Quality Reviews Comments from SAB Members on the SAB Draft Reports:
(1) Review of the All Ages Lead Model External Review Draft 2.0
(2) Technical review of EPA's Computable General Equilibrium Model, SAGE

List of comments received
June 22, 2020

COMMENTS ON THE DRAFT SAB REPORT: REVIEW OF THE ALL AGES LEAD MODEL EXTERNAL REVIEW DRAFT 2.0 3

Comments from Lead Reviewers 3
Comments from Dr. Janice Chambers 3
Comments from Dr. Susan Felter 4
Comments from Dr. John Guckenheimer 6
Comments from Dr. Sue Marty 11

Comments from other Chartered SAB Members 15
Comments from Dr. Rodney Andrews 15
Comments from Dr. Barbara Beck 15
Comments from Dr. Tony Cox 17
Comments from Dr. Otto Doering 17
Comments from Dr. Thomas Parkerton 18
Comments from Dr. Mara Seeley 21
Comments from Dr. Richard Smith 21
Comments from Dr. Kimberly White 22

COMMENTS ON THE DRAFT SAB REPORT: TECHNICAL REVIEW OF EPA'S COMPUTABLE GENERAL EQUILIBRIUM MODEL, SAGE 23

Comments from Lead Reviewers 23
Comments from Dr. Otto Doering 23
Comments from Dr. Richard Williams 24

Comments from other Chartered SAB Members 25
Comments from Dr. Rodney Andrews 25
Comments from Dr. Hugh Barton 26
Comments from Dr. Tony Cox 26
Comments from Dr. John Guckenheimer 26
Comments from Dr. Thomas Parkerton 27
Comments from Dr. Richard Smith 28
Comments from Dr. Kimberly White 28

OTHER COMMENTS ON THE DRAFT REPORTS PROVIDED BY SAB CHEMICAL ASSESSMENT ADVISORY COMMITTEE MEMBERS..... 30
Comments from Dr. Dennis Paustenbach 30
Comments from Dr. Ted Simon..... 31
Comments from Dr. Eric Smith..... 31

<u>Comments on the Draft SAB Report: Review of the All Ages Lead Model External Review Draft 2.0</u>

Comments from Lead Reviewers

Comments from Dr. Janice Chambers

1. Were the charge questions to the Panel adequately addressed?

The charge questions seem to have been adequately addressed. The Panel had detailed answers to all of the questions. The Panel provided an analysis with literature citations to support their points as well as specific information on some of the points being made. The Panel provided evidence of trying to use the model, along with some of the difficulties encountered in these attempts. The Panel identified some deficiencies in the draft report as well as some data needs and some terms which should be clarified in the text. In addition, a few errors were pointed out for correction by EPA staff. Points of confusion in the current draft were identified with suggestions for clarification.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No error or omissions noted.

3. Is the draft report clear and logical?

Generally the report is clear and logical, but there are a few items that should be addressed for greater clarity and utility to the EPA staff who will use the report to improve the draft:

   a. Some of the recommendations are short and to the point, while others are relatively long and contain additional explanation of the reasoning behind the recommendation (examples include recommendations for Charge Questions 3c, 5, and 7); the latter explanations would be better placed in the text describing the Panel's deliberations preceding the recommendations. It would be more useful to EPA to have all the recommendations short so that EPA will have the Panel's guidance focused on single points within each recommendation. The explanations should be moved out of the recommendations and into the preceding text if they are not already in those sections, or deleted if the explanations are redundant with the preceding text.
   b. Two formats were used for the recommendations, some being declarative and others being imperative. One format should be selected and used throughout the report for consistency.

c. In a few cases the explanatory text used imperative statements that should be changed to be declarative statements for consistency; examples include pg 52, lines 2, 23 and 44.
d. Many EPA reports contain an Executive Summary but this one does not. An Executive Summary would be useful to EPA staff to provide the major points and most important recommendations in a single place. A summary of the major points was not included in the letter to the Administrator, and the major points might be useful in this letter as well.
e. The report should be carefully proofread and edited to make the entire report more consistent in format and more consistent with formal writing; examples include: elimination of contractions (e.g., don't); elimination of the use of the first person (e.g., we); providing consistency in line spacing and eliminating the large space on page 40 for better aesthetics; identification of any definitions of abbreviations that follow instead of precede the first use (e.g., definition of AF, absorption fraction, occurred on pg 29 after it was used on the preceding page).
f. While the report was well written and essentially free of typographical errors, the use of "verse" on pg 50 line 21 probably should have been "versus".

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations seem to be reasonable and supported by the body of the report.

Comments from Dr. Susan Felter

Quality Review of Draft SAB Review of the All Ages Lead Model External Review Draft 2.0

1. Were the charge questions to the committee adequately addressed?

Overall, the report is well-organized and all charge questions were adequately addressed.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

One point that comes up many times in the draft SAB report relates to occupational exposures and short-comings in EPA's report/model to address these. It's not clear to me that the AALM is intended to address occupational exposures – if yes, this should be emphasized as a critical need; if no, the report should be modified to remove the multiple references relating to this.

I was surprised to see that the updated model is still in Fortran (with excel interface). Is this still commonly used for PBPK modeling?

3. Is the draft report clear and logical?

Cover Letter:

The cover letter (ll 31-33) states: "The Panel recommends that the Agency make those changes, clarifications, corrections, and edits to the model and documentation needed to allow use of the AALM 2.0 for research and additional testing" and goes on to state that the AALM 2.0 is currently available on the SAB website such that the EPA should "implement these Tier 1 actions as quickly as feasible…" Given that this will take some time, should the SAB recommend that precautionary language be added to make potential users aware of problems that have been identified? Given the urgency indicated in this recommendation, it would be helpful to summarize (in the cover letter) in concise form the nature of the corrections needed (or at the very least, point the section of the report that addresses this). I

It also seems that there is a bit of a disconnect with the language above and the final statement in the cover letter that, "As the EPA finalizes its External Review Draft AALM Draft 2.0, the SAB encourages the Agency to address the panel's concerns raised in the enclosed report" – this does not suggest the same sense of urgency as the previous language did.

Report: Overall the report is well-written and well-organized. It is especially helpful to see the clear prioritization of recommendations. Following are some page-specific comments:

p. 7, ll 39-42: The definition of Tier 2 should be looked at carefully as the first part of the definition says that EPA is encouraged to adopt these recommendations, but the second part says say EPA should consider other factors first. Should the definition be revised to say that EPA should "*consider whether to adopt*"?

p. 8, ll 4-5: Last sentence of Introduction states that, "All dissenting opinions (if any, or additional comments provided at the concurrence step) are presented within Appendix B." The report should make it clear up front if there are (or are not) dissenting opinions, rather than say "if any…"

p. 11, ll 3-4: Text states, " The model structure has been altered by removing the transfer of lead from diffusible plasma to bladder contents (i.e., the transfer rate is now zero)." Please check this – I still see an arrow going from diffusible plasma to the bladder in Figure 2-1.

p. 24, ll 29-30: The draft report as assigned a question relating to breast milk as a Tier 2 recommendation. Please consider whether this should be elevated to Tier 1, given the importance of lead exposure during early life.

p. 25, ll 34-35: draft report states that "Clarification is needed for whether dermal absorption is included as a specific pathway…" It seems the SAB should ask for more than just clarification. If it is not included, would we want to make a recommendation that it be added? (note, this comment also pertains to p. 31, ll 35-36 where this statement is given as a Tier 1 reco).

Bottom of p.25/top of p. 26: text refers to "relatively small environmental lead particles" and "larger particle sizes." These should be defined.

p. 28, ll 2-4: Text refers to ciliary action (related to inhalation by workers – see my earlier question regarding occupational exposure) and states that "inhaled particles that are removed by ciliary action and swallowed during and after meals where absorption efficiency can increase

substantially from the default of 12% oral absorption of lead from the small intestine." Is there a basis to conclude this? Ciliary action is continuous such that the relevance to 'during and after meals' is not clear.
From https://www.sciencedirect.com/topics/medicine-and-dentistry/mucociliary-clearance: "Particles deposited in the ciliated airways are cleared out by the mucociliary escalator usually within 24–48 h"

p. 29, ll 5-6: This text refers to Pb "ingested during outdoor recreation or work when food is not eaten" – is this a reference to hand-to-mouth transfer of lead, or mucociliary clearance following inhalation (in which case, see previous comment re. text on p. 28).

p. 31, ll 24-25: Text seems to be questioning whether bioavailability of lead is age-dependent. I think this is fairly well-substantiated for ingested lead.

p. 36, ll 17-18: Reco is made here to update default body weights (make heavier) because "Body weight is a key parameter in biokinetic models, because it influences blood and organ mass and perfusion." While true, we know from PBPK models for pharmaceuticals that sometimes it is best to model using actual body weight, and other times it is more appropriate to use ideal bw or even lean bw. Do we know which is best for Pb? If actual bw is most appropriate, this should be described along with the reco to update the default value for bw.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Overall, yes. That said, it would be helpful to make sure that the Tier 1 recommendations are especially clear. As an example, p. 11, l 32 provides a Tier 1 recommendation that:

- Figure 2-1 needs to be modified in order to be more accurate.

This should be expanded up to be clear what the recommendation is (and please see my question above relating to a statement made on p. 11). There are many other examples where some recommendations are quite abbreviated (and not clear by themselves what is needed) and others are quite detailed – it would be helpful to make them more consistent.

Comments from Dr. John Guckenheimer

Quality Review Questions (answered at the end of this assessment)

1. Were the charge questions to the Panel adequately addressed?
2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
3. Is the draft report clear and logical?
4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The All Ages Lead Model v2 (AALM) estimates lead concentrations in blood, bone and other body organs resulting from changing lead concentrations in the environment. The model evolved

from three models created in the early 1990's: the IEUBK model for lead concentrations in children ages 0-7, a model Leggett developed at Oak Ridge National Laboratory in connection with studies of biological accumulation of radionuclides , and a physiologically based model developed by O'Flaherty, initially fit to experimental data on rats. The original AALM fortran model has been modified over time, reimplemented in the proprietary acslX language and given an excel interface for users. Both this review panel and previous review panels found it difficult, at best, to run the model and verify that its output matches the Technical Support Document (TSD). Despite these difficulties, this review panel and previous ones judged the AALM to be a good tool that should be supported and further improved. I find this conclusion questionable and present here a more critical analysis of the AALM which addresses the quality review questions listed above.

Charge question 8 for the Review Panel asks whether the AALM is consistent with EPA Regulatory Environmental Model Guidance (cred_guidance_0309.pdf). This EPA guidance document reminds us that the scientific context and objectives of models should be stated clearly in plain language. As noted by the Review Panel (pp.62-63) the AALM does not make such a statement. I looked for existing or potential EPA applications of the software that might highlight its usefulness. I found no documented applications, but here are four potential ones:

1. Estimate how much lead accumulates in varied body tissues from lead in drinking water and how quickly it is depleted when lead concentrations in water are reduced.
2. Estimate how much lead accumulates in varied body tissues from lead dust in houses containing lead paint and how quickly it is depleted when the lead paint is removed.
3. Estimate how quickly lead is depleted in body tissues of individuals who accumulated high lead levels through long time exposure in their work environments.
4. Analyze the significance of lead radio nucleotides as carcinogens in the aftermath of nuclear accidents, Chernobyl being a particular important case that motivated Leggett's work.

Most lead in the body accumulates in blood and bone. The health effects of lead concentrations in these compartments and other organs are outside the scope of the model. Measurements are difficult, so there is relatively little data available to parameterize the AALM. The biokinetics of lead does not appear to be a very active research area: the most recent of the twelve references cited by the Review Panel (Section 2.4.3) as suited for model evaluation is from 2005 and the next most recent is from 2001. I found no data from "high throughput" measurements of lead in the body. Thus, time series of lead concentrations have large intervals between measurements. Nonetheless, the scope of the AALM is broad and has the objective of fitting lead concentrations in several different body. There are no quantitative metrics to assess model fits or even a discussion of the accuracy authors and reviewers expect. Attempts by reviewers to implement simulations of the AALM for comparison with data and with other models have encountered

missing information as well as technical problems in running the models successfully. When the AALM has been used to simulate different data sets, fits required ad hoc changes in parameters. Still, prior reviews have not questioned the conceptual structure of the model and have expressed only modest frustration about how hard it was to run the software. If the model is to be used as a tool for regulatory purposes, we need to be clear about its accuracy and reliability.

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

The numerical integration issue is a fundamental weakness of the AALM. Abstractly, differential equation models have the form $x'=f(x)+i(t)$ where x is a vector encoding the state variables (e.g., amounts of lead in each body compartment), f is the "right hand side" which expresses the rates of change in the state variables and i(t) is a vector of inputs (lead from the environment). Approximate trajectories are computed in discrete time steps. Numerical integration algorithms require the user to code the right hand side which evaluates f(x) and specify initial values of x at the start time and the input functiont i(t). The AALM is not organized in this way. It incorporates an explicit low order formula (Eq. 2.3-2 in the TSD) for its time stepping that is intermingled with the formulas that evaluate the right hand side. This yields unacceptable run times for simulations having sufficient accuracy, prompting further ad-hoc modifications to the software. Furthermore, the current version of the AALM buries the integration algorithm beneath an excel spreadsheet that calls fortran libraries with a run-time library that is specific to the visual basic language used by excel The review panel attempted to extract f(x) for use in a matlab reimplementation with standard numerical integration algorithms, but they encountered difficulties in making this work. Almost all modern computational science software includes fully implemented and documented examples that can be used to test the software on different computers. The lack of such examples and the arcane computing environment required by the

AALM are serious deficiencies. I do not think further efforts to remedy these deficiencies are warranted because the conceptual foundations of the Leggett model are also weak.

The Leggett model begins with the assumption that the right hand side of the model is linear. This limits the number of parameters required to specify the model and yields solutions given by sums of exponential functions. Engineering systems are often linear. When data gives poor fits to the engineering models, a common strategy is to add more state variables that yield more exponential time constants. For the AALM, this results in splitting single compartments into multiple compartments solely for the purposes of fitting the data. However, biokinetic processes are seldom linear, leaving the Leggett model with weak scientific foundations. The models created by O'Flaherty are much better in this regard, but the AALM still follows the Leggett approach at its core. When time series of lead concentrations are not fit by single exponentials, new compartments are created to yield sums of exponentials with different time constants. No pretense is made to establish biological principles for the extended models. Thus, the Leggett model can be viewed as "data driven" with a tenuous relationship between model variables and identified physical quantities.

Would the resources of the EPA to be better used to create a new model rather than to improve and extend the AALM as recommended by the Review Panel? The deficiencies described above and additional limitations noted by the Review Panel are strong arguments for reimplementation. Little would be lost scientifically by abandoning the AALM because there are few, if any, applications of the AALM to studies of lead accumulation and retention in the scientific literature. I note that the AALM played no role in the recent SAB report on lead in water systems.

The accuracy of the AALM as tool to estimate the uptake, retention and excretion of lead by the body is hardly clear, so it does not seem ready for use in the context of EPA rule making. For example, the EPA is reconsidering the "action level" for replacing lead pipes and fittings in public water systems to reduce the toxic effects of lead concentrations in children. Since most of the lead in the body is retained in blood and bones, the EPA might use the AALM to estimate the correlation of lead concentration in people with the lead concentrations in an individual's environment. However, there is still too much uncertainty in the model to trust its results. Reference data sets should have been chosen and used for quantitative evaluation of the model with regard to its regulatory objectives. Moreover, as described by the Review Panel, comparison of model output and data ideally would take account of individual variation, stochastic fluctuations and measurement errors. I see no evidence that the AALM can be modified with reasonable effort to meet these objectives. If the SAB agrees with this conclusion, then we should make alternative recommendations to the. Here are a few suggestions.

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

Computers and computer software have changed dramatically during the twenty five years since the AALM was first created, but the evolution of the model has taken relatively little advantage of these improvements. Open source software (including packages specifically designed for investigation of dynamical models) and high level programming languages like Python, Julia and Matlab (or its open source alternative Octave) make it far easier to implement models of moderate complexity and enable much more extensive exploration of their properties. The deficiencies of the AALM strongly suggest that the EPA stands to benefit far more from creating a new model to simulate the biokinetics of lead than by investing more resources into the AALM. One possible strategy is for the agency to support an interdisciplinary team that will create and implement a new model while simultaneously conducting empirical studies to calibrate and test their model. Joint programs of the NSF and NIH to support collaborations that span the interface between mathematics and biology have demonstrated the effectiveness of this strategy in quantitative modeling of biological systems. Based on this analysis, here are answers to the questions that I was asked:

1. Were the charge questions to the Panel adequately addressed?

Most of the charge questions were adequately addressed. However, the charge questions and the Panel responses hardly address fundamental issues about the utility and quality of the AALM.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

The weakness of the scientific foundations and the numerical methods in the AALM should have been given more emphasis in the report of the Review Panel. The report does a good job in pointing to extensions of the software needed to deal with random effects and systematic comparisons of the software with data .

3. Is the draft report clear and logical?

Yes.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report.

No. Individual items in the report identify many shortcomings in the AALM software. The Panel was charged to review the draft technical support document rather than the software itself. Nonetheless, they made recommendations for improving the software. The poor numerical and scientific foundations of the AALM support the conclusion that the EPA should create new software tools for analyzing lead in the body rather than investing further effort in the AALM.

Comments from Dr. Sue Marty

Please address the four quality review questions below from the vantage point of your own expertise:

1) Were the charge questions to the committee adequately addressed?

The All Ages Lead Model (AALM) covers the contribution of lead exposure across various media (air, water, food, dust and soil) on lead concentrations in blood, bone, and tissues in infants through adults 90 years of age. The SAB provided an excellent review of the AALM, including a review of model features, the scientific basis for parameterization, ways to evaluate the predictive accuracy of the model and the clarity and user-friendly nature of the accompanying User's Guide. The SAB should be commended for their thorough review of the AALM, especially for finding important errors/disparities in parameter values and for providing first-hand feedback on downloading and running the model with application of the User's Guide. Thus, the SAB adequately addressed the charge questions. and provided detailed justification for the requested revisions. In addition, the three-tiered approach for recommendations (Tier 1 – recommended revisions; Tier 2 – suggestions; Tier 3 – future considerations) provides a clear account of SAB's priorities when EPA revises the AALM and accompanying report.

Some important comments by the SAB that resonated with this reviewer are:

- It is important for the EPA to clearly identify its audience and uses for the model and guidance as this drives the level of technical complexity that should be included in the guidance manual and User's Guide. This reviewer also agrees with the SAB advocates for development of a less technical guidance document as one potential solution to engage a greater breadth of stakeholders.

- Clearly present the strengths and limitations of the model. This will identify scenarios where the model can be used, situations for which the model is not appropriate and will help to identify where additional data can improve model predictions.
- Suggestions made by SAB to make AALM more user friendly are valuable. Currently, implementation may be problematic for less experienced modelers, which will limit model use. The recommendations for additional training materials, including text with screen shots, training videos and library of training materials (including input data) for different exposure pathways/examples and technical support. Typical scenarios modeled should be highlighted in the User's guide.
- Allowance of different relative bioavailability (RBA) from different sources is an important point to allow for multiple lead intake values at different times/scenarios for the same medium (e.g., occupational lead in air vs. environmental lead in air where factors like particle size and solubility can differ and will affect RBA). This will be important to understand the relative contribution of different exposures to overall body burden.
- The SAB noted that incorporation of particle size and ventilation rates to reflect activity are important (p. 16-17). Particle size also affects deposition in the respiratory tract and subsequent transfer to the GI tract by mucociliary clearance. This seems particularly relevant for children, a sensitive subpopulation with relatively high levels of activity.
- The SAB made several useful suggestions to evaluate the model parameters, model performance and model uncertainty, including additional data sets that can be modeled.
- For some aspects of the AALM, the SAB rightly acknowledges the lack of available data (e.g., the possible contribution of nasal olfactory update of ultrafine lead to brain lead levels), but these parameters are important to recognize for future versions of the model when data become available
- This reviewer agrees with the SAB recommendation to consider adding lactation to the model. Maternal bone turnover increases during lactation, resulting in redistribution of lead from bone into plasma. Thus, both bone and diet can contribute to lead in breast milk. However, it is recognized that this may be a longer-term goal as there is some disagreement on the magnitude of transfer of lead through breast milk (i.e., reported values are highly variable). Furthermore, milk is a complex matrix, which may complicate collection of these data.

Overall, the SAB provided an excellent review the their proposed revisions will strengthen both the AALM and its supporting documents.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

This reviewer did not identify any technical errors or omissions in the SAB review. Overall, the draft report was very well done. The following suggestions on prioritization are offered for consideration by the SAB:

- Updating age- and sex-specific growth curves/body mass is reasonably straightforward and these parameters impact several other model variables (blood volume, organ mass, perfusion), thereby potentially compounding model uncertainty. Consider moving this recommendation to Tier 1.
- Incorporation of variables to better capture lead levels at various life stages will improve the use of this model for sensitive subpopulations and establish more realistic values for chronic/lifetime lead exposure.
    - Consider whether a greater priority should be assigned to the addition of a pregnancy life stage to the AALM. This is a sensitive period for lead exposures and contributes to the overall lifetime body burden of lead. Bone lead stores are mobilized during pregnancy with lead levels increasing as pregnancy progresses. Lead readily crosses the placenta by passive diffusion and reports indicate that maternal blood lead levels are highly correlated with umbilical cord lead. There are data to show that lead in the fetal skeleton likely originates from the mother. Iron status and calcium intake may be important factors in maternal-fetal transfer of lead across the placenta. Maternal age also appears to be a factor as older women tend to have more lead stored in bone and may release more to the developing fetus.
    - There are other age-related changes in uptake and release of lead from bone. For example, postmenopausal women have higher blood lead concentrations due to higher bone turnover and release of lead from bone. Lead also may be released during joint replacement procedures. Thus, age scaling for bone growth and remodeling, possibly sex-dependent, would be useful.
- The SAB should verify that all acronyms are defined on the acronym page. Perhaps a second page of acronyms of model parameters would be beneficial to ensure that EPA and SAB reviewers are referencing the same points (e.g., CILIAR, BR 1-4, DFs, TEVF, TRBC, TORBC, TOORBC – in some cases, the difference between two variables discussed in the report are minimal so this would ensure that there is no confusion.

Typos:

p. 9, l. 22-23: "…applications in which ~~use of~~ the AALM in its current form can be used."

p. 10, l. 9 "…version 5 of the ICRP model to a hybrid ~~of~~ model is significant."

2.3.4 (p. 38, l. 5-6) Sentence repeated from above: "Evaluate whether to retain the plasma-D to bladder and sweat elimination pathways in the model".

3) Is the draft report clear and logical?

Yes, the draft report is both clear and logical. The tiered recommendations make it easy for the EPA to identify priorities that need to be addressed before the reports are finalized.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations are adequately supported by the body of the report. As stated above, the recommendations highlight the thoroughness of the SAB's review.

5) Does the Letter to the Administrator adequately reflect the findings of the SAB report?

The conclusions of the SAB review committee are briefly stated in the Letter to the Administrator; however, the letter also provides an opportunity to emphasize some 'high level' SAB recommendations. Thus, in the letter, the SAB could consider adding a paragraph on some of the most critical changes to the AALM, technical guidance document and User's guide. Specifically, the SAB may wish to highlight that:

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

Comments from other Chartered SAB Members

Comments from Dr. Rodney Andrews

1. Were the charge questions to the Panel adequately addressed?

Yes.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

None that I could discern as a non-SME. The statements made in the report are clearly supported by either literature citation or by inclusion of data or example.

3. Is the draft report clear and logical?

Yes. The report was clear and logical, often including specific examples or references.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Barbara Beck

Comments on the SAB All Ages Lead Model (AALM) Review Panel Report

Barbara D. Beck, PHD, DABT
June 22, 2020

The Review Panel Report is thoughtful and well-written. The expertise of the panel members clearly shows through.

My comments fall mainly into two categories: a) the need to consider the applicability of the model to EPA risk assessment/risk management activities and b) the need to take fuller advantage of some prior studies on lead exposure and modeling.

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 recommendation to allow a mechanism for inputting dust lead loading cannot be over-emphasized for the model to be applicable to exposure to lead in the home. Because of regulatory requirements, dust lead loadings are often more available than dust lead concentrations. As noted in the panel comments the

US EPA 2019 Technical Support Document for Residential Dust-Load Hazard Standards Rulemaking describes a method for converting dust lead loading into dust lead concentration. However, the non-linearities in the relationship between loading and concentration are a source of uncertainty in the model. EPA should give consideration to restricting the use of the relationship between loadings and concentration to the linear range.

The author of the panel report refer to the lack of a lead dermal uptake component as an uncertainty. Given the poor dermal uptake of inorganic forms of lead[1], I would suggest that the impact of excluding this pathway is not much of an uncertainty. I recommend EPA perform a simple sensitivity calculation to evaluate the dermal uptake. I expect such a calculation would demonstrate that this pathway is unlikely to have a significant impact on the model.

The panel report recommends that the AALM should be compared with the IEUBK and the ALM with additional examples. This is a very important recommendation, especially for the AALM use in a regulatory context. There are some important considerations with such a comparison:

- The IEUBK and the ALM models aim to predict geometric mean (GM) blood lead levels (BLL) and a distribution, based on the addition of a geometric standard deviation (GSD) to the predicted GM. The panel's recommendation that EPA discuss how they would address this point as part of a comparisons across models is important.
- It is unclear to me whether the BLL predicted in the AALM (described as a central tendency) is intended to be a GM (the appropriate metric for BLLs) or an arithmetic mean. EPA should clarify this point to determine whether the post-hoc addition of a GSD to predicted BLLs is appropriate for this model.
- The AALM and the panel report are silent on how the AALM relates to the Stochastic Human Exposure and Dose Simulation (SHEDS) IEUBK model. Given that the SHEDS IEUBK was used in both the US EPA 2019 Technical Support Document for Residential Dust-Load Hazard Standards Rulemaking and in EPA's Proposed Lead and Copper Rule Revisions (recently reviewed in 2020 by this panel), I recommend that EPA discuss the SHEDS IEUBK model in any comparison with existing models.

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

The relative bioavailability (RBA) of lead in fasting versus fasting conditions is a potentially important consideration; however, it must be made in context of the duration over which food can reduce uptake of lead from the gut (typically over several hours) and the frequency with which a fasting state occurs, especially in the context of the long half-life of lead in the body. That is, an occasional fasting situation may have little impact overall on BLL. On the other hand, if fasting is more persistent (e.g. a worker never consumes breakfast), the impact could be greater. I agree with the panels' recommendation that EPA further evaluate this issue. I note that this point could be addressed through some sensitivity calculations and suggest that EPA consider performing such calculations in the next iteration of the AALM.

I strongly endorse the panel's recommendation that the user be able to input different RBA for the same medium. This could be especially relevant to lead in soil at a contaminated site where lead from different sources (e.g. paint, versus mine tailings, versus smelter sources) could be present.

[1] While organo-lead forms (e.g. tetraethyl lead) are well taken up, their use has been banned in gasoline for many years and they do not persist in the environment. Hence, it is unlikely that they would present any typed of concern in the US today.

I didn't find see any discussion in the panel report of the potential impact on particle deposition of nasal breathing versus oro-nasal breathing, especially under high activity, occupational conditions. I expect this could be too complicated to incorporate into the model at this point; however, I recommend EPA discuss this issue as an uncertainty.

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

I strongly agree with the panel's recommendation that steady decline of soil ingestion rates from ages 2 – 15 years be reconsidered. This assumption by EPA is inconsistent with the general literature on soil ingestion rates. For examples, studies demonstrate that hand to mouth activity (the primary mechanism for dust and soil ingestion) for peaks around age two and declines dramatically afterwards. Further, as described in O'Flaherty (1995) in her PBPK model for lead in children, infection with *Toxicara canis*, a soil parasite, peaks at age 3.

Comments from Dr. Tony Cox

Preliminary Comments on *SAB Review of the All Ages Lead Model External Review Draft 2.0*

1) Were the charge questions to the Panel adequately addressed? Yes. This is a clear, technically cogent review.
2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report? Not that I found.
3) Is the draft report clear and logical? Yes.
4) Are the conclusions drawn or recommendations provided supported by the body of the draft report? Yes, they are well supported. This is a good piece of work.

Comments from Dr. Otto Doering

1. I believe that the charge questions to the Panel were adequately addressed.
2. I did not find technical errors or omissions or issues that were not adequately dealt with in the draft report.
3. I believe that the draft report is clear and logical. Good organization of responses after charge questions and very helpful prioritization of recommendations.
4. I believe that the conclusions drawn and/or recommendations provided were supported by the body of the report.

Comments from Dr. Thomas Parkerton

1. Were the charge questions to the Panel adequately addressed?

RESPONSE: Yes, the charge questions were well addressed by the Panel.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

RESPONSE:
P15 Under the Tier 3 recommendations, it is recommended that EPA obtain more data to address the direct inhalation exposure pathway to the brain via direct nasal olfactory uptake. It would seem logical to also recommend that future enhancements to the AALM model explicitly consider this pathway.

P19 L27 Provide a reference to support the baseline concentrations of lead in water (0.9 ppb) that is mentioned.

P39 L37-39 Suggest further justifying why the adjustment for bone Pb based on bone mineral does not provide the expected answer while the alternative equation proposed does as this may not be obvious.

P58 L17-18. It is stated "Attributes of study quality are also addressed in a series of articles on this subject written by Leggett and colleagues; these articles should be evaluated by the Agency." However, the specific references to which the Panel are referring are not provided. Recommend adding the relevant citations here.

P60 L21-22 Is there a citation or two that can be added to support the statement "EPA has long recommended the default GSD of 1.6, although use of site-specific GSD is permissible."

3. Is the draft report clear and logical?

RESPONSE: The report is generally well written and organized. The sections that summarize and categorize of recommendations after responding to each charge question should be particularly helpful to EPA in using this report to inform next steps for finalizing the AALM.

I offer a number of editorial suggestions and recommendations for clarifications that may be helpful improvements.

Letter to administrator

Consider revising:
The Panel has described ~~many of~~ these actions in its Tier 1 recommendations

Suggest clarifying the sentence:
"These recommendations are largely described in the Panel's Tier 2 recommendations and in some Tier 3 recommendations."
since it is unclear what Tier 3 recommendations are covered in this remit

P7 L14 delete “realatively-steady”

P8 The sentence “All dissenting opinions (if any, or additional comments provided at the concurrence step) are presented within Appendix B.” is confusing. It should be clear if or if no dissenting opinions are included in Appendix B.

P9 L17 delete “itself”

P9 L39-41 Suggest rewording sentence as follows:
The Panel questioned how the growth curves were defined, implemented and discussed in terms public health and medical practitioners could understand.

P10 L9 delete “of”
P10 L14-18 Suggest following revision
“…the O’Flaherty model needs to be made more transparent. Many of O’Flaherty’s equations appeared in the TSD, since the growth equations are used in AALM. For the childhood and adolescent part of the model, Leggett has a significant discussion about the uncertainty of lead mass transfer parameters in childhood and adolescence due to limited data available for calibration.

P10 L20-21
Clarify “check” do you mean “predictions” ?
L20 are the values published in Legget estimates or are they measured values based on autopsy data, suggest clarifying.

P11 L 7 change “would” to “could”

P14 L24 typo .. data are

P18 L36 delete “in any manner”

P28 L1-4
It is not clear why the absorption efficiency can increase from the default value .. it may be helpful to refer the reader to next section where the reason is explained.

P29 L8-9
Replace “It further calculated ..” with “Further calculations were provided for ..

P31 L7 spell out red blood cells (RBC)

P36 L39-40
Reword …”Popovic et al. (2005) compared blood and bone concentration in a cohort study of women with a history.”

P38 L5-6 The first charge question needs to be moved up before this issue is addressed and recommendations provided on P37 L7-11.
Delete extraneous text “*Charge Question 3 continued”*

P38 L24-26 suggest revising text to:

Since these parameters are in different compartments in the two models this result is unexpected. The present discussion does not provide a satisfactory explanation to account for the significant impact these parameters serve on model outcomes.

P38 L34-35 delete “of their”

P49 L45 delete ‘and”

P51 L1-5 suggest clarifying recommendation as follows

- Develop an application manual for the broad range of potential users that is less technical and historical than the TSD and excludes details on the computer set-up and running than the User’s Guide. The manual should focus on describing the current model structure and parameter values, how to run and interpret model results, and describe model strengths and limitations including key uncertainties.

P61 L22 Based on these data

P81 L38 correct typo

P57 L26-37
It is stated that:
“Tables of key uncertainties of inputs and outputs: These tables should make key uncertainties clear to model users and risk assessors. It should be clearly conveyed to users that uncertainty in model outputs will vary. For example, there are simply more data sets available with measured blood lead versus brain lead levels and there is thus more uncertainty around the prediction of brain lead.”

It is not clear what is to be included in these tables .. the earlier paragraph specifically mentions input parameter uncertainty. Further, the availability of more data sets for blood lead does not indicate model uncertainty is reduced. Please clarify this point and also be more specific on what the Panel envisions needs to be included in the Tables requested and how this relates to the WHO/IPCS PBPK Guidance tables for characterizing uncertainty and variability that is then cited. This clarified text should also be reflected in the corresponding Tier II recommendation provided at the end of this section.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

P15 L2-7
The panel designates that the following recommendation be considered as Tier II

- *Obtain additional datasets that document the decline in blood lead concentration following abrupt cessation of long-term elevated lead exposure.* Evaluate AALM.FOR model predictions for blood lead decline after extended intervals of moderate to high lead exposure to characterize the accuracy of the model.

However, given the concerns expressed by the Panel (P13, L5-41) that the current model formulation may significantly underestimate blood levels over long exposure periods, I question if this recommendation should not be designated as a high priority. Suggest reconsider elevating this action to Tier 1.

P31L41-45 … It is stated "However, when pre- and post- retirement blood lead presented on one worker in Figure 3 of Nie et *al*., 2005 were extracted and used by one committee member to model trabecular and cortical bone lead in a MATLAB version AALM, trabecular bone lead declined to less than cortical bone lead beginning approximately 5 years post-retirement."

It might be helpful to include a further description and results of this simulation in an Appendix.

Comments from Dr. Mara Seeley

AALM Quality Review

1. Were the charge questions to the Panel adequately addressed?
   The Panel seems to have adequately addressed the charge questions

2. Are there any technical errors, omissions or issues that are not adequately dealt with in the draft report?
   There are no readily apparent technical errors, omissions or issues that are not adequately dealt with in the draft report.

3. Is the draft report clear and logical?
   Some sections of the report, including 2.3, 2.4 and 2.5, are clear and logical, and the discussion is easy to follow. Other sections of the report (2.1, 2.2, 2.6) could be more concise, cohesive, and better organized.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
   The conclusions and recommendations are supported by the body of the draft report.

Comments from Dr. Richard Smith

Lead report:

1. Were the charge questions to the Panel adequately addressed?

Yes

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No

3. Is the draft report clear and logical?

Yes

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Kimberly White

1. Question: Were the charge questions to the Panel adequately addressed?
Answer: The All Ages Lead Model Review Panel was tasked with addressing nine charge questions. The draft report is organized to address each charge question and recommendations are provided based on priority for completion (i.e. tier I, II or III). All questions appear to be adequately addressed in the draft report.

2. Question: Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
Answer: I did not identify technical errors, omissions or issues that were not adequately addressed.

3. Question: Is the draft report clear and logical?
Answer: The draft report appears clear and logical. The draft report could benefit from shortening of some of the text associated with each charge question. For example, in several areas throughout the report there are paragraphs proceeding the recommendations which appear to recap or introduce several of the recommendations that follow those sections.

4. Question: Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Answer: The conclusions and recommendations appear to be supported by the body of the draft report.

<u>Comments on the Draft SAB Report: Technical Review of EPA's Computable General Equilibrium Model, SAGE</u>

Comments from Lead Reviewers

Comments from Dr. Otto Doering

A Lead Review of the 'SAB Technical Review of EPA's Computable General Equilibrium Model, SAGE'
Otto Doering
Purdue University

Overall I believe this is an excellent and most constructive review that should be most valuable for EPA in the development of this new analytical capacity. I come away from reading it with admiration for the work of the review panel.

1. I believe that the charge questions were adequately addressed by the panel. EPA's staff provided charge questions that were excellent and most relevant to assessing and improving the model which helped the review team to be most effective in its review.

2. I did not identify important technical errors or omissions or issues that were inadequately dealt with in the draft report.

3. I found the draft report both clear and logical. This was driven by the clear charge questions and then the review committee's excellent job of organizing their responses into the relevant sub-topics. The prioritization of recommendations under these sub-topics added to the clarity and logic of the review committee's response and should aid EPA in directing its resources towards improving the model.

4. The review team provided clear concise support for the recommendations in both theory and practice.

Comments:

First, I believe that the recommendations and the priority given to the recommendations are well targeted to key characteristics of CGE models and what should be expected of them.

It is important that EPA recognizes that the review panel's Tier 1 Modeling Recommendations are essential if the model is to do what a GCE model is intended to do - i.e. capturing the aggregate welfare and/or distributional impacts of a policy while taking cross-price and cross-

market effects into account and being driven by a framework of consumer and producer maximization. The three Tier 1 modeling recommendation areas highlighted in the transmittal letter are particularly important for this task. There is one recommendation that I might elevate to tier 1 status. That is recommendation CQ10-9 on page 23, Allow Imperfect Competition. The assumption of such things as perfect competition in CGE models is violated in the real world by government price setting or deal making and monopoly situations. The model should be prepared from the outset to consider this situation as an important sensitivity analysis scenario. I also support a related concern of the review panel reflected by the Tier 1 recommendation on page 13 to Relax the Small Open Economy Assumption of the model.

Last, when one constructs and operates a CGE model, one bias may be to fervently believe it. This amplifies the importance of getting it right as much as possible at the outset, approaching it's results with healthy skepticism, and creating the flexibility to run different scenarios based on very different basic economic and behavioral assumptions.

Comments from Dr. Richard Williams

Review of the Transmittal of the Science Advisory Board report on its technical review of EPA's 15 Computable General Equilibrium Model, SAGE, dated [TBD
June 22, 2010

Although not an expert in this area, I have reviewed the above SAB technical review as a non-expert in this area and have addressed the following four quality review questions.

1) Were the charge questions to the Panel adequately addressed?
P. 14. Charge question 2.4 - There are multiple places where testing the model is addressed although it is not clear whether there are retrospective reviews of the predictions of the model.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
Page 4, line 5. – "The model includes (presumably) a number of diagnostics that provide confidence in the resulting solution. On page 15 lines 4-7 the SAB recommends additional diagnostic tests. On page 22 lines 4-6 it notes that stronger empirical parameterization will allow the agency to move toward formal probabilistic uncertainty analysis.
These three sections appear to be addressing uncertainty through "diagnostics" but it should be clear, not "presumably" that models, data, and choices of distributions should be subject to uncertainty analysis, as is done for partial equilibrium models.
p. 7 line 34 – I'm not an expert in this area but my understanding of CBO practices is that they are bound by certain unrealistic assumptions. For example, Lawrence Kotlikoff has repeatedly

argued that CBO debt estimates don't take into account full financial obligations for transfer payments
.
3) Is the draft report clear and logical?
The draft report is clear and logical although in it is not clear who the "Less Technical Readers" are in section 2.1.1 on page 2. Are they for stakeholders who are evaluating the results of the model or possibly agency policy makers who are making decisions based on the results? This could be clarified.
p. 6 line 9 – Is there any sense of confidence in a model of this sort going out 41 years?

4) Are the conclusions drawn or recommendations provided supported by the body of the draft *report?*

They appear to be comprehensive.

Comments from other Chartered SAB Members

Comments from Dr. Rodney Andrews

Comments on the Technical Review of EPA's Computable General Equilibrium Model, SAGE

1. Were the charge questions to the Panel adequately addressed?

Yes. Charge Question 4 was very broad and it would be unrealistic for the panel to address all possible outcomes; however, the response was as adequate as possible within that context. The response to Charge Question 10 may go beyond the request for near term improvements, but is well within the scope of the overall report.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

None that I could determine as someone without specific expertise in this area.

3. Is the draft report clear and logical?

Yes. I found both the text and the organization very clear and logical.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Hugh Barton

Comments on the Technical Review of EPA's Computable General Equilibrium Model, SAGE

1) Were the charge questions to the Panel adequately addressed? No answer as this is not my field.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report? No answer as this is not my field.

3) Is the draft report clear and logical? Yes.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report? Yes

Comments from Dr. Tony Cox

Preliminary Comments on *SAB Technical Review of EPA's Computable General Equilibrium Model, SAGE*

- Model validation is not discussed much, but is crucial for assessing the value of the information provided by SAGE (or other CGE or AGE models). (https://www.researchgate.net/publication/304452270_Catching_up_with_history_A_methodology_to_validate_global_CGE_models)
- How should SAGE be updated in response to events such as the COVID-19 pandemic?

Comments from Dr. John Guckenheimer

Assessment of the two SAB Panel Report on Computable General Equilibrium (6-4-20)
John Guckenheimer

1. Were the charge questions to the Panel adequately addressed?

The Panel Report gives thorough answers to the charge questions, including many recommendations for changes and additions to the SAGE model.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not identify any. However, further assessment of numerical issues associated with SAGE would have been helpful. The Report implicitly assumes that the software just runs.

3. Is the draft report clear and logical?

Yes.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Thomas Parkerton

1. Were the charge questions to the Panel adequately addressed?
   Yes, the charge questions were all thoroughly addressed and recommendations effectively prioritized.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

   P 23 It is unclear if Recommendation CQ10-6 is a tier 1, 2 or 3 action. Please clarify.

3. Is the draft report clear and logical?

   Yes the report is well written and organized. A few editorial comments are provided below.

   P6 L25 .. revise to "… fuller discussion of this topic."

   P10 L 18-20 suggest rewording this sentence as follows:
   "…EPA assumes a real interest rate of 0.045 (Council of Economic Advisers, 2017) and calculates the time preference rate that would be necessary to achieve the assumed interest rate."

   P11 L20 … revise to "…EPA consider this approach."

   P14 L34-35 suggest rewording this sentence as follows:
   "…helping analysts outside the agency consistently interpret model output reliably."

   P19 L 3 typo "that" used twice

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

   None that I could identify given my limited expertise in this field.

Comments from Dr. Richard Smith

CGE report:

1. Were the charge questions to the Panel adequately addressed?

Yes

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No

3. Is the draft report clear and logical?

Yes

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Kimberly White

SAB draft report titled "Technical Review of EPA's Computable General Equilibrium Model, SAGE"

General Comments: The Computable General Equilibrium Model, SAGE, is outside my area of expertise but I have reviewed the draft report and addressed the quality questions below.

1. Question: Were the charge questions to the Panel adequately addressed?
Answer: The CGE Model Review Panel was charged with addressing nine questions related to three topics: (1) technical accuracy and defensibility of the model, (2) approach to model versioning and peer review of future model updates and (3) priorities for improvements of the

model framework. All the charge questions appear to be addressed and recommendations for improvement, as applicable, are included.

2. Question: Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
Answer: I did not identify technical errors, omissions or issues that were not addressed in the draft report.

3. Question: Is the draft report clear and logical?
Answer: The draft report appears to be clear and logical.

4. Question: Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Answer: The conclusions and recommendations are supported by the body of the draft report and the authors have presented their recommendations in three tiers, thus offering the Agency priorities for implementation of the recommendations.

Other Comments on the Draft Reports Provided by SAB Chemical Assessment Advisory Committee Members

Comments from Dr. Dennis Paustenbach

Review of EPA's "All Ages Lead Model" (External review Draft II)

I have reviewed the Charge Questions and the Responses to Charge Questions that were distributed on June 4, 2020. I have had quite a lot of experience with the various models used to predict blood lead concentrations based on classic input parameters.

I have reviewed many SAB reviews of EPA work and I found this document, signed by Hugh Barton, to be among the top three evaluations that I have read over the past 30 years.

I can only say that it would be terrific if the Agency can accommodate all of the recommendations.

It is extraordinarily well-done.

Review of EPA's Computable General Equilibrium Model (Sage)

I have reviewed the Charge Questions and the Responses to Charge Questions that were distributed on June 4, 2020. Because this body of work is not one in which I have much experience, my comments are limited.

1) Charge question 1: I agree with the recommendations offered on Charge question 1. I agree that it should be more approachable for the readers/users who don't work in this space. The other comments appear reasonable.

2) Charge question 2: I agree with the panel's recommendations regarding Model Structure and Assumptions. The specific comments should be weighed by the Agency

3) Charge question 3: I agree with the recommendations.

4) Charge question 4: No comments

5) Charge question 5: I agree with the recommendations.

6) Charge question 6: No comments

7) Charge question 7: No comments.

Comments from Dr. Ted Simon

Comments on the draft SAB report, *Review of the All Ages Lead Model External Review Draft 2.0*

Page 9, line 12. A useful way to present the context and applications of the model is as a domain of application, as is done for assays or testing platforms
Page 9, line 39. How do these O'Flaherty growth curves compare to recent NHANEs data?

Page 11, line 11. Region 8 used a probabilistic lead model in the 1990s. Perhaps some aspects of that model could be used to ameliorate the proposed AALM. Phil Goodrum, an SAB member, developed that model and will probably have much to add.

Page 20, line 42. Bone remodeling is subject to hormonal influences and these influences account for mobilization of lead from bone stores in post-menopausal women. Since nursing mothers are exposed to a variety of hormonal influences, the underlying science may be quite complex and consideration of such no easy task.

Page 37, line 3. This section partially addresses my previous comment.

Page 42, line 42. Having the model available in open source software such as R or Julia would be a good suggestion. ACSLXtreme is no longer available but the package Magnolia is very similar and available without charge at https://www.magnoliasci.com/. Magnolia was developed by Conrad Housand, who also developed ACSL. MATLAB is hugely expensive. Excel, although widely available and widely used, is a poor modeling platform for time-dynamic models involving ODEs. A version in R would address the Apple/PC divide as well. EPA has many staffers highly knowledgeable in R, esp. in the NC CompTox group. They might be able to provide additional insight.

Page 51, line 40. Whilst I've not had a chance to use the software, testing with various numerical methods including those mentioned here. Excel

Comments from Dr. Eric Smith

E.P. Smith comments on **TECHNICAL_SUPPORT_FOR_AALM_2.0-MAY2019**

1. Equation 3.4 has an intercept term of -3.89. This does not seem correct (note figure 3.13 seems to go through the origin). Although there are 406 measurements on

individuals, the number of values in the graphs are not 406, please give the number of points or groups.

2. Equation 4.3 is not f'(x) rather it is f'(x)/f(x) / dx/x. Can f'(x) be dropped?
3. Equation 4.6 defines "residual". This definition is not consistent with standard statistical definitions that define residual as "observed – predicted". Perhaps it was intended to call this a standardized residual (as in equation 3.1) as it is a residual divided by standard deviation. It also seems unusual to divide by the standard deviation of the mean or equivalently the standard errorThe criteria that all residuals be between -2 and +2 seems restrictive given this definition since as sample size becomes large the denominator should get small. The criteria that r^2>= 0.7 seems low (is there a reference for this rule?), especially if there is any tuning of the model. So
    a. Define the denominator with a formula. Perhaps more should be discussed about the data reduction of the 406 measurements (how many groups, etc). The denominator is probably the standard deviation of the means of the observed values. Consider just calling it the standard deviation of observed values.
    b. Rethink the formula - Normally one would divide by the standard deviation of the numerator.
    c. Comment that the average of the residuals will not be zero but will reflect the average bias in the model.
    d. A useful reference is below (Pineiro et al., 2008)
    e. Note that Equation 3.1 is for a standardized residual but still might need a correction to the denominator's name.
4. The figures associated with the residuals: Figure 4-15. Illustrates possible confusion related to the definition of residuals. The top right figure gives a plot predicted versus observed (note that this is not observed vs expected as would be suggested by the formula for the residuals). The bottom two figures are associated with residuals and shows values between -2 and +2. The figure is atypical in that the values are not centered around zero as one might expect. The bottom left plot shows bias for the AALM-LG model. This is indicated by the value of the intercept of regression model: -1.01. Similarly, the other model has a bias of 1.64. The relevant questions seem to me to be (1) is the intercept different from zero (ie no bias)? and (2) is the slope different from 1.0? These can be addressed either statistically through a test or by a pre-determined criteria (I.e. is being off on average by 1 unit relevant?). Also, the pattern in the residuals in the second plots suggest a nonlinear relationship.

    Reference: G. Piñeiro, S. Perelman, J.P. Guerschman, J.M. Paruelo
    How to evaluate models: observed vs. predicted or predicted vs. observed?
    Ecol. Modell., 216 (2008), pp. 316-322, 10.1016/j.ecolmodel.2008.05.006
5. Equation 2.2-1 and others. Shouldn't *n* be defined for completeness?
6. Page 19 line 1. dYj/dt is defined as the change in Pb mass in compartment *j* over time *t*, but is should be over time dt.

7. Page 56 line 6. Why specify $r^2>0.8$ when you can give the exact value?

Miscellaneous
Page 81 line 6 observation is misspelled
Page 61 line 23 (r^2 0.81). should be ($r^2 = 0.81$)
Page 65 Line 23 refers to 409 adults not 406 as in line 26 page 59
Figure 3.14 indicates n=25 and n=7 however only 4 circles and 4 squares are displayed. Are there multiple values that are not displayed? Perhaps consider jittering the points.
Figure 3.15 Again specify number of means that are displayed. Are the bars standard errors? Why in 3.13 are there error bars in both directions but in 3.15 they are only in the y direction?
Figures 3.16, 3.17 – it is often useful to also plot the 1-1 line to get a sense of deviations.
Figure 3.17 indicates the model is biased as the intercept is 2.3 (same for 3.18)