assumptions are made.

28
29 It is unclear if the final sentence in this section applies to the original Leggett model, or to this
30 document:
31 *This approach was designed to provide maximum flexibility and versatility rather than user-*
32 *friendliness.*

33
34 **Section II.** Overview of the Excel User Interface discusses the Excel user interface file, an input
35 file template, the Leggett executable, and supplemental files (User's Guide and Leggett model
36 text file). The explanation of the "pieces" is confusing. There are other Tabs in the interface file
37 that are not discussed. It is not clear that that the "input file template" are some of the Tabs in the
38 interface file. There is a second Excel file called the Intermediate Exposure Time Series file that
39 is not referenced or explained. Committee members were not able to locate the "Leggett text
40 files" indicated. The executable file is problematic in that it gives no other indication it is
41 functional other than a "blink" of a black rectangle on the screen.

42
43 Exhibit 1 does describe the 3 Steps. However, it is not explicitly stated that the buttons are
44 the activators of the Steps and it was initially unclear that every run simulation required
45 clicking on each of the boxes named "Step 1," "Step 2," and "Step 3." This only became

1 obvious after trial and error. If the executable program is not functioning, the buttons don't
2 work, and there is no message as to the source of the error, the user may not realize these are
3 active buttons, and spend considerable time looking for the Step Initiators. A "dashboard"
4 Screen Shot of the Simulation Control Sheet with descriptors and arrows would be
5 advisable.
6

7 The Note under Step 3 in the guide, particularly the last sentence, is disconcerting. Particularly
8 when the first attempt to run the program returns errors:
9

10 *"However, the code returned errors in the compilation during our testing."*
11

12 This suggests the user should be looking for the proprietary compiler. These types of editorial
13 messages, apparently provided to model developers, should be removed.
14

15 **Section III. Setup and Run** 16

17 The reviewed document's Subsection 1 provides instructions to unzip the files and place in
18 folders with read/write permissions. Brief descriptions of read/write permissions and how to
19 modify permissions would improve the document. This section also contains numerous
20 references to the "Excel File" however there are two Excel files provided and the instructions
21 apply alternatively to both. Nowhere in the Guide does it describe the purpose and function of
22 the Intermediate File, except as a summary of the lead input to the biokinetic module, although it
23 does suggest this file is vital to execute the model. The instructions to add a runtime library to
24 this Excel file are confusing. Several committee members indicated the screen shots were
25 dissimilar to those in the User's Guide.
26

27 These instructions might also be more user-friendly if implemented in steps. The first step
28 would include a screen shot of the Excel File. Step 2 should be to load the VB Editor. An
29 explanation of runtime library, VB (or VBA as later abbreviated) Editor and the purpose of the
30 Function would be helpful. The VB acronym (and others in the document) is never defined. It is
31 also noteworthy that the Alt F11 key does not work unless the user is in the Excel file, and that
32 these functions and screen shots are different for different versions of Excel. It is unclear if these
33 cautions apply to Excel in total, or to one or both Excel files? Also, are these instructions
34 applicable to other operational systems?
35

36 Step 2a would be Select Tools with an appropriate reference to the Dropdown Menu, then a
37 second shot Step 2b showing the Dropdown menu with the appropriate Box to check. The Tools
38 menu is not on the control ribbon in some versions of Excel and must be accessed through
39 Options. Also, it should be noted that a new window will appear called "References-
40 VBAProject" and that the proper entry must be checked in this Box. The Step 3 should be close
41 the VB Editor.
42

43 A caution should be added to enable Macros in all Excel files after enabling editing. This should
44 be mentioned before trying to implement the VB Editor. A screen shot indicating the yellow bar
45 etc. would be helpful.
46

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

6
7 Several committee members endorsed U.S.EPA internalizing the entire Time Step procedure and
8 with an appropriate algorithm that would allow the User to simply select the simulation Time
9 Step for the model and the frequency of the output. This would avoid having to include
10 confusing statements such as:

11
12 *One final nuance: TSTOP and the total number of cycles may not actually match each other*
13 *based on user input, and the FORTRAN code will use whichever is shorter. If TSTOP = 80, the*
14 *actual simulation period will be 80 days. On the other hand, if TSTOP = 180, the actual*
15 *simulation period will be 137.5 days (the number of cycles specified in the time step input table).*
16

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

22
23 Some description of the considerations for TSTOP would be advisable. Discussion regarding
24 changing the NDELTA is confusing. The reference to entering the value of DELTA in cell H20 is
25 somewhat confusing as the DELTA value is entered in cell I20. Also, the text indicates that Time
26 Steps 2, 3 etc. should be entered in H21, H22 etc., but these are not colored yellow to indicate
27 allowable input. Should the user do the Step numbers in these cells? The example on page 11
28 indicates NDELTA=3 (two different time steps). Should this not be 3 total time steps or 2
29 additional time steps? Shouldn't there be a warning issued regarding the "one final nuance?"
30

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

38
39 Saving the Intermediate Exposure Time Series.csv file does summarize the inputs to the Leggett
40 biokinetic modules. However, there is no apparent way to save a Table indicating inputs to the
41 Simulation Control Tab and Exposure Tabs, and Model Run Parameters corresponding to the
42 output file as opposed to summarizing the calculated inputs to the biokinetic model.

43
44 In the discussion of interpolated versus stepwise exposure time series, the term "time stamps" is
45 used but never defined. When selecting either stepwise or interpolated exposures and it is unclear
46 if the selection applies to all exposures.

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

9
10 The text indicates that, presumably internal, programming to translate exposure profiles into the
11 Leggett model is intricate and refers to a "tool" that accomplishes this translation. It is unclear
12 why this is of interest to the user or what tool this references.

13
14 The reference to the "tool" also discusses the application of the RBA tab. The text indicates that
15 the user should specify a "generic" bioavailability for (e.g., food) and then relative
16 bioavailability for the other media compared to food. This description could be at odds with the
17 use of the term relative bioavailability in other U.S.EPA applications, usually related to
18 particular lead salts dissolved in water. The discussion here should be amended to reflect
19 bioavailability determinations consistent with other EPA models and Programs.

20
21 The discussions regarding nuances of the AALM.CSL verse AALM.FOR are likely of concern
22 to the programmers doing the conversion but inclusion of the notes in a User's Guide is not
23 necessary, e.g.:

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

26
27 Section 4. Necessary Changes to the Biokinetic Input Tabs briefly notes the location of
28 biokinetic parameters but provides little information regarding these variables. Any
29 considerations for changing these values would be referred to the Support Documentation which,
30 in some instances, is insufficient to support any changes. This Section references the Pounds.dat
31 output file that has never been described throughout the document.

32 33 **Charge Question 5 Recommendations**

34 35 **Tier 1**

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

39 40 **Tier 2**

- 41 • Build up a library of training materials (pdfs of presentations, videos of tutorials) over
42 time designed for a broad user audience. These would address topics such as getting
43 started with the model and using the model to address a range of exposure scenarios.
44 Updating or extending these training materials needs to be considered a part of any tasks
45 to update or extend the model.

- Develop an application manual for the broad range of potential users, that is less technical and historical than the TSD and less focused on the computer set-up and running than the User's Guide. It would be more focused on describing the current model structure and parameter values, how to use them and interpret the results, and strengths and limitations including uncertainties of the modeling results obtained.

Tier 3

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

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

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

Fecal Excretion and Mass Balance

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

Addressing Particle Size

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

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. This is a feature that would make the model more user friendly as noted in Charge Question 6, but it also would help

1 to ensure that spurious results are not obtained due to incorrectly setting the integration step size.
2 Until such change is made, further explain the approach used for controlling numerical
3 integration error during the model simulations, as described in section 2.3.1.
4

5 Post-Exposure Kinetics 6

7 In Figure 4-19 (p 178 of the TSD, pdf p 189), the predicted decline in cortical bone lead
8 predicted from the AALM.LG appears to be very close to the decline observed in retired
9 workers. However, predicted blood lead tends to be lower than observed. This is particularly the
10 case in the first few years post-retirement where the difference between predicted and average
11 observed BLL is substantial (observed is about 14.5 ug/dL and predicted is about 10.4 ug/dL).
12

13 Although the AALM has been compared with the Hattis data to see whether measured relative to
14 model-predicted post-strike blood lead levels in chronically exposed workers are on average
15 similar (Figure 3-7 p 81, pdf p 92), further examination of the bone/blood relationship following
16 the methodology presented by Hattis (1981) is needed. Hattis emphasized that it is also
17 important to examine the model's performance relative to the number of days of workplace
18 exposure prior to the cessation of workplace exposure. He presented a reasonable method for
19 assessing the influence of workplace exposure tenure on the model's ability to predict blood lead
20 levels on average as expected (i.e. a near zero slope of the BLL relative to days of workplace
21 exposure).
22

23 Consider using Hattis's method for examining model performance relative to length of job tenure
24 (see page 25 of Hattis 1981). This is a check on whether model predictions are dependent on
25 length of employment. For example, predictions from the original Leggett model (Vork and
26 Carlisle. 2020) and the O'Flaherty model (Sweeney 2015), show some tendency to predict BLLs
27 after a 273-day strike that are too low on average for workers with shorter job tenures with a
28 trend toward predicting higher BLLs on average for workers with longer tenures. The goal is to
29 have no trend across the range of job tenures and predicted BLLs. Hattis (1981, page 25)
30 suggests that such a trend might indicate that "...less lead might be stored in slow-exchanging
31 pools than called for in the model, or the rates at which the slow-exchanging pools accumulate,
32 and release lead might be somewhat off."
33

34 Body Weight and Body Mass Index 35

36 Using age and sex (i.e., standard growth curve data) to define exposed subjects has some
37 problems as initially discussed in charge question 3c. It assumes that all women are smaller than
38 all men, which is a limitation. Parameters such as body weight, and BMI determine respiratory,
39 water and food intakes, organ sizes, blood content and partitioning in fat, muscle and water
40 compartments of the body. Also, growth curves differ among ethnic groups.
41

42 Pregnancy, Fetal and Infant Exposures 43

44 Add a gestation model for the fetus. Blood levels in the fetus relate to that of the mother, and the
45 pre-birth exposure routes are maternal blood and amniotic fluid. If a child starts life with Pb in its
46 blood, that should be added to the lifetime exposures. Otherwise the calculated blood levels and

1 risks will be underestimates. Existing pregnancy models for other chemicals would serve as a
2 good starting point, although factors that are important for lead pharmacokinetics may need
3 additional research to include them in the pregnancy modeling, e.g., red blood cells and
4 hematocrit, serum binding proteins.

6 Chelation Modeling

8 The technical guidance indicates that chelation can be simulated with the model (Section
9 2.3.1.2). When a reader gets to page 301 and Table D-1, page 313, however, the definition of
10 ICHHEL indicates that in the EXCEL implementation of the model, chelation is turned off. The
11 Excel file indicates that these parameters are fixed for no chelation and the cells in the sheet are
12 not highlighted, indicating that these parameters cannot be changed. This functionality (or lack
13 thereof) was confusing and needs to be further explained at least, but preferably would be made
14 active in the model. Further, it is not clear whether the modeling of ATSDR data described in
15 Section 3.3.8 (p 61) was done with or without chelation being modeled. This model has the
16 potential to be useful for characterizing, even predicting, changes in blood lead following public
17 health and clinical interventions (e.g., removal of exposure, chelation treatment). There are
18 concerns whether it clears lead too rapidly as noted above (Charge Question 2 – Post-exposure
19 lead kinetics). The model and appropriate parameter values, the documentation, and the
20 validation against data need to be clarified and strengthened.

22 **Charge Question 6 Recommendations**

24 **Tier 1**

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

28 **Tier 2**

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

32 **Tier 3**

- 33 • Describe methods to obtain initial values for blood and tissues to start simulation (e.g., child
34 at birth). Further check the initialization of mother model.
- 35 • Add a pregnancy model, which could be based on existing models for other chemicals.
36 Include amniotic fluid for biomarker measurements. Include capability to assess fetal
37 exposure.
- 38 • Activate or add capability to simulate chelation. The model and appropriate parameter
39 values, the documentation, and the validation against data need to be clarified and
40 strengthened for potential public health or clinical predictions.

1 **2.7. Charge Question Seven: How could specific features of the AALM be further refined**
2 **to make it more user-friendly?**

3 The committee discussed a wide range of ideas to improve the model's overall functionality as
4 well as applicability for a broader range of scenarios. Many committee members found it
5 challenging to navigate the user interface. The committee members have a range of opinions
6 with respect to the choice of model platforms (i.e., Excel). Some members appreciate the
7 transparency of the Excel worksheet environment, where equations and parameter values are
8 easily accessible. Other members recommended that EPA switch platforms altogether, citing the
9 example of EPA's Benchmark Dose Software (BMDS) – presumably referring to earlier
10 versions, given that the current version utilizes an Excel workbook interface.

11 The committee felt that it would be beneficial for the broad range of stakeholders to be able to
12 use this model. It is highly likely that it could have quite valuable roles in public health practice
13 and research, as well as in risk assessment and risk management. For the model to be broadly
14 accessible and user friendly, it needs to be structured to readily accept the kinds of information
15 that are available to public health professionals (e.g., dust lead loading, as reported by public
16 health agencies in mcg/ft²), and researchers as well as risk assessors.

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

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

24 **Charge Question 7 Recommendations**

25
26 **Tier 1**

- 27 • Create a library of input files (or example Excel workbooks) that correspond with
28 example scenarios. Then use those scenarios as part of the User's Guide and other
29 training materials to coach new users on various common scenarios, and how to populate
30 the dialogue boxes. The current User's Guide gives an example for water intake. The
31 Committee recommends providing at least one example for each exposure pathway and
32 environmental medium.
 - 33 • Improve the consistency in naming conventions for model input variables between the
34 user interface (Excel file) and the accompanying documentation.
 - 35 • Create additional user options to specify parameters for the relative bioavailability (RBA)
36 term. Currently, a single RBA applies to all intakes for a specific exposure medium as
37 previously noted in charge question 3b. This seems counter to the model's flexibility in
38 allowing for multiple values of Pb intake in soil or dust at different times of the day (or
39 week). It seems likely that the soil or dust in different occupational, residential, and
40 public setting may have different solubility, particle size, and chemical composition, and
41 by extension, different RBA.
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Tier 2

- Create a single worksheet in which figures are automatically generated for some of the more common x-y scatter plots (e.g., time series for blood, plasma, bone, etc.; blood vs plasma; intake vs blood Pb; etc.)
- Eliminate the user option to change the step size and rely on a predictor-corrector algorithm.
- Provide a plausible range of input values (for the central tendency estimates), at least for selected parameters for which source information is uncertain.
- Create a single worksheet for risk characterization. It might apply an assumed lognormal distribution model and generate a plot automatically (also see response for charge question 9 on approaches to addressing variability and uncertainty). Include a short set of entries at the top of the page that are dynamic (i.e., change the plots when the entries are changed). Incorporate user-specified GSD and age ranges to display. Include a tabular summary of common risk metrics: 1) probability of exceedance of user-specified threshold; 2) predicted blood lead concentration at user-specified percentile.
- As part of the Simulation Control worksheet, include an option (toggle) for the user to enter a constant media concentration for each of the common exposure media (e.g., soil, dust, air, water, etc.), as an alternative to populating the age-specific concentrations in each separate worksheet. This should allow entry in units that arise in a range of different settings, including for example amount of Pb per square foot for dust ug/ft² in addition to the currently entered ug/g.
- Consider including the Adult Lead Model directly in the current workbook such that entries are automatically populated (linked) to the entries specified by the user when running AALM. As a research tool, this will facilitate the understanding of AALM's application in a risk assessment context, including features that have been enhanced and/or changed.
- How to effectively implement age-related changes in food intake needs to be clarified in the model documentation and examples created. EPA should consider including an appendix to the model documentation of suggested sources or values for age specific intake rates or other parameters needed for implementing this pathway.
- Since this is a life-stage model and simulations can be started from birth, accounting for breast milk exposure would be essential. Add text to explain how it can be done.

1 **Tier 3**

- 2 • One application of the AALM might be to assist clinicians in estimating and interpreting
3 the future pattern of blood lead in a patient who presents with an elevated value and is
4 ostensibly removed from further exposure. If the blood lead did not decline as predicted
5 by a physiologically based pharmacokinetic model such as the AALM, this might raise
6 suspicion of occult ongoing exposure that merits further investigation. To enhance
7 potential use of the AALM for this purpose, future versions may be able to use available
8 information on a subject's current blood lead, age, and approximate exposure history to
9 create a modeled version of the subject in which each tissue compartment has been
10 primed with compatible estimates of lead mass. An application like this, would also need
11 to be compared to appropriate data to demonstrate its reliability.
12
- 13 • Consider a module that allows for exposure or kinetics parameters to be modified to
14 account for co-exposures to other chemicals. Exposure to lead typically occurs in
15 conjunction with simultaneous exposures to other heavy metals of concern to human
16 environmental health, especially susceptible populations. AALM may sufficiently model
17 Pb exposures in most scenarios, although it seems monolithic in that it cannot model
18 exposures to real-life exposures to multiple metals. This should be viewed as a limitation
19 of the model, possibly significant, especially when one considers the weight of evidence
20 in the published scientific literature that Pb, Mn, Hg and other metals may converge on
21 absorption, transport, metabolic, and neurotoxicity pathways.

22

23 **2.8. Charge Question Eight: Is the AALM consistent with the Agency's Regulatory**
24 **Environmental Model Guidance found at URL:<http://cfpub.epa.gov/crem/>**

25

26 The Panel agreed that the model documentation and development processes for the AALM have
27 generally been consistent with the EPA CREM guidance. The guidance document presents
28 evaluations of the AALM.FOR (and other AALM versions—AALM.OF and AALM.LG) against
29 (some) existing data and compared the AALM.FOR to the IEUBK model and the Adult Lead
30 Methodology. In addition, EPA has conducted peer reviews of past versions of the model and
31 they are now conducting this peer review. The CREM guidance provides extensive lists of
32 recommended practices. Many of these have been addressed for AALM such as the summary of
33 recommendation for model development at the beginning of Section 3 and aspects to be peer
34 reviewed (p 24 and Box D2 p 63 of CREM Guidance).

35

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

41

1 The link for the guidance document given in the charge question did not work. However, Panel
2 members were able to find it at: [https://www.epa.gov/sites/production/files/2015-](https://www.epa.gov/sites/production/files/2015-04/documents/cred_guidance_0309.pdf)
3 [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.

4
5 CREM guidance indicates that a primary step in model development includes the need to “(a)
6 specify the environmental problem (or set of issues) the model is intended to address and
7 develop the conceptual model (EPA 2009 CREM guidance, page vii). This is currently absent in
8 the review version of Technical Support Document for AALM.FOR. A revision should include
9 a detailed discussion of intended model applications that describes when use of the AALM is
10 appropriate or is not appropriate, or when the model parameters would require modifications.
11 Applications where the model is believed to have the strongest and weakest predictive
12 capabilities should be identified. If this model is used for a scenario or with data that it was not
13 designed to address, the outcomes may not be valid, and this should be clearly explained. For
14 example, as discussed above in the response for Charge Question 3b, the strengths and
15 weaknesses of applying the model to occupational inhalation exposures should be highlighted.
16 For example, compared to airborne environmental lead exposures, occupational exposures could
17 be characterized by larger particles with different deposition locations in the respiratory tract, as
18 well as ventilation rates that exceed defaults for most adults with community lead equations.

19
20 Given the high sensitivity of the model to some parameters as discussed in the response for the
21 final part of Charge Question 3, the Panel recommends performing uncertainty analyses. A
22 weakness of this model, like other complex pharmacokinetic models, is deriving parameter
23 values from data requiring underlying assumptions. Elements that are recommended for
24 inclusion as part of the uncertainty analysis:

25
26 Tables of key uncertainties of inputs and outputs: These tables should make key uncertainties
27 clear to model users and risk assessors.

28
29 It should be clearly conveyed to users that uncertainty in model outputs will vary. For example,
30 there are simply more data sets available with measured blood lead versus brain lead levels and
31 there is thus more uncertainty around the prediction of brain lead.

32
33 The WHO/IPCS PBPK Guidance (WHO/IPCS 2010), containing tables for characterizing
34 uncertainty and variability, could be useful in uncertainty evaluation for the AALM. It is
35 recommended that the Agency evaluate this document and include similar tables in the
36 documentation for the AALM. Specification of uncertainties should then focus future research
37 efforts to address those needs.

38
39 Bayesian statistical analysis using Markov Chain Monte Carlo methods incorporates parameter
40 correlations and should be performed on at the very least, blood lead, in order to obtain
41 uncertainty estimates in kinetic parameters. Separate analyses should be performed for
42 biokinetics and for the exposure module in order to obtain uncertainty estimates for the two
43 separate parts of the model. MCSim, which is free software, can be used to perform Bayesian
44 analyses and can be found at: <https://www.gnu.org/software/mcsim/> (accessed March 12, 2020).

1 There are numerous parameter values included in this model, and many of the variable value
2 selections should not be made in isolation. In addition to uncertainty analyses, additional
3 sensitivity analyses might be conducted that examine the effects of multiple variable interactions.
4 These findings might lead to additional guidance cautions about the appropriate ranges and other
5 parameter settings that might be considered in altering input values.
6

7 An understated strength of this model is that it can be applied across a large range of biological
8 effects, age and exposure/dose considerations. There is an unfortunate tendency in Agency
9 efforts to focus modeling and research efforts on current U.S. exposure levels. This model is also
10 applicable to the higher levels of lead intoxication observed globally in vulnerable populations. It
11 could be of immense service to international institutions implementing health and environmental
12 responses. The calibration and verification efforts should continue to be across the full range of
13 lead intoxication levels previously observed in the U.S.
14

15 It may be useful to compare the data used in Leggett's original model and the updated AALM to
16 develop and/or update parameters values with criteria listed in the CREM guidance on study
17 quality. Attributes of study quality are also addressed in a series of articles on this subject
18 written by Leggett and colleagues; these articles should be evaluated by the Agency. In addition,
19 comments about the quality of data used to calibrate and test model parameters from the original
20 Leggett (1993) publication should be extracted and commented on in the technical guidance.
21 The assumptions, rationale, and limitations of parameter values listed in the original Leggett
22 model should also be checked and commented on.
23
24
25

26 **Charge Question 8 Recommendations**

27 **Tier 1**

- 28 • Develop a clear statement of model applications considered appropriate for the current
29 status of the model and the available parameter values. Providing examples of these
30 applications would also benefit users.
31

32 **Tier 2**

- 33 • Assess AALM parameters and outputs using CREM guidance on study quality and
34 consideration of comments in Leggett (1993). Add results of analysis to model
35 documentation.
- 36 • Develop a plan to characterize uncertainties in the model outputs, along with those in
37 model inputs, and begin implementing the plan. Initial steps would likely be more
38 qualitative, e.g., table recommended in the WHO/IPCS PBPK Guidance. Later steps
39 would be increasingly quantitative, e.g., Monte Carlo or Markov Chain Monte Carlo
40 analyses.
41

1 **2.9. Charge Question Nine: What additional information (if any) about AALM might be**
2 **useful to users who want to assess a hypothetical or real-world risk assessment**
3 **problem, in order to facilitate the correct application of the model and to**
4 **communicate its modeling outcomes correctly and efficiently?**

5 **2.9.1. Evaluating lead concentrations in exposure media associated with benchmark**
6 **changes in blood lead**

7
8 Risk managers and other stakeholders occasionally encounter risk management questions for
9 which it is desirable to examine the isolated contribution to blood lead (or another biomarker of
10 lead burden) arising from a certain medium and/or route of exposure. For example, risk
11 managers may be interested in discerning the isolated contribution of a certain concentration of
12 lead in soil to blood lead concentration in a certain demographic group, such as a two-year-old
13 toddler or an outdoor adult worker. In a notable peer-reviewed article, scientists with the
14 California Office of Environmental Health Hazard Exposure (OEHHA) expressed their opinion
15 that with respect to environmental lead exposure, an increase in blood lead of 1 $\mu\text{g}/\text{dL}$ to a young
16 child would constitute a reasonable benchmark change for environmental decision-making
17 (Carlisle et al., 2009).¹ OEHHA then utilized the California Department of Toxic Substances
18 Control's slope-factor model, LeadSpread, to calculate that a concentration of lead in soil or dust
19 equal to 77 $\mu\text{g}/\text{g}$ would yield a benchmark blood lead increment to a child of 1 $\mu\text{g}/\text{dL}$ at the 90th
20 percentile (CalEPA 2009). In like manner, OEHHA applied EPA's Adult Lead Model (EPA,
21 2005) to calculate that exposure of a pregnant adult worker to a soil concentration of 320 $\mu\text{g}/\text{g}$
22 would yield a 1 $\mu\text{g}/\text{dL}$ increment in the blood lead concentration of the neonate at birth (CalEPA
23 2009). For each of the foregoing assumptions, OEHHA entered various default values in the
24 respective models for parameters such as exposure frequency, soil intake rate, and geometric
25 standard deviation. Intake of lead from other pathways was considered to be zero. For the adult
26 worker scenario, the geometric mean background blood lead concentration was assumed to be
27 0.6 $\mu\text{g}/\text{dL}$.

28
29 It may be envisioned that the AALM could be utilized to address questions of a similar nature
30 relating soil exposure to estimated increment in blood lead. The design of the AALM requires
31 assumptions about prior lifetime lead exposure history and the corresponding lead content of
32 various tissue compartments. This could be addressed by developing certain generic datasets or
33 libraries of past lead exposure depicting representative lifetime lead exposure patterns for various
34 receptors, such as a two-year-old child, or a 25-year-old male or female adult. When used in
35 conjunction with the AALM, these datasets could be used as a point of departure to solve for a
36 certain concentration and pattern of soil lead exposure (e.g. exposure to X ppm of lead in soil for
37 90 consecutive calendar days, or 250 consecutive work days) that would be associated with a
38 benchmark increment in blood lead concentration (e.g. 1 $\mu\text{g}/\text{dL}$). As currently structured, the
39 AALM would yield an exposure that would apply to a benchmark blood lead increment at the
40 central tendency, or median. Application of methods to estimate variability around the central

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

1 tendency, e.g. by use of an assumed GSD or Monte Carlo modeling, could be added to the
2 AALM to yield medium-specific lead values that would yield a benchmark change in blood lead
3 to the 95th percentile receptor.
4

5 **2.9.2. Population variability in AALM outputs to facilitate use in risk assessment and risk** 6 **management**

7
8 As noted above, the current construction of the AALM.FOR yields outputs for tissue
9 compartments, such as blood lead, that represent central tendency estimates derived from the
10 selected exposure inputs and biokinetic settings. While these central tendency estimates are
11 informative, risk managers often require outputs that also present tissue concentration such as
12 blood lead at the upper end of a population distribution, e.g. the 95th percentile. For example, the
13 IEUBK model is used in risk assessment to calculate the geometric mean blood lead
14 concentration, the 95-percentile confidence interval about the geometric mean, and the 95th
15 percentile of the lognormal distribution. The latter value represents the blood lead concentration
16 that will be exceeded by no more than 5% of children subject to the exposure inputs (e.g. soil
17 lead concentration) of the modeled situation. IEUBK calculates the 95th percentile using a
18 geometric standard deviation (GSD) that is intended to capture the variability in everything
19 except the concentration term. Specifically, the GSD incorporates variability inherent in behavior
20 that contributes to the exposure (such as hand to mouth activity), relative bioavailability of lead
21 in soil, and biokinetics. EPA has long recommended the default GSD of 1.6, although use of
22 site-specific GSD is permissible.
23

24 Several approaches would be possible to depict variability around central tendency estimates
25 generated by AALM.FOR. As with the IEUBK, it would be possible to assume that the
26 population distribution is lognormal and can be calculated using an assigned GSD. Some
27 panelists cautioned that unlike the long term experience with IEUBK that has validated the use
28 of a default GSD of 1.6 for childhood blood lead, there is insufficient data and experience with
29 the AALM.FOR to identify a default GSD valid for the myriad of settings and age ranges for
30 which the model is intended.
31

32 Probabilistic methods, incorporating Monte Carlo simulations for exposure and biokinetic
33 parameters, would represent an alternative approach to estimation of variability in AALM.FOR.
34 Monte Carlo modules have been developed for use with IEUBK (Goodrum *et al.*, 1996), for the
35 O’Flaherty model applied to childhood blood lead (Beck *et al.*, 2001), and for the O’Flaherty
36 model applied to adults with occupational lead exposure (Sweeney, 2019). Panelists suggested
37 that variability in the AALM.FOR outputs could be generated using either conventional (random
38 seed) Monte Carlo methods, or Markov chain methods, applied to both exposure and biokinetic
39 parameters.
40

41 **2.9.3. Multiple user-friendly model outputs**

42
43 A key area of research is to develop a better understanding of what measures of lead in the body
44 best relate to neurotoxicological outcomes. Since AALM calculates lead levels in blood and

1 different tissues, it could assist in research on such questions. What measures of lead in blood
2 (e.g., circulating unbound lead levels, average daily lifetime blood lead level, area under the
3 curve for blood concentration, cumulative blood lead levels), brain, or bone would be most
4 informative about health outcomes? Would expansion of the brain model beyond a single
5 compartment be useful? Is there an “ideal” bone for measuring lead deposits, what contributes to
6 the differences, and what role does bone injury play in re-exposure to deposited lead?

7
8 Pb in bone, as measured by non-invasive K x-ray fluorescence (KXRF) has been shown in
9 various studies to be a biomarker of an individual’s blood lead level over time (cumulative blood
10 lead index, or CBLI). As reported in several publications from the Normative Aging Study, a
11 person’s bone lead concentration at mid to late life, or an increment bone lead concentration
12 across a given age strata, are better predictors than blood lead (or change in blood lead) of
13 significant health endpoints such as cardiovascular morbidity and mortality and cognitive
14 function. The ability of the AALM to include bone lead concentration as an output is likely to be
15 helpful for risk assessment. By reference to investigations such as the Normative Aging Study,
16 this information may facilitate assessment of the health risks associated with cumulative lead
17 exposure.

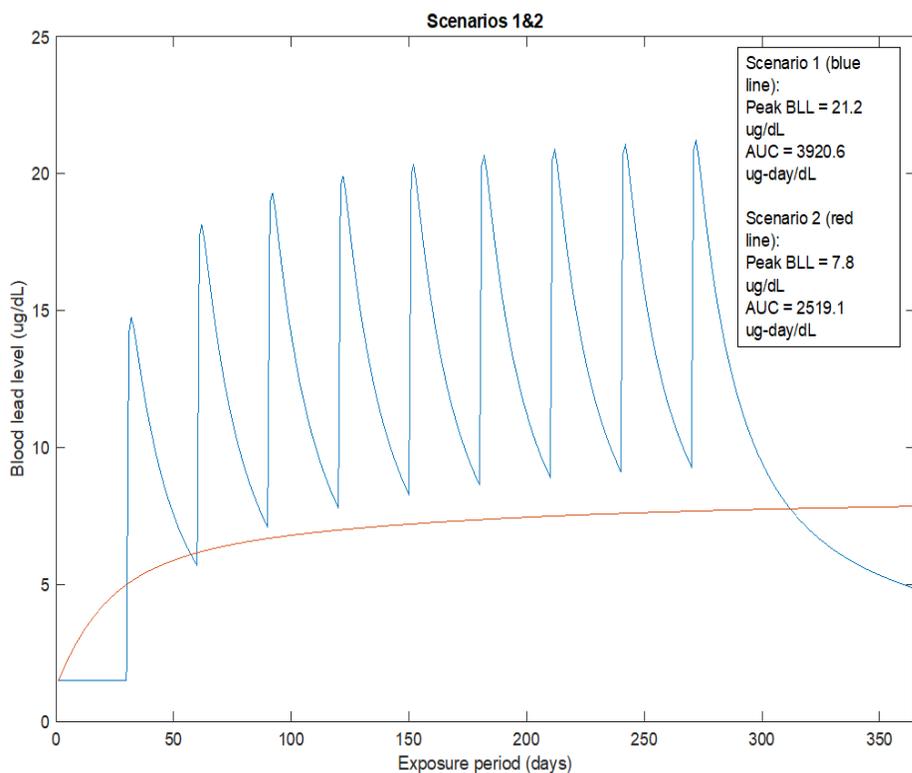
18
19 The validity of KXRF as a biomarker of cumulative lead has primarily been established by
20 favorable comparison of a single KXRF measurement to long term blood Pb biomonitoring in
21 occupational cohorts. In most cases, the Pb exposure of these cohorts has been relatively stable
22 for many years, (sometimes with a gradual decline over time). Based on this data, Person A with
23 a cumulative blood lead index (CBLI) of 300 $\mu\text{g}/\text{dL}\cdot\text{years}$ will predictably have a higher KXRF
24 bone lead concentration than person B with a CBLI of 200 $\mu\text{g}/\text{dL}\cdot\text{years}$ where Person A
25 sustained 20 years of blood lead of 15 $\mu\text{g}/\text{dL}$ and person B sustained 20 years of blood lead of 10
26 $\mu\text{g}/\text{dL}$. However, it’s not clear how the KXRF bone lead measurements would compare if Person
27 B’s CBLI of 200 $\mu\text{g}/\text{dL}\cdot\text{years}$ were instead accrued through 15 years of blood lead of 5 $\mu\text{g}/\text{dL}$
28 followed by 5 years of blood lead of 25 $\mu\text{g}/\text{dL}$. Outputs from the AALM that include estimated
29 bone lead burden is likely to facilitate research into the utility of KXRF as a biomarker.

30
31 In like manner, a few epidemiological studies have found that CBLI is a significant predictor of
32 adverse health effects. This metric may grow in use in the future. It would be useful for
33 AALM.FOR to calculate CBLI (essentially the area under the curve of blood lead by time plot)
34 as an output. For example, this may be helpful in illustrating how infrequent exposure to high
35 levels of lead in air, e.g. during infrequent maintenance work, might result in considerably more
36 cumulative lead exposure than regular daily exposure at lower levels.

37
38 For example, the consider two scenarios evaluated by the OEHHA Leggett+ model. The area
39 under the curve (AUC) in the model represents CBLI for this time interval.

40
41 Scenario I. A 25 year old worker who starts work with a BLL of 1.5, and whose only lead
42 exposure for the next year is one 8 hour day, once a month for 9 months, engaged in heavy work
43 (breathing rate of 8.67 $\text{m}^3/8$ hour) where the airborne lead is 500 $\mu\text{g}/\text{m}^3$. The second scenario is
44 the same worker, but this time he begins work characterized by moderate exertion, 5 days a
45 week, for 12 months, at an air lead concentration of 10 $\mu\text{g}/\text{m}^3$. Over the course of one year, AUC

1 for scenario 1 = 3075 ug-day/dL, for scenario 2 it is 2477 ug-day/dL. This illustration depicts the
2 pitfall of exempting workers with only infrequent lead exposure from medical surveillance.
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9 Figure 9-1: Simulations of blood lead concentration for two different exposure scenarios over the
10 course of a year: one day of high exposure each month for nine months, versus 5 days a week
11 lower level exposure, using the 2015 OEHHA Leggett + model.

12 2.9.4. Comparison of multiple model simulations

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

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1 **2.9.5. Assessing exposure due to paint**

2
3 Guidance on how to estimate and assess lead exposure from lead-based paint would be useful
4 (maybe in the context of presenting some examples with real-world exposures/exposure
5 patterns). Estimates of how much paint children might ingest at different ages and examples that
6 estimate lead intake based on the lead content of paint from XRF measurements would be much
7 appreciated. There is probably a lot of uncertainty around these types of data but even some
8 guidance on recommended values would be helpful. Any guidance on how to evaluate cases
9 with paint exposures or lead from other sources (pottery, dishes, etc.) would be helpful.

10
11 **Charge Question 9 Recommendations**

12
13 **Tier 1**

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

18
19 **Tier 2**

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

32
33 **Tier 3**

- 34 • Provide guidance on addressing exposures arising from the presence of lead in paint.
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APPENDIX A: EDITORIAL CORRECTIONS

- 1
- 2
- 3 The SAB recommends that the following editorial corrections be made to the AALM Technical Support
- 4 Document.
- 5
- 6 P 3 line 1: strike “A Brief History of”
- 7 P 3 line 14: delete “minimal”
- 8 P 3 line 14: Title line –Setup or Set Up ?
- 9 P 8 line 9: options or option ?
- 10 P 9 line 8: is age 20 missing from series?
- 11 P 9 line 12: change “intakes concentrations” to “intake concentrations”
- 12 P9 line 13 and 19: Appendices are at the end of the document, not in this chapter.
- 13 P 9 lines 27-30: Needs to be at least two sentences. Fix grammar.
- 14 P 10 Inset: Change “word to Wise” to “Warning”
- 15 P 10 Inset, last line: Delete “slightly”
- 16 P 13 line 17: Add “at” before “different”
- 17 P 15 lines 1 and 3: use a better descriptive term or define “tool”
- 18 P 15 lines 8: should be “water” pathway not “air”?
- 19 P 18 line 7: For completeness, add plasma protein and extravascular to the listing of compartments that
- 20 lead in diffusible plasma can exchange into.
- 21 P 18 lines 22 and 29: Appendices are at the end of the document.
- 22 P 23 line 11 – There are small errors in the Table.
- 23 P 23 line 29 – The equation for UPTAKERT did not provide the expected results, which were obtained
- 24 from $UPTAKERT = (1 - CILIA) \times \sum(YR_i \times (1 - e^{-BR_i}))$. Note that other equations appear to have a
- 25 similar error and need to be corrected.
- 26 P 23 line 32: BR_i is a rate not a fraction
- 27 P 27 line 4: Correct Eq. 2.3-35 to match to equation in Table 2-2.
- 28 P 27 line 20: Delete “of binding”
- 29 P 31 line 35: Change “form” to “from”
- 30 P 32 line 12: Delete “up”?
- 31 P 32 line 23: Delete “in”
- 32 P 53 lines 31-34: long, complex, incomplete sentence
- 33 P 57 line 26: make “period” plural
- 34 P 59 line 33: make “Figures” singular
- 35 P 61 line 13: fix “were parameters were”
- 36 P 66 line 20-21: delete one “renovations” from this sentence
- 37 P 80 line 5: fix grammar, “experienced”?
- 38 P 279 line 8: “TRW” undefined and unreferenced
- 39 P 281 line 10: Change “ventilation rates” to water intake
- 40
- 41
- 42 Throughout the document, “CLS” should be changed to “CSL” when discussing ACSL model files. For
- 43 example, on p. 1 (lines 17-19; pdf page 12), “AALM.CLS” should be “AALM.CSL.”
- 44
- 45 Page 303 Appendix D: Calculation of RDIFF from $\ln 2$ /half-life has a typo, 0.00231.

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Editorial Comments Relevant to Charge Question 3(a)

1. Table A-1

a. Soil submodel, p. 195: typo on subscript “Soil” on RBA term

Exposure	Soil	For each discrete age: $IN_{soil_{discrete}} = Soil_{TWA_{discrete}} * IR_{Soil} * RBA_{Doil}$
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b. Other submodel, p. 197: subscript “1” on Other1

Exposure	Other	For each discrete age: $Other_{Total_{discrete}} = Other_1 + Other_2 + Other_3$
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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: $EAT = IN_{ingestion_{total}}$

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

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

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

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

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

2. Table B-1.

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

IR_water	unitless	C	S	Female of male
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2 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
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4 c. Confirm that term “indoor soil” is intentional – is it better defined as simply “soil”?
5 p. 257

Age_soil_IR	day	A	F	Age for indoor soil ingestion rate
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7 p. 259

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

12 a. p. 276, table at Line 4: following the units in the footnote, explain the statistics given in the table
13 (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

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

5 Data on dust Pb loading on indoor surfaces ($\mu\text{g Pb}/\text{ft}^2$) provide additional source estimates of

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17 b. p. 276, line 13: delete the word “of” in the phrase “A value of equal to...”; line 14: add hyphen for
18 “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).

19
20 Furthermore, modify the sentence to explain how the corresponding soil Pb concentration is 25 $\mu\text{g}/\text{g}$, 50
21 $\mu\text{g}/\text{g}$, or 250 $\mu\text{g}/\text{g}$ depending on proximity to historical emission sources and the age of the housing
22 stock. In total, suggest the following revision:

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

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

Full Transect (n = 4841)	Statewide Average (n = 48)
25 (8, 44) ^a	30 (14, 68) ^b
Units: µg/g. Statewide average is the average of state means. ^a 5 th -95 th percentile range ^b range	

- 4
 5 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

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

- 7 Suggest the following notes:
 8 units (GM, median, mean): µg/g
 9 GM, geometric mean; GSD, geometric standard deviation

- 10 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

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

- 12 f. p. 281, line 8, delete extra “e” at end of line
 13 g. p. 281, line 10, change “ventilation rates” to “drinking water ingestion rates”

14 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:

- 15 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
≥18250	1.04		≥18,250	50	1.04

2 The same comment applies to the following summary tables:

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

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

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

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

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

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

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

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

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

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

19 p. 291

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

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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
Model users and applications														
Clarify audience	Tier 1													
Create "Application" Manual	Tier 2									Tier 2				
Specify appropriate model applications	Tier 1			Tier 1										Tier 1
Training materials										Tier 2				
Variable step size algorithm											Tier 2			
Modernized interface										Tier 3				
Editorial														
Editorial and Clarifying Changes in Documentation	Tier 1	Tier 2												
Consistent nomenclature					Tier 1									Tier 1
Distinguish "prediction" and "output"							Tier 1							
Fix Model Structure Figure	Tier 1													
Edit Users Guide for AALM.FOR										Tier 1				
Hyperlinks in documentation	Tier 3													
Inhalation														
Ventilation rates and activity			Tier 1											
Particle size				Tier 2							Tier 2			

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

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Topics of Recommendations/Charge Questions	Q.1 Documentation	Q.2 Model support	Q.3a Intake rates	Q.3b Absorption	Q.3c Distribution & Elimination	Q.3 Model assumptions	Q.4a Predictive accuracy	Q.4b Code verified	Q.4c Other data	Q.5 AALUM Fortran Guide	Q.6 Improve predictions	Q.7 User friendly	Q.8 CREM Guidance	Q.9 Model applications & out put
BW, BMI					Tier 2									
Sweat elimination					Tier 3									
Variability in urinary clearances							Tier 2a							
Peak blood lead modeling							Tier 2a							
Initial values for blood and tissues											Tier 3			
Exposures														
Additional exposure examples												Tier 1		
Constant media concentration & background or baseline exposures			Tier 1&3- dust,soil									Tier 2&3		Tier 2
Soil and dust			Tier 2 - water		Tier 2									
Lead in paint modeling			Tier 2											Tier 3
Occupantional Exposure			Tier 2				Tier 2a							
Chelation											Tier 3			
Sex, life stage, & health														
Reassess data for females							Tier 2							
Infants - reevaluate Figs 3-14&15							Tier 3							
Breast feeding (Lactation)			Tier 2									Tier 2		
Pregnancy											Tier 3			
Menopause & bone kinetics					Tier 2									
Inhalation and respiratory diseases			Tier 3											

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

*Tier 2a: A single recommendation covers these topics