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WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

November 13, 2006

EPA-SAB-07-002

Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: EPA Science Advisory Board (SAB) *Ad Hoc* All-Ages Lead Model Review Panel's Peer Review of the "All-Ages Lead Model (AALM) Version 1.05 (External Review Draft)"

Dear Administrator Johnson:

EPA's Office of Research and Development (ORD) has developed the All-Ages Lead Model (AALM), which is designed to predict lead concentrations in body tissues and organs for a hypothetical individual, based on a simulated lifetime of lead exposure. The precursor to the AALM was the Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead in Children, which underwent peer review by the EPA Science Advisory Board (SAB) in 1991. In response to ORD's request, the SAB convened an *ad hoc* expert panel to conduct a peer review of the model (Version 1.05) and the Guidance Manual on October 27-28, 2005 in Washington, D.C. The SAB panel members were generally supportive of progress in developing the model. However, in the judgment of this Panel, *the current version of the model is not ready for deployment* due to a number of deficiencies, as detailed in the report.

Regarding features and operation of the model, the SAB Panel recommended that the AALM be made more transparent and easier to understand by diverse users. The Panel noted that the predictive accuracy of the model could be improved by incorporating new biokinetic data that has been available since 1993. These data fall generally into three areas (that is, absorption, skeletal turnover, and blood/plasma components). Both of the existing Leggett and O'Flaherty models are incomplete and do not include current understanding in these areas. EPA should sponsor experimental and computational research to improve the AALM parameterization in these three areas. Panel members also suggested a more rigorous examination of all lead models, including a summary of each model's advantages and limitations, as well as differences in their conceptual structures, and use these as a basis for justifying the structure of the AALM. Three different components of the model need to be addressed: dust exposure, gastrointestinal absorption of lead, and soil exposure. Bioavailability, particularly with respect to soil, is not

addressed in the model and should be one of its key parameters. Differences in bioavailability among lead in soils of different origins and character, is likely to be a major factor in model predictions. Real-world data should be used to evaluate the predictive accuracy and reliability of the model (*i.e.*, environmental lead values compared with blood urine and bone lead for children and adults). Improvement is also needed in the predictive accuracy and reliability of the model. The model needs to predict a distribution rather than predicting a single value. Furthermore, the model needs to incorporate uncertainty more directly. In particular, a high degree of uncertainty is introduced in the modeling effort by specifying so many parameters.

The user interface of the model was generally deemed to be quite good. The menu-driven interface is intuitive and the learning curve is not steep; however, the SAB panel suggested additional features. The guidance manual was useable but still in need of improvement. The manual should provide both a theoretical framework to understand the structure of the model and its scientific basis, and a step-by-step procedure from data input to evaluation of the predicted outcomes. The parameters dictionary was judged to be an extremely important component of both the guidance and the help feature. The Panel also identified problems in quality control. The model often did not perform correctly, at times yielding strange results, with coding errors suspected. Lastly, the SAB Panel recommended that the model be run with the same datasets as the Leggett model, that plausibility checks also be run, and that other human lead pharmacokinetic data sets be examined.

Detailed suggestions for improvement of the draft AALM are presented in the report, organized by four sub-group areas: (1) conceptual construct of the model; (2) predictive accuracy and reliability of the model; (3) computer coding and quality assurance; and (4) AALM documentation (*e.g.*, guidance manual, parameters dictionary, *etc.*)

In conclusion, the SAB encourages the Agency to continue its development of the AALM. The SAB stands ready to offer additional advice and recommendations to assist EPA in this effort, and wishes the Agency staff well in this important endeavor.

Sincerely,

/Signed/

Dr. Granger Morgan
Chair
EPA Science Advisory Board

/Signed/

Dr. Meryl Karol
Chair
SAB *Ad Hoc* AALM Review Panel

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SAB *Ad Hoc* All-Ages Lead Model Review Panel

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U.S. Environmental Protection Agency
Science Advisory Board

PEER REVIEW
of the
ALL-AGES LEAD MODEL (AALM)
Version 1.05 (External Review Draft)

by the
SAB *Ad Hoc* AALM Review Panel

October *xx*, 2006

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Executive Summary

The AALM Panel strongly supports the Agency's development of the model, but offers extensive suggestions for its improvement. Importantly, however, the current version of the AALM does not model a population response and therefore does not meet the goals of EPA. Accordingly, in the judgment of this Panel, the AALM is not ready for use. The Panel offers the following comments and suggestions for improvement of the model.

I. Conceptual Construct of the Model

The model should be more transparent and easier to understand by diverse users. The AALM Guidance Manual should define each of the various lead pharmacokinetic models, including their advantages and limitations, and differences in their conceptual structures. This review, with appropriate literature references, should be used to help justify the structure of the model. Another general recommendation is the need for standard units of measure to be used throughout the model and reported in all outputs, including graphics; this feature is currently missing and makes it difficult to understand the outputs. The AALM Panel further recommends that the descriptions of the biokinetic parameters in the AALM be made more consistent with the Leggett model's descriptors. Bioavailability, particularly with respect to soil, is not addressed in the model and should be one of its key parameters. In addition, pica should not be used in the model as a surrogate for soil ingestion.

In terms of model performance, it is critical to compare its "outcomes" (model results) with the empirical predictions from existing, high-quality databases that relate measured lead concentrations in environmental media to blood lead and bone lead concentrations in exposed populations, *i.e.*, the AALM should be shown to be capable of providing as accurate a reflection as possible of the empirical outcomes from these databases. For purposes of protecting the most highly exposed, it is also vital that the model yield predictions of blood lead and bone lead that can be compared with both the mean and the upper percentiles of the distribution of measured concentrations. The model should allow users to incorporate information on variability in exposure, uptake, and biokinetics. In addition, it would be useful to allow users to separately characterize variability and parameter uncertainty in order to compare confidence intervals in both the model output and the empirical measurements.

The model should be modified to assure that all biokinetic parameters remain internally consistent, since a change in one biokinetic parameter without corresponding adjustments in all the transfer and tissue/organ deposition streams will affect the reliability of the outputs. Likewise, exposure parameters are also linked and should be synchronized. Caution should be provided to users about the consequences of implementing parametric changes. Second, EPA should consider allowing adjustments to the intake and uptake parameters, since such adjustments are required for site-specific or circumstance-specific lead scenarios of direct interest to users, but it should restrict alterations in the biokinetic parameters, as with the IEUBK model. If the Agency does allow variation in biokinetic parameters, the user should be warned if a particular parameter value was estimated by calibrating the model to match empirical data on blood lead concentrations or other variables. In these cases, changing the parameter values may result in model predictions that are no longer supported by previous calibration exercises. Third,

the overall complexity of the model gives it aspects of a "black box." This might be partly addressed by allowing users to evaluate intermediate outputs from individual modules. Fourth, checks for mass balance errors need to be included in the model. If the AALM uses fractions of rate constants, how is the sum of fractions maintained to have a sum of 1? A warning should be provided the user when a mass balance has not been achieved.

Other specific recommended changes include: (a) the need to differentiate and explicitly address three different components: dust exposure, gastrointestinal absorption of lead, and soil exposure; (b) implementation of more realistic age range breakouts for the youngest age bands. The peak in oral exploratory activity and hand-mouth activity occurs at 12 to 30 months of age. The current age interval for toddlers too broad and unlikely to capture the heightened exposures of 12 to 30 months of age toddlers; (c) breast milk exposures should be accounted for; (d) age-specific intake exposure factors (*e.g.*, breathing rate, drinking water intake rate, etc.) need to be consistent with EPA's "Child-Specific Exposure Factors Handbook" (EPA-600-P-00-002B; 2002); and (e) bioavailability and bio-accessibility differences should be developed outside of the exposure module in a manner consistent with how this lead will be treated in the Absorption module.

II. Predictive Accuracy and Reliability of the Model

Several suitable data sets were identified that could be used to examine the models predictive veracity, and to calibrate the model. These existing data sets include environmental lead values paired with blood, urine and/or bone lead values for children and adults. Suitable data sets for validating the model include the National Health and Nutrition Examination Survey (NHANES) data set and the Lanphear compilation of multiple studies.

Regardless of the actual values predicted by the model, several issues of internal consistency were noted. For example, blood lead values changed abruptly with age, which was troublesome. These results appeared to be sensitive to the step size selected. Also, the integration algorithms need to be verified.

The model should predict a distribution of blood lead values. For the AALM to be used to characterize variability and uncertainty in blood lead and other output variables, a probabilistic approach is needed. The AALM Panel generally recommended the use of Monte Carlo analysis in which exposure and/or biokinetic parameters are characterized by probability distributions. Both variability and uncertainty in an output variable can be characterized depending on the choice of input distributions and the choice of Monte Carlo simulation methods. A second probabilistic approach may also be desirable as an alternative to Monte Carlo analysis, and to facilitate the transition from the IEUBK model to the AALM. Currently, users of IEUBK are familiar with the use of a lognormal distribution assumption applied directly to the output variable (*i.e.*, the geometric standard deviation [GSD] term). While the process for selecting site-specific GSDs has been a source of considerable debate among the risk assessment community, it is a simpler method of characterizing distributions and can be informed by empirical data. One shortcoming of this approach is that it does not allow for quantitative uncertainty analysis, since plausible bounds or confidence intervals on model predictions cannot be determined.

The predictive accuracy of the model could be improved by including newer information about absorption and internal distribution of lead, RBC-plasma partitioning, and air-dust relationships. The default values should be reexamined, and the ability to change selected biokinetic parameters should be added. In addition, a high degree of uncertainty is introduced in the modeling effort by specifying so many biokinetic model parameters for which there is limited information about their values.

III. Computer Coding and Quality Assurance

The user interface of the AALM is quite good. The menu-driven interface is intuitive, and the learning curve is not very steep. However, there are additional features that would enable the model to be more useful for either hypothetical or real-world risk assessment problems. Limitations of the AALM include the following:

- A batch mode is needed similar to the current functionality of the IEUBK model to facilitate an evaluation of the proportion of the population that exceeds a target risk-based concentration in an exposure medium. The user should be able to specify an input file with a set of site-specific factors (*e.g.*, paired concentrations in soil, dust, and water at a residence). The AALM would benefit greatly by allowing either point estimates or probability distributions to be calculated for each exposure unit.
- The AALM needs to incorporate variability and uncertainty more directly. It would be useful to be able to specify expected distributions of parameters, and get out a probability distribution of blood lead for a population. Default distributions, rather than default point estimates, for these parameters would be preferred so that variability and uncertainty are more properly accounted for in the risk assessment without the requirement of tedious repetitions by the risk assessor.
- Even for the research community, caution should be given about changing the biokinetic parameters, since they were not derived independently, and changing one often implies changes to others. The results would also no longer correspond to the Leggett model. Interest was expressed in adding the physiological (O'Flaherty) model option.

Specific suggestions for the AALM include: eliminating the need to set the gender option in three locations; and increasing flexibility in the graphic display.

Regarding the Quality Assurance/Quality Control (QA/QC) concerns of the program, the AALM does not perform correctly. For example, Manton and Cook's data indicate that plasma lead should be about 0.2% of blood lead when blood lead is less than 25 mg/dL. The Leggett model, on which the AALM is based, predicts this successfully. However, the AALM not only does not meet this design criteria, it produces non-single-valued functions. Small errors in the parameterization of the kinetics of this compartment can propagate very rapidly to errors in the amounts of lead in all other compartments. Since the AALM derives from the Leggett model, it is assumed that this is a result of coding errors.

In addition, plausibility checks should be run such as making sure results behave as expected as the number of years is lengthened, that different intakes for different periods behave

as one would expect, given cumulative dose, *etc.* It would also be worthwhile to examine other data sets. Finally, several of the input assumptions are unreasonable, and should be changed. This includes assuming the same gut absorption rate for food and water lead, the default values for water lead concentration, *etc.*

IV. AALM Documentation

The AALM Panel deems that the present Guidance Manual is useable, but should be made more user-friendly. It is incomplete in several areas and contains many errors and confusing wording. The manual should provide both a theoretical framework for the uninitiated user to understand the structure of the model and its scientific basis, and a step-by-step procedure that would walk the user from the data input to the evaluation of the predicted outcomes. EPA should also consider developing and releasing a companion Technical Support Document to augment the Guidance Manual that includes verification and validation exercises, utilizing real world demonstrations, and appropriate cautions that would aid the user in understanding, interpreting and utilizing the model.

In addition, the AALM Panel notes that the output options provided in Version 1.05 are interim choices and will therefore need to be developed more fully in subsequent releases. The data files, if possible, should be exportable to other traditional software programs. More explanation of the structure, underlying nature and accessibility of these data sets should be provided. There should also be explanation regarding the type of environmental information to be entered, so that it is standardized to the type for which the model was calibrated. The Parameters Dictionary was an extremely important component of both the guidance and the help feature. The AALM Panel suggests that more specific information be provided in the guidance and support documents with regard to each individual parameter, including its origin, source of support data, possible range of values, any information regarding central tendencies and variance, uncertainty, the rationale for the default setting, relationship to other parameters, and appropriate cautions as needed for modifications.

To the extent practicable, the AALM approach, guidance and application should be consistent, and evolve concurrently with similar models and guidance presently endorsed by EPA. The Agency should consider issuing guidance regarding the required (or recommended) use of the default or prescribed bio-kinetic parameters in regulatory applications. Finally, the AALM should be evaluated relative to the Agency's current *Draft Guidance on the Development, Evaluation, and Application of Regulatory Environmental Models.*

Background and Introduction

The EPA Science Advisory Board was established by 42 U.S.C. § 4365 to provide independent scientific and technical advice, consultation, and recommendations to the EPA Administrator on the technical basis for Agency positions and regulations. The SAB is a Federal advisory committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App. The AALM Panel consists of 14 members, two of whom are also members of the chartered SAB appointed by the EPA Administrator. The AALM Panel provides its advice

through the SAB, and complies with the provisions of FACA and all appropriate SAB Staff Office procedural policies.

EPA's Office of Research and Development (ORD), National Center for Environmental Assessment (NCEA), requested that the SAB Staff Office form the AALM Panel to provide advice and recommendations to the Agency on EPA's recently-developed AALM. The AALM is designed to predict lead concentrations in body tissues and organs for a hypothetical individual, based on a simulated lifetime of lead exposure. Statistical methods can be used to extrapolate to a population of similarly-exposed individuals. The precursor to the AALM was the Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead in Children. The IEUBK Model underwent peer review by the SAB in 1991 and was subsequently revised in response to that review, leading to release of Version 0.99d of the IEUBK Model in March 1994. Since then, the IEUBK Model has been widely accepted and used in the risk assessment community as a tool for implementing the site-specific risk assessment process when the issue is childhood lead exposure. Based on further refinement of the IEUBK Model and its expansion for use with additional age groups beyond pediatric populations six years old or younger, the AALM has recently been developed to cover older childhood and adult lead exposure. The anticipated outcome of this model is reduced uncertainty in lead exposure assessments for children and adults.

Compiled Responses to Agency Charge Questions from Panel Sub-Groups

I. Conceptual Construct of the Model

❖ **Charge Questions**

(1) In general, to what extent are the parameters and relationships represented by various AALM features adequately supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings? That is, are the specifications of key components of the AALM model scientifically supportable in characterizing particular parameters or relationships of the types noted above?

Standard units of measure should be used throughout the model and should be reported in all outputs, including graphics. This is critical for both comprehension of AALM outputs and for ease of application in the regulatory world. For example, the output levels in Window Figure 8 are total lead content values that require different metrics for routine use, *e.g.*, µg/dL for whole blood Pb, and ppm for wet weight of soft tissues. Use of routine measurements and specifications would eliminate much confusion.

All the assumptions utilized in the model, both on the computational and the biological side, should be specified and made as transparent as possible. Users of the model may not be using a common vocabulary and nomenclature, nor have the requisite background to comprehend discipline-specific issues in the same way.

The committee recommends that the Guidance Manual define all of the models more lucidly, including delineation of the differences in the conceptual structures of the models. Users of the models who are not toxicokineticists or pharmacokineticists need to understand the distinctions among the models, including their advantages and limitations. Currently, there are abstract definitions in the literature of what comprises a "PB-PK" model but no universally accepted features of existing models for simulation of human lead exposures that define them and functionally distinguish one model from another. Indeed, there seems to be actual disagreement regarding labeling among those who have introduced various models. O'Flaherty (1998) states (p. 1501, col. 1) that "The IEUBK [Integrated Exposure Uptake Biokinetic] model developed by the U.S. EPA is not physiologically based in the sense in which either the Leggett/ICRP model or the O'Flaherty model is…" Pounds and Leggett (1998) state (p. 1507, col. 1) that "The IEUBK model is the most commonly used physiologically-based pharmacokinetic (PBPK) model for lead in children." The Draft AALM Manual states (p. 40, Bottom) that: "The Leggett method is generally considered to be anatomically-based...The O'Flaherty method is physiologically based..." NCEA/EPA's 10/20/05 draft models background document describes the IEUBK model (p. 10, last par.) as a "multicompartmental pharmacokinetics" model. A more in-depth presentation of these models' limitations is critical to understanding the rationale for the current model.

One issue that requires additional consideration is the need to modify the model to assure that all biokinetic parameters remain internally consistent. That is, a change in one biokinetic parameter without corresponding adjustments in others will affect the reliability of the outputs. The EPA AALM designers should highlight the consequences of such scenarios for the edification of, *e.g.*, risk assessors, using concrete examples. One possible consideration is, when programming, to link the parts of the computational stream in the model that are affected by isolated parameter changes. In this way, if a non-modeler arbitrarily makes changes in isolation, appropriate changes are automatically made in other parameters to produce mass balance. Alternatively, such changes could trigger a dialogue about the consequences and a directive with respect to other parameters that would have to be changed. This would address the situation in which a change in one parameter would potentially require changes in numerous other biokinetic parameter combinations, not simply one or several.

Some Panel members suggested that EPA should consider the desirability of allowing adjustments to the intake and uptake parameters, but restricting alterations in the biokinetic parameters. This is the situation with the IEUBK model in which the intake and uptake parameters can be edited, but few of the biokinetic parameters are accessible. It is difficult to foresee circumstances where typical users would be more interested in changes in the biokinetic parameters than lead intake and uptake. The latter are much more driven by site-specific or circumstance-specific lead scenarios of direct interest to users than are parameters in the Biokinetic module. The logic for making the IEUBK Biokinetic module inaccessible to users applies as well to users of the AALM. That logic (stated on Page 4-58 of the 1994 IEUBK guidance manual) is:

> *"The IEUBK model has a very detailed biokinetic modeling component. This component of the model is not accessible to the user because, in our judgment, most users will neither wish to change the biokinetic parameters nor have the need to change any of*

the biokinetic parameters. The biokinetic parameters are used to define intrinsic biological variables that do not change from one exposure scenario to another once a child's age is specified."

Similar to the above, once an age interval is specified in the AALM, the biokinetic parameters should not require changes by the user.

There is significant complexity in the individual modules and even greater complexity when the interaction of the modules is considered. This complexity makes it very difficult to evaluate the specification of the parameters within and across the modules in the abstract. This might be partly addressed by allowing users to evaluate intermediate outputs from individual modules, although such an option will not address the inter-module complexity.

The model fails to specify parameters relating to exposure and uptake of Pb in soil. Although the model addresses gastrointestinal absorption of "dust", and "pica" ingestion, it does not explicitly address soil. This is more than a semantic problem. Clearly, there is exposure via ingestion of soil by both children and, to a lesser extent, adults. This exposure pathway is one of the major drivers for hazardous site cleanup decisions. "Dust" is generally considered to be large diameter indoor particulates, but indoor dust contains both soil-derived particles as well as particles derived exclusively from indoor activities. Some members of the Panel also suggested that it appears that the model envisions dust to include the top, easily accessed layer of soil, but this does not necessarily correspond to the way soil is accessed — particularly by children, and by some adults, including gardeners. Additionally, it also appears that the model envisions "pica" to be the intentional ingestion of bolus quantities of soil. However, pica is more properly viewed as the persistent eating of non-nutritive substances for at least one month in a manner inappropriate to the developmental level and without cultural sanction. (Citation: *Diagnostic and Statistical Manual of Mental Disorders,* 4th Ed., Text Revision. Washington DC: American Psychiatric Association, 2000). While there are, indeed, children who ingest bolus quantities of soil, in general soil ingestion occurs along a continuum, with some children occasionally consuming bolus doses, and others continually ingesting small quantities of material on their hands over the course of the day. "Pica" should not be used in the model as a surrogate for soil ingestion. Some members of the Panel further suggested that it is necessary that the model consider exposure to soil as a separate, clearly defined component including that part of indoor dust that is soil-derived. Without such an approach the model cannot be used to define Pb-contaminated site cleanup goals. Finally, some AALM Panel members also suggested that bioavailability, particularly with respect to soil, is not addressed in the model and should be one of its key parameters. Differences in bioavailability among Pb in soils of different origins and character, is likely to be a major factor in model predictions.

Historical exposures were not addressed in any quantitative way by the Panel. This leaves unresolved how well one can evaluate or calibrate the AALM output. Arguably, in model testing, users of the model would be confined to those data sets where one or the other of the pairs of data may have measurement problems peculiar to this type of site testing. For example, PbB testing at such sites is typically done only once. Mining, milling and smelting sites have produced such pairs of measurement data but the statistical handling of the measurements can be problematic.

Simulations in which EPA is dealing with a contaminated site that has a likelihood of producing lifelong exposures for affected communities, starting with current newborns, entails a number of assumptions about the relative stability of the environmental Pb levels that serve as exposure inputs. For example, the galena form of lead ore in milling wastes weathers to more bioavailable lead carbonate (cerussite). Bioavailabilities estimated for current chemical species of lead might well be underestimates for future decades.

Another important issue regarding specification of parameters is the use of point estimates for default parameter values in the AALM. Given the variability in exposure and biokinetics in populations, it is critical that predictions of lead exposure be capable of addressing not only the mean exposure but also the upper percentiles of the exposure distribution. This is important since highly exposed individuals may differ from the mean by several standard deviations. Many of the parameters are too poorly characterized to be adequately described as distributions. Clarification is needed on a case-by-case basis, particularly since full distributional descriptions are not necessarily required to allow a reasonable estimate of the distribution of the outcome parameter (*i.e.*, blood or bone lead). Estimated or screening distributions such as triangular distributions can often be derived from limited data, and can provide adequate input to an overall distributional analysis. The ability to fully describe all parameters with distributions notwithstanding, useful information can be generated even by limiting the distributional descriptions to a single module in the AALM. In particular, exposure parameters are generally well characterized, and many, if not most, of the relevant parameters have been described by distributions in the published literature.

Once obvious errors and deficiencies in the model have been identified and addressed (see below), the appropriate question about the specification of the model and its components at this point should not relate to a parameter-by-parameter assessment of the science underlying the specific values and model structures. Rather, the performance of the model should be compared with the empirical predictions from those existing good quality databases that relate measured lead concentrations in environmental media to blood lead and bone lead concentrations in exposed populations. As is clear from existing databases, there are differences among individuals in biokinetics of lead. There will also be errors of measurement in characterization of exposures, both human and environmental. Nevertheless, these are the data that often serve as the basis for decisions regarding public health policies and interventions. Therefore, the model should be shown to be capable of providing a reasonable reflection of the empirical outcomes from these databases. If significant differences are found, comparisons can be made on a more detailed level, including sensitivity analyses.

More specifically, what are the AALM Review Panel's views with regard to:

(a) The adequacy of the values specified for the exposure parameters for different media and how well the model interprets exposure throughout the various age groups;

A detailed review of these parameters should be undertaken as a specific and focused effort on a module-by-module basis. There was some concern that the AALM does not appear to have taken full advantage of the extensive development of exposure parameters in the IEUBK

model exposure modules. This is true with respect to age breakdowns, ingestion rates, route-specific bioavailability and bio-accessibility and historical exposure default values. These parameters have proven to be highly useful in regulatory risk assessment and risk management activities and should not be "left behind" in advancing lead health modeling efforts by the Agency.

More realistic age range breakouts should be considered for the youngest age bands. The current 6 to 48 months age interval for toddlers is too broad and unlikely to capture the heightened exposures of 12-24 or 30 months of age toddlers due to increased hand-mouth activity. This adjustment will require revision within the exposure module, specifically the parameters seen in Window Figure 21. Figure 21 shows a daily dust intake of 85 mg/d for toddlers (42 months age interval total) and 135 mg/d for preschoolers (24 months interval). The IEUBK model exposure module more correctly shows dust/soil intakes of 135 mg/d in children 12 - 48 months of age.

It is not clear where the values in Figure 21 are from. The Leggett (1993) paper says nothing about this set of parameters. For example, are they 40% lower for these infants and toddlers than those in the IEUBK model because of removal of the discrete soil component? If so, this is all the more reason not to put soil in a subsidiary role under "pica" but to place it within the main media tabs. Also, where does the value 135 mg/d for preschoolers, age 49 - 72 months, come from? It is not plausible that the older a child, the more dust he/she will ingest. Also, the use of the 135 mg value suggests that an altered role of soil in these intake amounts is not the reason for the change from the IEUBK.

EPA/NCEA's current "Child-Specific Exposure Factors Handbook" (EPA-600-P-00-002B; 2002) reviewed the totality of the soil ingestion literature and concluded (Chapter 5, p. 5-21, Table 5-19) that the best estimate of the soil ingestion portion of the soil + dust pair is 100 mg/day. Addition of interior dust to that figure makes 135 mg/d as it appears in the IEUBK exposure module. This is much more plausible for infants and toddlers than 85 mg/d.

Restoration of the two lead-containing media as in the IEUBK model, while simultaneously refining the age band for the youngest childhood subsets, will have the net effect of making the PbB outputs consistent with a childhood lead exposure literature showing a broad peak in PbB around 24 months, see, *e.g.*, Figure 9, O'Flaherty, 1998; Clark et al., 1985; Billick *et al.*, 1979.

Additional specific recommended changes include the following:

- The uptake value for Pb in drinking water should be close to 100% as the Pb is already in a soluble form.
- Breast milk exposures should be accounted for.
- The default media lead concentrations need to be more scientifically justified.
- Age-specific intake exposure factors (e.g., breathing rate, drinking water intake rate, *etc.*) need to be consistent with existing EPA exposure factor guidance.

(b) The adequacy of the uptake/absorption parameters or any need for modification of the methodology for determining absorption for various routes of exposure;

Several considerations, some related to those raised in (a) above should be considered:

- Bioavailability should be a key component of the uptake module.
- The absorption of Pb in drinking water should be reconsidered.
- There is concern that the AALM has combined soil and dust under a single route that seems to have a fixed absorption rate in the gut identical to that for water and food. The absorption rate requires that bioavailability and bio-accessibility differences be developed outside of the exposure module in a manner cognizant of exactly how this lead will be treated in the absorption module.
- The fraction absorbed as a function of age needs to be better validated and made consistent with the scientific literature.
- Scientific justification of transdermal absorption of lead is needed before this parameter is made part of the AALM.

(c) Whether there are any errors in AALM methods for determining biokinetic distribution or errors in assigning values to biokinetic parameters;

Little information is available to answer this question without relying on the original Leggett publication. The biokinetic parameters of the AALM are not all consistent with the parameters used by Leggett. EPA appears to have used a different approach by employing fractional rate constants (deposition fraction) that scale off the overall rate of elimination from the diffusible plasma compartment. While this is the approach that Leggett used, Leggett only reported the individual rate constants for transfer between compartments (total transfer rate times the deposition fraction). Although a semantic issue, the user may refer to Leggett and see that the AALM has used a different approach. In addition, the "Transfer Rate from RBC" entry in the AALM corresponds with the parameter that Leggett calls "red blood cells (RBCs) to Plasma-D". This is a subtle, but important difference. EPA's entry seems to imply this is the overall elimination from RBCs to all compartments. Leggett's is more specific. The Panel recommends that the descriptions of the biokinetic parameters in the AALM be more consistent with Leggett's descriptors and that differences between the two approaches be made more explicit. EPA should provide specific information as to whether Leggett's original values have been adopted or modified, why, and whether and how additional information accumulated over the past twelve years influenced that determination.

Table 1, p. 40, and Figure 42, p. 41, appear to have the wrong "RBC Threshold Concentration." The figure of 60 µg/dl is more correct for the value of whole blood Pb, PbB, above which the equilibrium ratio of plasma/serum Pb to PbB becomes curvilinear upward (Bergdahl et al., 1997; Manton and Cook, 1984; de Silva, 1981; Marcus, 1985; discussions in U.S. EPA's lead criteria document, 1986, Ch. 10; and NAS/NRC, 1993, p. 159). That is, the level of lead in plasma plotted against PbB remains stable (linear) until ca. 40-60 µg/dl PbB, when the relative plasma level increases. A PbB value of 50 µg/dl corresponds to an approximate Pb-RBC value of 125 µg/dl (PbB/0.4 = Pb-RBC); for 60 µg/dl, the erythrocyte Pb

level is 150 µg/dl. This is based on a hematocrit of 40%. The relationship is depicted in Figures 10-2 and 10-5 in Ch. 10 of the EPA 1986 lead criteria document. This curvilinear relationship with increasing PbB has been suggested as one biokinetic explanation for the Chamberlain (1983) observation that the relative lead excretion rate in adults increases with increasing PbB.

The Leggett model is a multicompartment model in which the model parameter values and their relationships to one another (because Leggett used fractions of rate constants to achieve an overall rate constant) are valid in their current state, only with the data sets for which it was parameterized. Allowing the user to modify the biokinetic parameters will most likely make the model inconsistent with the literature with which the Leggett model was parameterized. Therefore, if EPA would allow the user to vary these parameters, the user must be warned explicitly that changing the values for the biokinetic parameters will most likely make the model invalid. Currently, the user is allowed to change the age cutoffs for the biokinetic parameters in the AALM. However, if this is done, the AALM will be inconsistent with the Leggett model

The specific values used for some of the tissue-specific rate constants in the AALM could not be reproduced and do not match those Leggett reported. For instance, the parameter "Depos[i]tion fraction of lead in the brain by age range" reports a value for the first age range of (Age Range, Depos[i]tion Fraction in Brain): (0.000, 0.00045). Leggett reports a value of (0.557/2000=0.000279). Why the difference? These values should be QA/QC'd. If the AALM uses fractions of rate constants, how is the sum of fractions maintained to have a sum of 1? Will this cause a mass balance error? A warning should be provided to the user when a mass balance has not been achieved.

(d) Does the AALM model correctly account for elimination of lead via various pathways?

Breast milk should be added if possible. Non-absorbed lead could be summarized in the output to provide a confirmation that all lead entering the body is accounted for in the AALM. If breast milk is incorporated, it will have to be accounted for as a route of elimination for the mother. The urinary excretion should also be reported as elimination (µg/day). This is the way that urinary excretion data are reported in many of the scientific papers on lead excretion. For validation purposes, the model should provide this as an option.

It is not clear if elimination via the dermal pathway is tied to a "skin" compartment that has feedback with the transdermal absorption pathway. If transdermal absorption is deemed scientifically justified, is the percent absorbed dependent on blood lead concentrations? If not, then the transdermal absorption factor can be described as an independent compartment. If the percent absorbed is found to be dependent on blood lead concentrations, then the skin compartment will have to be incorporated into the model in a way that the blood lead concentrations can have a "feedback" type control over transdermal absorption.

II. Predictive Accuracy and Reliability of the Model

Several data sets were identified that could be used to examine the models predictive veracity. These existing data sets include environmental lead values paired with blood, urine

and/or bone lead values for children and adults. The AALM could be calibrated with these data sets. Regardless of the actual values predicted by the model, several issues of internal consistency were noted. For example, blood lead values changed abruptly with age, apparently a result of the step size selected. Also, the integration algorithms need to be verified.

The model should predict a distribution of blood lead values. For the AALM to be used to characterize variability and uncertainty in blood lead and other output variables, a probabilistic approach is needed. The AALM Panel generally recommended the use of Monte Carlo analysis in which exposure and/or biokinetic parameters are characterized by probability distributions. Both variability and uncertainty in an output variable can be characterized depending on the choice of input distributions and the choice of Monte Carlo simulation methods. A second probabilistic approach may also be desirable as an alternative to Monte Carlo analysis, and to facilitate the transition from the IEUBK model to the AALM. Currently, users of IEUBK are familiar with the use of a lognormal distribution assumption applied directly to the output variable (*i.e.*, the geometric standard deviation [GSD] term). While the process for selecting site-specific GSDs has been a source of considerable debate among the risk assessment community, it is a simpler method of characterizing distributions and can be informed by empirical data. One shortcoming of this approach is that it does not allow for quantitative uncertainty analysis, in that plausible bounds or confidence intervals on model predictions cannot be determined.

The predictive accuracy of the model could be improved by including considerably newer information about absorption and internal distribution of lead. For example, much has been learned about age-dependent bone kinetics. Additionally, improvements to the modeling could be made in RBC-plasma partitioning, and air-dust relationships. Introducing an "Injection term" is suggested to isolate the Biokinetic module from the Exposure and Absorption modules. The default values, particularly for water lead and for the indoor/outdoor lead ratios, should be reexamined, and the ability to change selected biokinetic parameters should be added. In addition, a high degree of uncertainty is introduced in the modeling effort by specifying so many biokinetic model parameters for which there is limited information about their values. Finally, suitable data sets for validating the model include the National Health and Nutritional Evaluation Survey (NHANES) data set and the Lanphear compilation of multiple studies.

❖ **Charge Questions 2 & 3: *Predictive Accuracy and Reliability of the Model***

(2) Based on EPA's demonstration of the model, what can be stated with regard to the predictive accuracy and reliability of the AALM regarding comparisons of: (a) model-generated outputs of projected blood lead distributions derived from real-world lead exposure data inputs with (b) actual distributions of blood lead (or bone lead) concentrations for individuals experiencing such lead exposures? In addition, have SAB Ad Hoc *AALM Review Panel members made any "test runs" to apply the current draft version (1.05) of the AALM to "real-world" datasets that may be available to them; and, if so, what were the outcomes of such efforts?*

COMPARISONS WITH REAL WORLD DATA

In that no outputs of projected blood lead were presented to the panel at this time, the panel considered various existing data sets that might be suitable. The following characteristics of such suitable data sets were suggested:

- Paired concentration of blood lead (PbB) and perhaps also bone lead data with multi-media lead exposure measurements.
- Dust data were collected in ways compatible with the methods used by the model as inputs. Different dust sampling methods generate both concentration (µg/g) and lead loading (µg/area) values.
- Data sets that had been examined by structural equation modeling.
- To include paint lead observation, but again with a caution about the units being consistent with the model's need for area loading or lead concentration.
- Age in months available, particularly if the time spent in different environments was also available.

Suitable data sets include the National Health and Nutritional Evaluation Survey (NHANES) data set and the Lanphear compilation of multiple studies. The data should have been generated with sufficient concerns for quality assurance, not simply screening data. The blood and the environmental data need to be paired for each subject.

Additional key lead pharmacokinetic datasets exist that could be simulated and would be helpful to the scientific community to determine how the AALM performs. These include (but may not be limited to):

- Manton & Malley (1983): urinary lead excretion (µg/day) versus blood lead (µg/dl)
- Van de Vyver *et al.* (1988) : bone lead versus blood lead for workers and the general population
- Other real-world datasets include those from areas where there is extensive lead contamination and areas where the ambient contamination is much less. These include Hu and Hernandez-Avila in Mexico, Guilson in Australia and several of the central European studies. In addition, NHANES (1999-2002) collected both blood and dust lead from a representative sample of the U.S. population that could be used for this purpose. The researchers might agree to provide unidentifiable data for this effort that would streamline IRB or OMB procedures. HIPAA should not apply in this case.

Dust and other environmental data need to be in the same format as that used by the model for calibration. For example, dust values (either concentration or surface loading) must be the same for the data set and the model, as must the location of the sample within the residence (floor, windowsill, furniture). Similarly, paint lead values need to be surface loading or concentration.

Calibration of the model should be done with data sets that have both concentration and loading of dust values. It is important that the way the sample was physically collected and assayed corresponds with the way the variable is specified to be entered into the model. The manual must address this point. For example, if the model asks for floor dust lead loading (µg/ unit area), because it was calibrated with that, then the measured dust samples, which will be

applied in the future to the model, must be in the same units and from the same location in the residence. Similar concerns apply to air, water, and other environmental inputs. This would be a necessary part of the benchmark calibration of the model.

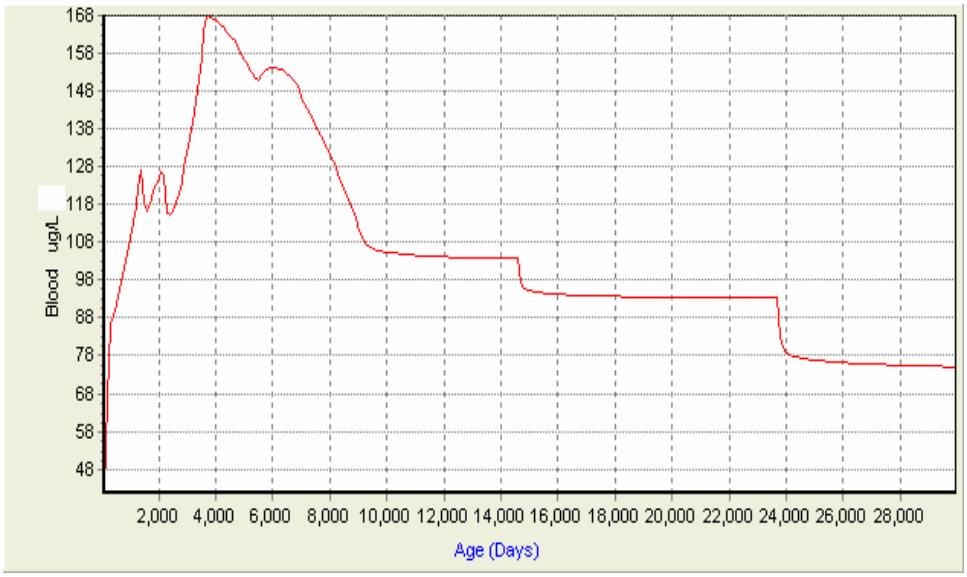
It will not be possible to further refine the various internal biokinetic parameters even if additional precise environmental lead values and matching tissue lead levels were generated. Because of the many degrees of freedom, fitting the tissue data will not yield unique solutions.

1. INTERNAL CONSISTENCY

Regardless of the actual values predicted by the model, which could be changed with calibration efforts, several issues of internal consistency were noted. Results appear to be sensitive to the step size selected — the integration algorithms needs to be verified. Different opinions were expressed on whether users should be given access to modify the time step. The step size could be hard-wired, *i.e.*, use a variable time step that is not accessible to the user. In any case, the manual should caution the user to not change the value.

The model needs to predict blood lead and bone lead trajectories that vary smoothly and reasonably with time, without abrupt changes at some ages or age boundaries. The abrupt changes in predicted lead at certain ages, for example, with the onset of middle age, are striking (see figure below). The current model has this numeric instability, which may be caused by integration step sizes being too long, or caused by abrupt changes with age at arbitrary age boundaries. Both of these causes of numeric instability need to be addressed.

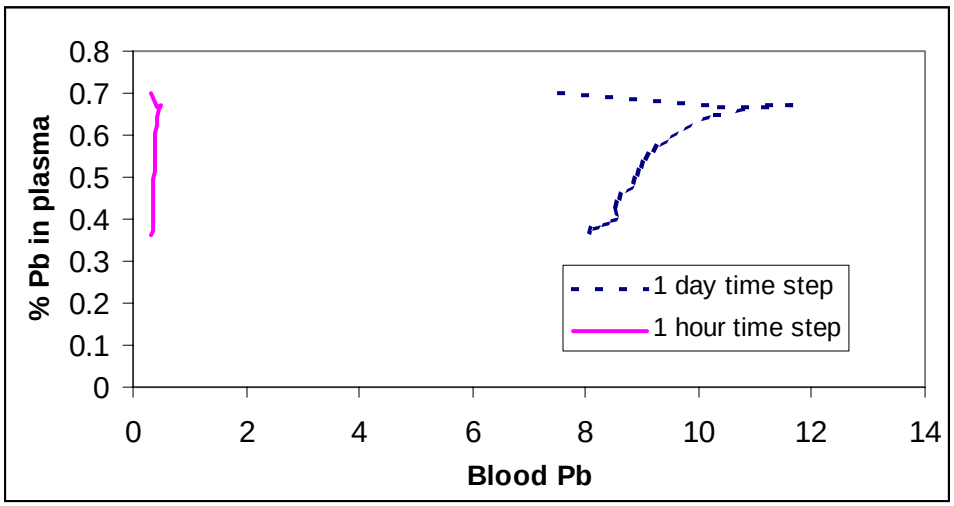
Abrupt Changes in Blood Lead with Age



The discontinuity in the various parameters (only blood concentration is shown above) between 15 years of age and 25 years of age is not justified in the manual and only barely justified in the 1993 Leggett paper.

Perhaps related to this were the observed whole blood-plasma irregularities. That the PbB vs. plasma curves do not overlap, suggests a coding issue. The predicted relationship between plasma and whole blood lead levels was neither constant nor smooth, nor consistent with the Leggett model. This requires investigation. It may simply be a matter of choosing more appropriate time step sizes.

In its current version, the model does not provide numerically correct solutions, *i.e.*, either there are coding errors or numerical integration errors. This may be occurring because the time step is independent of the transfer rates. Plasma lead turnover rate is in the order of a few minutes, yet the default integration time step is one day and the minimum possible time step is 1 hour. In addition, point changes in biokinetic parameters at specific ages should be smoothed over time. For example:



The two curves in this figure show the fraction of blood lead in the plasma for children from birth to 6 years versus blood lead calculated using 1 day time steps and 1 hour time steps. The curves are very different, indicating the computer model has errors.

Predicted values should be continuous. One of the discontinuities, for example at ~ 3 years of age, does not occur at a point where there is a dramatic change in biokinetic parameter values. Regardless of the time step, the fraction of Pb in plasma is too high. It should be around 0.2%. (Leggett [1993], fig. 15, at PbB values below 20 µg/dl). Independent of the time step used, there should be only one function, relating Pb in plasma and Pb in whole blood.

2. OTHER CONCERNS FROM RUNNING TESTS OF VERSION 1.05

A. Using environmental values from Boston, applied to children, the model appears to overestimate PbB by more than five fold. Some calibration is likely necessary.

B. Examining the slopes of relationships should be encouraged. In evaluating the model, it would be useful to look not only for predicted lead levels, but, also to compare the predicted and observed slopes for the blood/dust , blood/water, or blood/air relationships, to see if they are consistent with published values from epidemiological surveys.

C. Attention should be given to achieving an appropriate variance in blood lead. To properly describe the variance of blood lead levels expected in a population, one suggested method would be to put a distribution of gut absorption rates into the model, rather than a fixed value. This would generate a distribution in blood lead values. Alternatively, with specified biokinetic and environmental values, a point estimate in predicted blood lead could be calculated and then transformed into a suitable (log-normal, perhaps) distribution. By either method, a reasonable range for blood lead distributions needs to be generated, rather than just a "point estimate."

3. NEED TO PREDICT A DISTRIBUTION

In its memo to the SAB panel, the EPA states that the goal in developing this model is to address lead-related regulatory or remedial action decisions. These decisions involve the estimation of the impact of lead in different media on body burdens of lead in a subpopulation. A model that would assist the decision maker in estimating the effect of such regulatory or remedial action would have to predict the impact of exposure on the particular population, not in a specific individual. The present version of the model is not capable of modeling a population impact and thus it does not meet the goals of the EPA. It is not clear what "actual distributions of blood lead" refers to in question (b). The model does not predict blood lead distributions, rather it provides single estimate versus time. Varying the biokinetic and exposure parameters can yield the desired distributions.

It would be possible to generate a distribution by varying the biokinetic parameters. There is a physiological basis for this approach. Indeed, the gut absorption rate is not a constant among people. Even in carefully controlled metabolic ward settings, with a constant diet, gut absorption rates vary in the same person from week to week, and vary even more from person to person (Rabinowitz *et al.* [1976]). By allowing the gut absorption rate to vary, the model would create a distribution of blood lead levels.

(3) What advice can the Panel offer with regard to identification of specific features of the AALM that should be further refined in order to improve its predictive accuracy or to make it more user friendly? For example, what comments can be offered with respect to default values assigned for various parameters in the current version of the AALM software? Which, if any, of those default values may need to be changed — and why?

1. IMPROVING THE PREDICTIVE ACCURACY OF THE MODEL

1.1 Include Newer Information

New biokinetic data, that have been available since 1993, should be incorporated into the model. The data fall generally into three areas (Absorption, Skeletal turnover, Blood/plasma

components). Both the Leggett and O'Flaherty models are incomplete and do not include current understanding in these areas. The EPA should sponsor experimental and computational research to improve the AALM parameterization in these three areas. Consideration should be given to the EPA STAR grant program, working within the Superfund Basic Research Program, or via research contracts.

Regarding absorption, experimentally measured values for gastrointestinal (GI) absorption range from near zero to almost complete absorption. Since publication of the Leggett and O'Flaherty models, many relevant studies have described GI absorption or bioavailability using stable isotope dilution, in humans, swine, *etc.* EPA should promote retrospective analysis of existing data and support new research to better define the multimedia bioavailability and age-dependent absorption of ingested lead. Such effort may require revising and reparameterizing the Absorption module, for example, to be more like the IEUBK with saturable uptake. Much new data about the more important metabolic rates can be obtained by stable isotope methods with fairly brief experimentation times. For example, with the ingestion of a single bolus of lead tracer, several days of fecal and urine collection, and a few blood samples, most of the basic, essential rates can be determined, for example, gut absorption, blood pool size, blood turnover rates, blood to urine rate, and a rate for the movement from blood to deeper pools.

The Absorption module needs to be improved to utilize current data. Gut absorption is such a driving variable of major importance, that more data about this rate is needed. Research on better understanding of gut absorption rates should be encouraged.

It should be emphasized in the AALM User's Guide that dust absorption needs to consider that dust can be re-suspended in the air, and this represents a pathway of exposure to dust lead. Personal $PM_{2.5}$ exposure studies suggest that the "personal cloud" is a non-trivial source of airborne exposure, and re-suspension is an important part of this cloud. The dust model appears to assume exposure only via ingestion.

Regarding absorption through the lungs, the absorption module does not appear to allow the deposition rate, or the transfer rate out of the lung, to vary with either the size of the particle, or the speciation, or at least some surrogate for bioavailability. Size and speciation matter in absorption. Partially-complexed divalent cations on the surface of a particle deposited in the lung are easily mobilized and detectable in the blood within 10 minutes of instillation. Stable oxides will behave quite differently. In addition, since 1993 there has been a great increase in knowledge of particle deposition in the lung. The information concerning $PM_{2.5}$ in the Agency's Final Air Quality Criteria Document (October 2004) is a good source of recent information regarding absorption in the lung, and deposition parameters in the model.

The Skeletal module needs to be improved to utilize data among age groups that were not previously available. Much improvement can be made, for example, from neurotrophins (NTs) and other biomarkers of bone turnover, much has been learned that could be incorporated.

The description of the age-dependent skeletal growth, bone turnover, and lead accumulation and loss by the Leggett and the O'Flaherty models are incomplete. There is much room for improvement in the parameterization of skeletal growth, and cortical and trabecular

bone formation and turnover. The literature describing bone density and mass using DEXA and bone formation and resorption using biochemical markers such as circulating osteocalcin, cross-linked collagen peptides, radioisotopes, etc, as well as skeletal lead (stable isotope, XRF studies) offers a rich source of information to better parameterize the skeletal lead compartments.

There are data on repeated measurements of tibia and patella lead over time in the Normative Aging Study, and NTX measurements (a surrogate of bone turnover) at one time. It would be useful to test the bone model against these data to see how well it predicts bone lead decline. The default turnover rate for cortical bone may be too small for older adults. A half-life of ~20 years is seen in the Normative Aging Study.

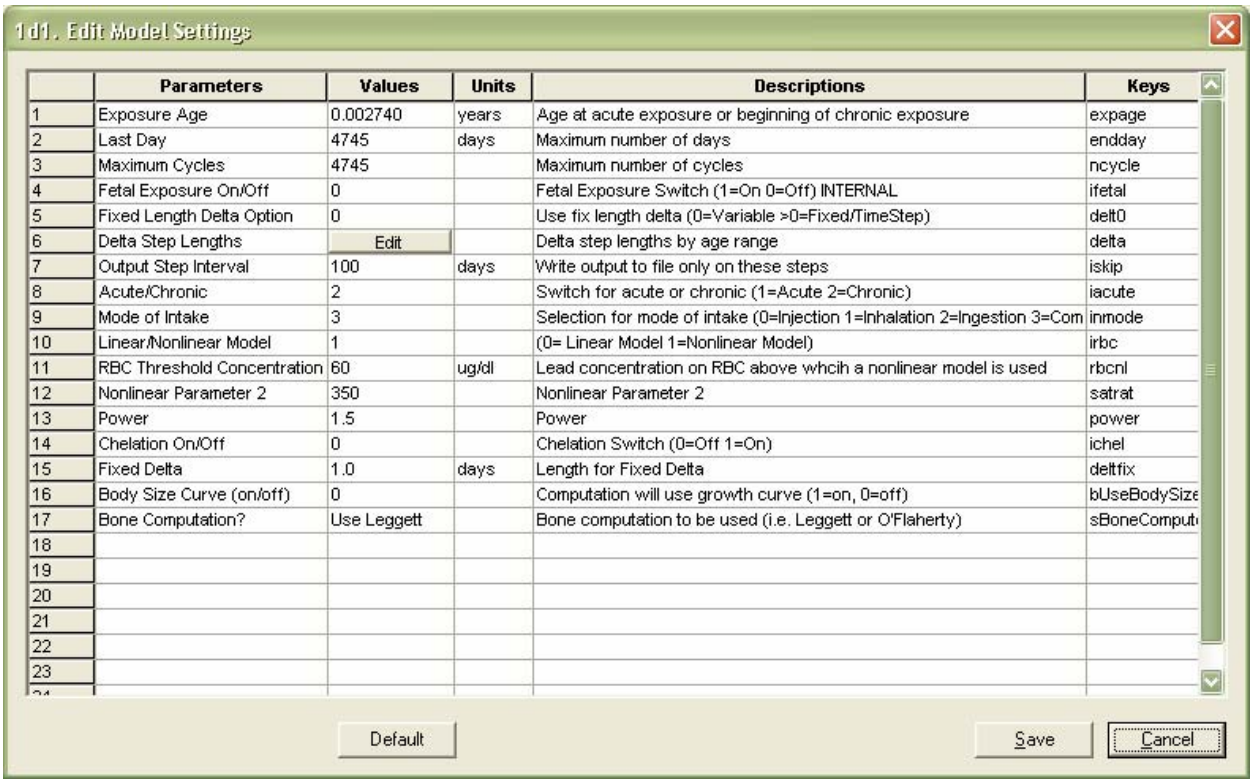
In the blood compartment, the speciation and partitioning of Pb, particularly in the small and rapidly exchanging plasma pool, needs to be re-considered. Several recent studies describe the partitioning of Pb in RBCs and plasma. The parameterization and structure of the Central blood/Plasma compartment should be revisited by reviewing the literature with emphasis on partitioning and speciation in plasma, including chelating agents. Generation of new experimental data may be warranted. The EPA should consider using stability constants to describe the speciation and equilibrium of Pb-small molecule complexes in plasma.

1.2 Improving the Modeling

Given the uncertainty in the biokinetic parameters, one appealing feature of the O'Flaherty model is that it is a simpler model than Leggett. Although bone as modeled in O'Flaherty model is not ideal because it doesn't lend to comparisons with XRF data, it could be useful.

Regarding hair and skin, in section 5.2.16, it is stated that lead removal through hair/skin and nails is a major route of lead excretion, two orders of magnitude larger than sweat because its deposition fraction (0.4) is two orders of magnitude larger than that of sweat (0.0035). This statement is incorrect. The 0.4 indicates that 40% of lead in the intermediate soft tissue pool is eliminated via hair/nails/skin but 0.0035 means that 0.35% of lead in diffusible plasma is eliminated via sweat. Since plasma lead turnover rate (<1 min =2000 per day) is much faster than intermediate soft tissue turnover rate (144 days= 0.007 per day or half life of 110 days) the amount of lead eliminated in sweat can be much higher than that eliminated via hair/skin/nails. *et al.*

Improvements in the biokinetic model settings screen are suggested. Several items in the editing menu are potentially confusing. Referring to the figure below:



	Parameters	Values	Units	Descriptions	Keys
1	Exposure Age	0.002740	years	Age at acute exposure or beginning of chronic exposure	expage
2	Last Day	4745	days	Maximum number of days	endday
3	Maximum Cycles	4745		Maximum number of cycles	ncycle
4	Fetal Exposure On/Off	0		Fetal Exposure Switch (1=On 0=Off) INTERNAL	ifetal
5	Fixed Length Delta Option	0		Use fix length delta (0=Variable >0=Fixed/TimeStep)	delt0
6	Delta Step Lengths	Edit		Delta step lengths by age range	delta
7	Output Step Interval	100	days	Write output to file only on these steps	iskip
8	Acute/Chronic	2		Switch for acute or chronic (1=Acute 2=Chronic)	iacute
9	Mode of Intake	3		Selection for mode of intake (0=Injection 1=Inhalation 2=Ingestion 3=Com	inmode
10	Linear/Nonlinear Model	1		(0= Linear Model 1=Nonlinear Model)	irbc
11	RBC Threshold Concentration	60	ug/dl	Lead concentration on RBC above whcih a nonlinear model is used	rbcnl
12	Nonlinear Parameter 2	350		Nonlinear Parameter 2	satrat
13	Power	1.5		Power	power
14	Chelation On/Off	0		Chelation Switch (0=Off 1=On)	ichel
15	Fixed Delta	1.0	days	Length for Fixed Delta	deltfix
16	Body Size Curve (on/off)	0		Computation will use growth curve (1=on, 0=off)	bUseBodySize
17	Bone Computation?	Use Leggett		Bone computation to be used (i.e. Leggett or O'Flaherty)	sBoneComput
18					
19					
20					
21					
22					
23					

Line 1. Why is this value expressed in units of years when all other inputs are in days? It would be less confusing to express age in post-natal days (*e.g.*, 0).
Line 4. Change description to (0=off, 1=on) to be consistent order with other switch descriptions.
Line 5. Should read 0=variable, 1= fixed…
Line 7. Is the unit for output step variable in days or in cycles? The original publication and many programs use cycles.

1.3 An Injection Term

"Injection" (exposure/uptake independent dosing) is an important feature to isolate the Biokinetic module from the Exposure and Absorption modules. This feature provides opportunity to compare various Biokinetic and PBPK models of lead and may be useful for simulating stable isotope studies. It would be appropriate and convenient to include a row for "injection" in the Exposure module. This approach would work well for situations where injections are chronic to circumvent the Exposure and Absorption module. For example, an "injection" of 5 µg Pb/d would facilitate understanding the role of age-dependent changes in biokinetic parameters in predicted PbB without the complication of age-dependent changes in person activities and absorption.

Unfortunately, "injection" simulations with only a single injection may be more complicated to organize through the Exposure module. For example, simulating an "injection" of

a stable isotope may be difficult through the exposure page. Thus accommodating "injection" may require some thought.

2. CHANGES IN DEFAULT VALUES

The water default values need to be re-examined. The flushed water value should be re-examined, and the daily water intake varying across ages, may not be suitable.

The estimates of the ratio of indoor-outdoor air can be improved based on recent literature. For the airborne exposure route, the indoor/outdoor ratio of 0.3 chosen for the default seems low. Many studies have looked at penetration rates and indoor-outdoor ratios in development of the particulate matter (PM) National Ambient Air Quality Standards (NAAQS). This literature should be incorporated here, since airborne lead is a particle. In general, readings of 0.3 are typical of winter-time studies, with summer ratios more like 0.6-0.7, and spring/fall ratios are closer to summer than winter values. The principal determinant of these ratios is ventilation rate, which varies geographically. In addition to choosing a more reasonable default, it would be useful to point the user to this literature, and raise the issue of regional variation.

In assigning the default values to biokinetic parameters, it should be noted that there are no biokinetic distributions in the model, just point estimates. The lead compartments and lead flows between compartments represented in the biokinetic component of the AALM are in reasonable agreement with the proposed kinetic behavior of lead and its disposition in tissues. However, all values assigned to the model are those presented in the Leggett paper. It should be noted that some of the compartments are model constructs without necessarily an anatomical correlate. For example, compartment liver 2 is added to account for a fraction of lead in liver with very low turnover rate. It does not mean that lead in liver is compartmentalized in two different physical reservoirs. The kinetic constant for this second compartment is a mathematical derivation necessary for a fully accounting of the kinetics of lead in liver as constructed in this model. In other words, other models of lead may choose to parameterize lead in liver differently and may not need a second compartment and a second rate, or may choose to have three rates. Because of this, it would be difficult to validate some of these rate constants against literature values because they are mathematical constructs of this particular model.

3. OTHER IMPROVEMENTS TO THE MODEL ACCURACY

An important part of the AALM validation process is to compare AALM performance to output of the IEUBK, Leggett, and O'Flaherty Models. The inputs and outputs of each module should be provided so the modules can be evaluated in isolation. Thus it is critical that the AALM provide outputs and inputs of each model to facilitate comparisons of inputs and outputs amongst these models (for example, the output of the Exposure module (µg Pb/d) in the .mod file). The data contained in this file can be reformatted as "intake" to the Leggett or O'Flaherty models making it possible to use identical "intakes" to the AALM, Leggett, and O'Flaherty models.

As discussed elsewhere in this document, the inadequate mathematical description of Pb

absorption and bioavailability of Pb in the gastrointestinal tract (GIT) is a central limitation of the current AALM version. The AALM program should develop an approach to manage variability in Pb INTAKE between individuals in a population, and in an individual in different physiological states, *e.g.*, fed *vs.* fasted. The future AALM should accommodate user control of INTAKE and UPTAKE parameters in time domains appropriate to simulate the existing and future UPTAKE and bioavailability data from studies utilizing stable isotopes. These features are necessary to support evaluation and simulation of media-dependent Pb bioavailabilities. The usefulness of a PBPK module to simulate Pb as part of the AALM or to compare and contrast with the Biokinetic module is limited in the absence of a more accurate and experimentally validated Absorption module. The time and resources required to incorporate a parallel PBPK module do not address or solve deficiencies of the Absorption module and thus, the improvement of the Absorption module should be the higher priority.

The historical dietary exposure data should be revisited to allow reanalysis with consistent assumptions on non-detects. The historical food data should be re-examined. The FDA, which generated these data, changed their method for inputting data when lead levels were below detection limits in their laboratories. Since many values were below detection limits, and the input methods changed, the values should be recalculated to get a consistent set of historical data.

Regarding historical air lead data, historical air lead concentrations can be well predicted from historical gasoline lead usage, which is available. The regression models to do this have been published (see: Schwartz J, Pitcher H. The relationship between gasoline lead and blood lead in the United States. J Off Stat 1990;5:421-431; Rabinowitz, M and Needleman H (1983) Gasoline lead sales and umbilical cord blood lead levels in Boston, Massachusetts. The Lancet 8314: 63; and Rabinowitz M, Needleman H, Burly M, Finch H and Rees J (1984). Lead in umbilical blood, indoor air, tap water, and gasoline in Boston. Archives of Environmental Health 39: 299 - 301.)

If breast milk is incorporated, it will have to be accounted for as a route of elimination for the mother. In terms of excretion, not only should breast milk be considered an excretory mechanism for the mother, but perhaps more importantly the fetus is an excretory mechanism.

4. OTHER MODELING CONCERNS

The observed nonlinearities provoke some unease. This is illustrated in the following observation from an AALM Panel member regarding the relationship of the model equations.

> "The model includes a very important non-linearity. It relates to the adjustment of all deposition fractions (and, thereby, rate constants) out from plasma, based on the deposition fraction from plasma to RBC (TOORBC). TOORBC is adjusted downward when RBC concentration (RBCONC) exceeds a certain limit (RBCNL). This results in an upward adjustment of all other deposition fractions from plasma (*i.e.*, see variable CF). Conceptually, what is being simulated is capacity-limited transfer of lead from plasma to RBC, with lead transfer out of plasma being diverted from RBC to other tissues, when transfer to RBC approaches capacity."

"... the Gear (in ACSL) runs slower (shorter cycle length) when the TOORBC adjustment is allowed than when it is not (the latter simulating capacity-unlimited transfer to RBC), presumably because it forces a shorter integration cycle to achieve the specific error limits on the integration."

It is quite possible that this non-linearity may cause the model to hunt while hitting the various limits imposed by the non-linearity. For example, when a person is being weighed on a true balance scale in the doctor's office, if the adjustments that are performed are too coarse, the balance simply bangs against one mechanical limit and then the other (limit cycles). In the actual body, although the process may be nonlinear, it is highly unlikely that the body goes through the same limit cycles.

In the IEUBK model, it was found that there was a very sensitive point involving two variables, CONRBC and TPLRBC. It is not suggested that a similar problem exists in the AALM, but it is a coincidence that the question involves RBC.

Stability of the model is also a concern. In general, for the linear portion of the model, the stability can be determined by the eigenvalues from the stated variable formulation of the AALM. For stability, these eigenvalues should be real and negative. It is unclear if the model has been formulated as such. However, in the IEUBK model, it was noticed that the eigenvalues started off as negative real, as the model evolved in time, these values were reduced in value approaching zero (0) towards the end of the model time (84 months). A major concern in the AALM is that the time period is much longer thus emphasizing the direction and magnitude of the eigenvalues. One test that should be run is the integration (simulation) over the entire time period with zero (0) input.

5. FRIENDLINESS

5.1 Guidance Manual

To be friendly, the manual needs to be free of textual errors. The current Guidance manual incurs many errors both in its paraphrasing of the Leggett paper and in mixing flows in and out of a compartment in the same section and even in the same sentence (sees examples below). Often these two flows are treated as dependent on each other when in fact they are not. For example: In 5.2.15 Transfer from fast soft tissue: the reader is directed to figures 68 and 69 which in fact describe parameters controlling the reverse transfer, from plasma to fast soft tissue. When this reverse flow is addressed in 5.2.23 Deposition fraction from diffusible fraction to fast soft tissue, figures 68 and 69 are repeated as figures 84 and 83. The same duplication occurs with the descriptions of plasma lead transfers to and from intermediate soft tissues, slow soft tissue, and brain.

In addition, several figures in the manual are never cited in the text (figures 35 through 40, and figure 43; figure 43 is a repeat of figure 35). The manual needs a thorough editing to identify these mistakes and insure that the conveyed information is accurate.

Below, are listed the instances where incorrect statements and confusing information were identified:

- In page 36: bottom paragraph: "This…" It is never stated what "this" refers to. The paragraph's last sentence is missing the contribution of plasma lead directly to the small intestine.
- Figures 37 and 38 are inconsistent for the age 0.274 (*i.e.*, .274 years, or roughly 100 days). Figure 37 lists 0.45 GI absorption and in the graph (figure 38) it is 0.66.
- In page 39 model settings: Two parameters referred as having drop down windows. There are in fact seven parameters with drop down windows.
- Page 43: "…biokinetic model settings, line 6 units are percent fraction per day…." Units are not percent, but fraction per day.
- Page 51: "… Transfer from the kidney has two components: Kidney 1 from the kidney back to diffusible plasma and kidney 2 to kidney 1 from the bladder…" It should be "… two components: kidney 2 from the kidney back to diffusible plasma and kidney 1 from the kidney to bladder…."
- Page 51, section 5.2.12: "…Urinary excretion…The model includes two routes: diffusible plasma to urinary path and diffusible plasma to Other kidney Tissue…" This is incorrect: It should read: diffusible plasma to urinary path and diffusible plasma to Urinary Bladder contents….
- Page 52 Section 5.2.13 is titled transfer from liver 2 (to plasma, should be added), but the text deals mostly with the outflow of lead from liver 1 to plasma and to other compartments.
- Page 53:"… this transfer from kidney 2 represents the amount of lead that passes to the bladder…" In fact, it represents the amount of lead that goes back to diffusible plasma
- Page 58: "…The deposition fraction for lead in feces is 0.006…and represents the lead entering the digestive tract from the mucocilliary…." This is incorrect. It is the lead entering the small intestine from diffusible plasma.
- Page 61:"…fraction of lead deposited in Liver 1 does not vary with age…" this is incorrect; it varies in Leggett's paper. This reference should be excluded from the section dealing with deposition fraction that does not vary with age. Furthermore the section makes reference to deposition fractions in general when in Leggett's paper the deposition fraction term is used to address the percentage of lead flowing to different compartment from diffusible plasma, and not the division of flow out of any other compartments. This needs clarification. The section continues: "…This Liver 1 fraction receives 4% of the lead released by diffusible plasma, giving a transfer rate of 80/day and a removal half time of ten days…" This section is misleading since it implies that the removal half time of 10 days for Liver 1 is a consequence of the input from diffusible plasma, when in fact it is due to the flows from Liver 1 to diffusible plasma, to liver 2 and to the small intestine, with a combined rate of 0.0693/day for a half life of ln(2)/0.0693/day = 10 days. The end of the passage states:"… Forty-five percent (0.45) of the liver 1

fraction is deposited in the Small intestine though the bile duct. Most of this is eliminated with feces; a small amount may be reabsorbed into the diffusible plasma…" This latter amount is not necessarily small. This lead is reabsorbed into the plasma at the same rate as ingested lead (page 605, Leggett's paper), *i.e.*, the fraction of lead from Liver 1 entering the small intestine that is reabsorbed is determined by the GI fractional absorption which starts at 45% in early childhood and decreases to 15% by middle adulthood. In the next paragraph:"…Most of the lead…." It is not most: it is 45%.

- In page 63: Section 5.2.24 needs thorough rewriting: "…This is the fraction deposited in intermediate Soft tissue from diffusible plasma, with a turnover rate of 25 to 300 days…" That is incorrect; the turnover rate of the intermediate soft tissue compartment is not a result of the deposition fraction of plasma-D but is dictated by its outflow to hair, skins and nails and back to plasma with a combined transfer rate of (0.00416/day+0.00217/day), resulting in an age invariable half life of ln(2)/ 0.013/day = 110 days. It continues "…this compartment has a deposition fraction from 0.005, giving a transfer rate of 0.00277…etc". The deposition fraction of plasma to this compartment and the outflow from this compartment are not related to each other, contrary to what the above implies.
- In page 64: "…A small amount of lead is transferred from diffusible plasma to slow soft tissue with a turnover rate from 1500 to 10000 days…" Again, the turnover rate of lead in the slow soft tissue compartment is not dictated by the incoming flow from plasma, which is very fast, but by the slow transfer rate of the compartment. These two rates are independent. Further, the removal half life of this compartment in age invariant ln(2)/ 0.00038/day= 1824 days and not 1500 to 10000 days.
- In page 66, section 5.2.27: "…The fraction of lead in bound plasma that is transferred to red blood cells is the deposition fraction…"; "in RBC" should be added. It continues:"…The fraction of lead that is deposited in Extra Vascular Fluids from diffusible plasma and red blood cells is 0.5…"; "and red blood cells" should be excluded since it is the fraction coming exclusively from diffusible plasma.

Some additional, minor editorial suggestions for the Guidance Manual are as follows:

- Page 3. Use sentence case for improved legibility
- Page 14. Change µg/g to µg Pb/g
- Page 18. Figure 13. Include unambiguous units in output name.
- Page 30. Figure 29. What are the units TS?
- Page 34. Paragraph 4. The statement that calcium, iron, and phosphorus are similar to lead is overly simplified.
- Page 34. Paragraph 5. Again, this paragraph is overly simplistic and incomplete. Lead speciation, gastrointestinal tract pH and contents are probably at least as important as digestive tract calcium. Moreover, this discussion ignores dietary

influences on lead uptake that may be mediated by hormones such as vitamin D (that is, there is a need for more details about factors influencing gut absorption).

- Page 35. Figure 34.
  - Change "Losses in hair…" to "loss to hair…."
  - Change "In Bone compartments, exchange…" to "…exchangeable…."
  - Change "RT Tract" to "Resp. Tract."
- The naming of subcompartments in "Other Soft tissues" is a little confusing; also, "tenacious turnover" is really "tenacious retention" or "slow turnover" and should be so described.
- Page 36. Figure 35. Line 1. Is the key "kdermal" correct?
- Page 36. Last paragraph. First sentence is not clear. "This" is a dangling participle; … and liver to the gastrointestinal tract?... "It" is a dangling participle. Delete "(slower)"
- Page 37. Figure 37 (and many other figures). Line 1. "Age Range" is actually the start age in years? "Decimal percentage" is confusing. Shouldn't this read "decimal fraction"?
- Page 37. Figure 38. The plotted data in Figure 38 do not match the data in Figure 37.
- Page 42. Figure 43. Change "Age cut-off" to "end age (days)."
- Page 43. First paragraph. Change "Pb decay rate" to "Pb radioactive decay rate."
- Page 43. Last paragraph. "This" is a dangling participle (both of them)
- Page 40. Last heading and paragraph. Change "EXCHANGE" to "EXCHANGEABLE."
- Page 51. Section 5.2.11 Change close up "kidney 1," *etc.* to "kidney1" to be consistent with program labels, liver1, *etc.*
- Page 51. Figure 61. What is the meaning of the label "indexes" in the Row 1? Shouldn't this be the end age in years for the variable?
- Page 53. Last paragraph. Change "…transfer for Kidney 2" to "transfer from Kidney2."
- Page 54. Last paragraphs. "Binding capacity" is mismatched to the term "strengths." The AALM Panel suggests that the binding "capacity" should be restated to relate to turnover. Also see comment above re: Page 35 related to "tenacious turnover."
- Page 60. Figure 78. This figure describing a "chelation" parameter should be deleted as the chelation is not yet implemented in the AALM.
- Page 61. Last paragraph. "This…" is a dangling participle.

In addition, as has been mentioned in other contexts, no guidance is given to the user as to how to measure "dust" lead. Different methods give different values for concentrations per gram or concentration per square centimeter (cm^2). As part of the validation process, determine which method seems to be closest to your "dust" input, and let people know.

5.2 Guidance Manual Cautionary Notes

The user needs to be warned against changing the biokinetic model parameters by stressing any changes in the biokinetic model parameters that can/will make the model no longer equivalent to the Leggett model. The discussion about the differences in the freedom to change parameters in the model for risk assessors versus researchers needs an explicit statement. The uncertainty surrounding the numbers generated by the IEUBK model is often not explicit. In this larger model there may be a temptation to tweak the various parameters to yield a desired outcome. This model is highly complex and includes numerous parameters for which there is limited information about their values. A high degree of uncertainty is introduced in the modeling effort by specifying so many parameters. A purely physiologically-based pharmacokinetic model, such as O'Flaherty's, has a much smaller number of lead specific parameters thus reducing the level of uncertainty but maintaining a high degree of complexity through the parameterization of human physiology in terms of perfusion rates and organ sizes. Uncertainty about the values of these variables is much smaller. The O'Flaherty model has been more thoroughly evaluated against real datasets than the Leggett model.

5.3 Making Data Entry Easier

The following are suggested to ease the process of data entry:

A. A batch mode option to simulate different distributions for different environmental concentrations.

B. A dialogue box, or balloons, that tells the user what the model parameters are and implications of changing them.

C. The activity patterns window could be improved by allowing the user to re-size it. For example, resizing the window horizontally would allow as many columns as needed to be viewed at once. This would be more convenient.

D. Consideration should be given to creating several pre-specified scenarios representing settings expected to be of particular interest. These might include: an urban child in high risk housing, an occupationally exposed male adult worker, an older female with osteoporosis having body burdens from historical exposures in the 1950's, 60's, and 70's, a resident near a Brownfield's superfund site. From entering the desired scenario, the user would have specified a set of environmental levels, and the ages of interest. This might prove to be a time-saver.

5.4 Running the Model (including glitches to fix)

The following are suggested to improve operation of the model:

1. What/where are the historical diet/air/dust values? Can these values be put in a separate file (.rtf, .xls, etc)? The check “use historical air Pb concentration” box does not seem to change the air Pb concentrations.

2. The age ranges should be edited to differentiate between infants 0-0.5 years, toddlers 0.5-3 years, preschool 3-6 years, and school age children 6-12 years. The exposure of two-year - olds is markedly different from that of four-year-olds. The model should categorize exposures by the ages of children. The exposure and biokinetic parameters are in some cases tied to age category, and the AALM should apply these consistently.

3. An algorithm with a variable time step would accommodate both chronic and acute exposures and would be a better than the current fixed time step. The time step of integration should not be accessible to the user. The time step is dictated by the degree of numerical stability and error tolerance in the integration, and the frequency of model output as specified by the user. The user should be able to specify the desired output frequency and the software should calculate the time step to be used based on the user input and the numerical needs of the integration algorithm. The time step should not be a user input.

4. Often, the model runs for longer than the age group specified. This happens after the software has been used for several model runs in which age groups had been deselected. Restarting the software avoids this glitch.

5. When run for different lengths of time, the model generates inconsistent results for the same age group even when the lead intake for the age group is the same in all simulations. This occurs occasionally and appears to be related to the opening and closing of a new model. For example if an age group is selected, and the model run, then the age group is expanded and the model run again, the results of the two runs are consistent. But, if the model is closed after the first run, and a new one is opened and run with an expanded age range and same exposure conditions, the outputs of the models runs on overlapping age ranges are inconsistent.

5.5 Improving Reporting of Model Output

The following are suggested to improve reporting of the model output:

The output should automatically report all of the key parameters. Printed graphic output should include a list of important variables including internal biokinetic parameters that may have been altered, and environmental variables that may be desired in the output report. The section explaining the output from the model is extremely poor. Instructions are needed regarding how to modify the plots, access previous model runs, and combine outputs from different simulations Instructions should be provided for batch runs.

The output of the AALM Absorption module (uptake to blood) should be written to a similar file (to the .mod) so that the research modeler can evaluate the behavior of the Absorption module in isolation. “Pb Uptakes” are not coded as output variables by Leggett (1993). The user should have the option to customize the default plot. Output files can have data stored as follows:

- Exposure Module Output (Intake as µg Pb/delta time)
- Interval Drinking Water Dust inhaled, *etc.*
- Total Intake GI Total intake RT Grand Total
- Absorption Module Output (Uptake µg Pb/delta time)
- Time interval uptake via GI uptake via RT Total uptake

The question, "How are Exposure outputs (µg Pb/d) passed to the Absorption module (*i.e.*, as Intake)"?, is essentially asking about the synchrony of simulation time steps as data are passed between the three modules. It is not clear how the modeler controls the time in these time steps.

It is assumed that the Hour/day switch on the initial AALM window defines only the Exposure module and that the simulation time steps for the Absorption and Biokinetic modules are controlled only by the "Edit Model Settings" menu. If this assumption is correct, how are Uptake values passed to the Absorption module? If the Exposure module simulates Uptake (µg Pb/hour), does the Absorption module simulate once per hour, and Biokinetic module model simulates 1 per day? Simulation comparing 1-hr vs. 1-day time steps (selected from the initial edit page) give appropriate values in the .mod file, but the model-predicted PbB values are very dissimilar (data not shown). The difference in predicted PbB may be the result of asynchrony between modules.

The AALM user should also be able to control the "default values" for plot display, not merely the display of the current plot. This control would facilitate consistency in the axes and other display parameters for purposes of publication, presentation, *etc.* The complaint is that, in its present form, the user must change the plot display every run. The label "age range" (Figure 8) should be made more precise. It can be used to identify a particular age, such as a Start or Stop Age. The default file name when exporting the MOD file is missing the period resulting in an incorrect filename.

III. Computer Coding and Quality Assurance

The user interface of the AALM is quite good. The model has an easy, menu-driven interface that is intuitive, and the learning curve is not very steep. However, there are additional features that would enable the model to be more useful for either hypothetical or real-world risk assessment problems. Limitations of the AALM include the following:

- A batch mode is needed similar to the current functionality of the IEUBK model to facilitate an evaluation of the proportion of the population that exceeds a target risk-based concentration in an exposure medium. The user should be able to specify an input file with a set of site-specific factors (*e.g.*, paired concentrations in soil, dust, and water at a residence). The AALM would benefit greatly by allowing either point estimates or probability distributions to be calculated for each exposure unit.
- The AALM needs to incorporate variability and uncertainty more directly. It would be useful to be able to specify expected distributions of parameters, and get out a probability distribution of blood lead for a population. Default distributions, rather than default point estimates, for these parameters would be preferred so that variability and uncertainty are

more properly accounted for in the risk assessment without the requirement of tedious repetitions by the risk assessor.

- Even for the research community, caution should be given about changing the biokinetic parameters, given that they were not derived independently, and changing one often implies changes to others. The results would also no longer correspond to the Leggett model. Interest was expressed in adding the physiological (O'Flaherty) model option.

Specific suggestions for the AALM include: eliminating the need to set the gender option in three locations; and increasing flexibility in the graphic display.

Regarding the QC of the program, the AALM does not perform correctly. For example, Manton and Cook's data indicate that plasma lead should be about 0.2% of blood lead when blood lead is less than 25 mg/dL. The Leggett model, on which the AALM is based, predicts this successfully. However, the AALM not only does not meet this design criteria, it produces non-single-valued functions. Small errors in the parameterization of the kinetics of this compartment can propagate very rapidly to errors in the amounts of lead in all other compartments. Since the AALM derives from the Leggett model, it is assumed that this is a result of coding errors. It is recommended that efforts be made to fit the AALM to the same datasets as the Leggett model.

In addition, plausibility checks should be run such as making sure results behave as expected as the number of years is lengthened, that different intakes for different periods behave as one would expect, given cumulative dose, *etc.* It would also be worthwhile to examine other data sets. Finally, several of the input assumptions are unreasonable, and should be changed. This includes assuming the same gut absorption rate for food and water lead, the default values for water lead concentration, *etc.*

❖ **Charge Questions 4 & 5: *Computer Coding and Quality Assurance***

(4) Based on any trial-run experiences of Panel members, what can be said about the "learning curve" needed to become sufficiently-familiar with the AALM software in order to effectively apply it? Furthermore, assuming that one had a need to apply the AALM to a hypothetical or real-world risk assessment problem, what additional information (if any) about the AALM might be useful for a user to have in order to correctly and efficiently apply the model and enhance effective communication of modeling outcomes? What comments can the SAB Ad Hoc AALM Review Panel offer concerning output features (e.g., tabular presentation of modeling results, graphic display options, etc.*)?*

(5) In the judgment of the SAB Ad Hoc AALM Review Panel, to what extent has the computer code comprising the AALM software been adequately verified and appropriate quality assurance checks carried out and/or planned? What additional quality control/quality assurance checks, if any, would the Panel recommend?

Question 4 relates to the user interface of the model. Overall, this subgroup found the user interface to be quite good, but for a more limited goal than would be desirable. The model has an easy, menu driven interface that is intuitive. The format for entry of exposure parameters was

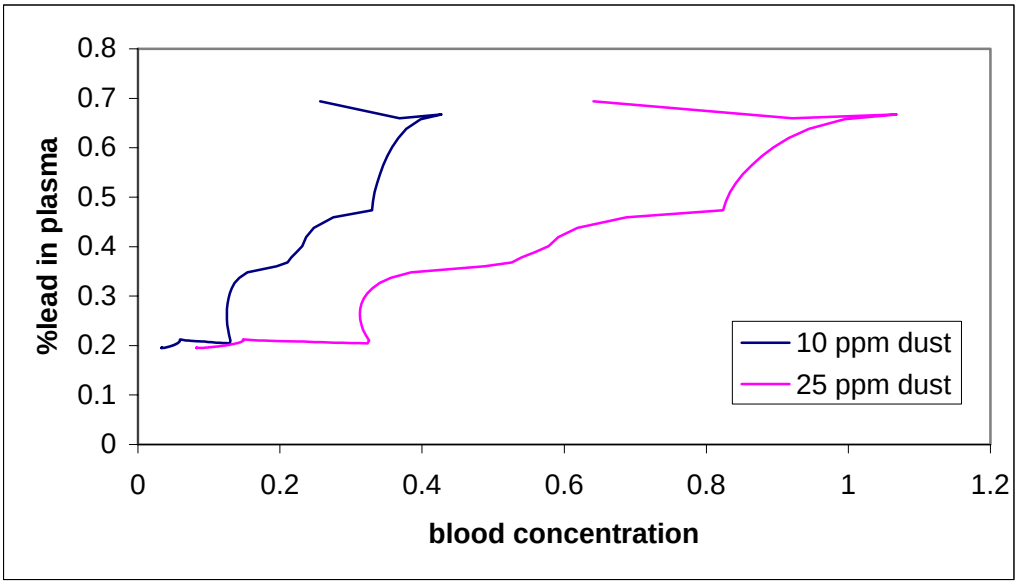
very useful and intuitive, and the results are generally presented well. Hence, the members of the AALM Panel do not think the learning curve is very steep. However, AALM Panelists do believe that there are additional features that would enable the model to be more useful for either hypothetical or real-world risk assessment problems.

The ability to vary a large number of parameters, while of use to the research community, may be confusing, and tempting, to the risk assessor. It is easy to get into trouble, and Panel members wonder whether a risk assessor option that fixes some of the choices would be a useful option.

Specific Suggestions/Comments:

- The gender option needs to be set in three locations. This is awkward, and can lead to errors, since the locations are not linked.
- The graphic display is too inflexible. Units are not displayed, axes scales are not flexible, and it is not clear how to save graphs. "Time" should not have a scale of days as this makes it too hard to examine longer term results.
- It is important to include a soil lead input that is separate from the dust lead input

Question 5 relates to QC of the program. Definite problems were found and quite simply, the model does not perform correctly. For example, Manton and Cook's data indicate that plasma lead should be about 0.2% of blood lead, when blood lead is less than 25 mg/dL. The Leggett model, on which the AALM is based, successfully predicts this. However, the AALM not only does not meet this design criteria, it produces non single-valued functions. Simulations were run from birth to middle age that assumed two different levels of dust lead intake, *i.e.*, lead inputs of 10 ppm or 25 ppm lead in dust as the only exposure. The figure below, with the results of those runs, can only be considered to be in error.



(Percent lead in plasma was calculated from the ratio of output variables Plasma and Blood, and the X-axis is the output variable Blood lead concentration.)

The numbers are out of range; they differ depending on the dust lead level used to arrive at the same blood lead concentration; and, as noted before, they are non single-valued functions. While the percent of lead in plasma is not a variable of importance from a regulatory perspective, the amount of lead in plasma is critical in this model because it is the compartment feeding lead to all other compartments with a very fast turnover rate. Thus, small errors in the parameterization of the kinetics of this compartment can propagate very rapidly to errors in the amounts of lead in all other compartments. Since the AALM derives from the Leggett model, it is assumed that this is a result of coding errors.

Validation using the NHANES data, and in particular demonstrating that the observed trends in U.S. population lead levels can be replicated, would be quite useful if the intent is to use to model to examine effects of NAAQS or other regulatory changes. Furthermore, since the aim of the "all ages" lead model is to address potentially susceptible groups beyond children, then pregnancy, lactation, and postmenopausal bone mobilization population options should be included.

IV. AALM Documentation

The AALM Panel deems that the present Guidance Manual is useable, but should be made more user-friendly. It is incomplete in several areas and contains many errors and confusing wording. The manual should provide both a theoretical framework for the uninitiated user to understand the structure of the model and its scientific basis, and a step-by-step procedure that would walk the user from data input to the evaluation of the predicted outcomes. EPA should also consider developing and releasing a companion Technical Support Document to augment the Guidance Manual that includes verification and validation exercises, utilizing real world demonstrations, and appropriate cautions that would aid the user in understanding, interpreting and utilizing the model.

In addition, the AALM Panel notes that the output options provided in Version 1.05 are interim choices and will therefore need to be developed more fully in subsequent releases. The data files, if possible, should be exportable to other traditional software programs. More explanation of the structure, underlying nature and accessibility of these data sets should be provided. There should also be explanation regarding the type of environmental information to be entered, so that it is standardized to the type for which the model was calibrated. The Parameters Dictionary was an extremely important component of both the guidance and the help feature. The AALM Panel suggests that more specific information be provided in the guidance and support documents with regard to each individual parameter, including its origin, source of support data, possible range of values, any information regarding central tendencies and variance, uncertainty, the rationale for the default setting, relationship to other parameters, and appropriate cautions as needed for modifications.

To the extent practicable, the AALM approach, guidance and application should be consistent, and evolve concurrently, with similar models and guidance presently endorsed by EPA and used by the Agency in the professional and scientific community. The Agency should consider issuing guidance regarding the required (or recommended) use of the default or prescribed bio-kinetic parameters in regulatory applications. Finally, the AALM should be evaluated relative to the Agency's current *Draft Guidance on the Development, Evaluation, and Application of Regulatory Environmental Models*.

❖ Charge Questions 6-9: AALM Documentation (*e.g.*, Guidance Manual, Parameters Dictionary, *etc.*)

(6) To what extent is the "AALM Guidance Manual" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved to help facilitate use of the model?

Implementation: The group felt that the model guidance was mechanically constructed in a typical "point and click" format. This had the advantage of making the model easy to access and implement. However, members thought users were able to "RUN" the model with almost no orientation or introduction to the purpose, structure, format or construct, and suggested that the guidance manual be significantly augmented with examples, demonstrations and appropriate cautions that would aid the user in understanding, interpreting and utilizing the model. The example screens provided in the guidance should be reproducible in the tutorials and demonstrations.

Options and Features: Most of the options and features were found to be confusing, largely because they were either unexplained in the guidance or were under development and not available. For some of the options that were implemented, the paraphrasing and descriptions in the text seemed inconsistent with either the information available in the Help Screens, or information that could be deduced from applying the option.

Outputs: The group understood that the output options provided in Version 1.05 are interim choices and will be developed more fully in subsequent releases. Accordingly, most of the comments may be addressed with adoption of new software. Such issues included units, rounding of values, scales, graphing inconsistent units on the same plots, *etc.* The panel felt that the plotting function was especially useful and should be included and upgraded in future releases. If possible, the data files should be exportable to other traditional software programs. In that light, more explanation could be provided of the structure, underlying nature and accessibility of these data sets.

Convenience: The group felt that several items would make the model more convenient for users. Inputs could be facilitated by employing "drag and click" or "copy and paste" options for the various age-groups, *etc.* Blood lead concentration should be a default output parameter and not be plotted with other compartments with inconsistent units. The guidance should explain the quantitative uncertainty in, and require more effort to vary, the bio-kinetic parameters. There should be explanation regarding the type of environmental information to be entered, so that it is standardized to the type for which the model was calibrated. Accessible interim (during model

setup and operation) output from different modules would be a great improvement. For example, providing a summary of route-specific inputs of lead via the dietary, soil and dust, water and air routes following the setup of the exposure module would be most helpful. Similarly, route or pathway specific summaries of absorbed lead would facilitate understanding of bioavailability and bio-accessibility. A batch mode application that aggregates results for multiple individuals in a population would be an important addition for risk assessors.

(7) To what extent are the entries in the "Parameters Dictionary" for the AALM sufficiently clear and accurate in explaining important elements of the AALM? How might the Parameters Dictionary be improved?

The Parameters Dictionary was considered an extremely important component of both the guidance and the help feature. As structured, the dictionary was helpful to programmers accessing the code. As this is expected to be an "open code" model, the information provided should be retained. However, the overall concern was that this is a "parameter rich" model and much more information should be provided in the guidance or available technical support documents. The group suggested that more specific information be provided in the guidance and support documents with regard to each individual parameter, including its origin, source of support data, possible range of values, any information regarding central tendencies and variance, uncertainty, the rationale for the default setting, relationship to other parameters, and appropriate cautions when modifying them. It was suggested that this information be accessible through "hot button" connections on-screen from the parameters dictionary or help menu.

(8) Are there any other comments or advice that the SAB AALM Review Panel wishes to provide with regard to ways that the AALM, its software, and other associated materials can be improved to help to facilitate its application and enhance the usefulness of its results?

The group chose to reiterate earlier concerns with regard to this charge. There were QA/QC related to the potential interactions and inter-relationships among parameters. There should be internal mass-balance checks, perhaps with an appropriate notice or warning that conservation requirements are met, when parameter modifications are attempted. It is unclear whether modifications to parameters in one screen cause (or necessitate) changes in related screens. It was unclear if it is the user's responsibility to conserve the mass balance when changing fractional parameters in the input screens. Special attention should be paid to units throughout the procedures, output and feedback. There should be appropriate discussions regarding uncertainty (both qualitatively and, to the extent practicable, quantitatively) in the model; sensitivity to particular parameters; and limitations of the model to selected applications.

(9) Does the AALM follow the Agency's Regulatory Environmental Model Guidance found at URL: http://cfpub.epa.gov/crem/?

To the extent practicable, the model approach, guidance and application should be consistent, and evolve concurrently, with similar models and guidance presently endorsed by EPA and used before the Agency in the professional and scientific community. The Agency should consider issuing guidance regarding the required (or recommended) use of the default or

prescribed bio-kinetic parameters in regulatory applications. Alternatively the Agency could release two versions of the model for researchers and risk assessors. Finally, the model should be evaluated relative to the Agency's current *Draft Guidance on the Development, Evaluation, and Application of Regulatory Environmental Models.*

Appendix A

Charge to the SAB *Ad Hoc* All-Ages Lead Model Review Panel

The Agency seeks the review and advice from the SAB regarding the scientific soundness of the All-Ages Lead Model, and requests that the AALM Panel focus on the following charge questions during its review of the AALM:

(1) In general, to what extent are the parameters and relationships represented by various AALM features adequately supported by available research findings in published peer-reviewed literature or by reasonable extrapolations from such findings? That is, are the specifications of key components of the AALM model scientifically supportable in characterizing particular parameters or relationships of the types noted above. More specifically, what are the AALM Panel's views with regard to:

(a) The adequacy of the values specified for the exposure parameters for different media and how well the model interprets exposure throughout the various age groups;

(b) The adequacy of the uptake/absorption parameters or any need for modification of the methodology for determining absorption for various routes of exposure;

(c) Whether there are any errors in AALM methods for determining biokinetic distribution or errors in assigning values to biokinetic parameters; and

(d) Does the AALM model correctly account for elimination of lead via various pathways?

(2) Based on EPA's demonstration of the model, what can be stated with regard to the predictive accuracy and reliability of the AALM regarding comparisons of: (a) model-generated outputs of projected blood lead distributions derived from real-world lead exposure data inputs with (b) actual distributions of blood lead (or bone lead) concentrations for individuals experiencing such lead exposures? In addition, have AALM Panel members made any "test runs" to apply the current draft version (1.05) of the AALM to "real-world" datasets that may be available to them; and, if so, what were the outcomes of such efforts?

(3) What advice can the AALM Panel offer with regard to identification of specific features of the AALM that should be further refined in order to improve its predictive accuracy or to make it more user friendly? For example, what comments can be offered with respect to default values assigned for various parameters in the current version of the AALM software? Which, if any, of those default values may need to be changed — and why?

(4) Based on any trial-run experiences of AALM Panel members, what can be said about the "learning curve" needed to become sufficiently-familiar with the AALM software in order to effectively apply it? Furthermore, assuming that one had a need to apply the AALM to a hypothetical or real-world risk assessment problem, what additional information (if any) about the AALM might be useful for a user to have in order to correctly and efficiently apply the model and enhance effective communication of modeling outcomes? What comments can the

AALM Panel offer concerning output features (*e.g.*, tabular presentation of modeling results, graphic display options, *etc.*)?

(5) In the judgment of the AALM Panel, to what extent has the computer code comprising the AALM software been adequately verified and appropriate quality assurance checks carried out and/or planned? What additional quality control/quality assurance checks, if any, would the AALM Panel recommend?

(6) To what extent is the "AALM Guidance Manual" sufficiently clear and useful in providing "user friendly" instructions for carrying out model runs for AALM applications? How might the AALM user's manual be improved to help facilitate use of the model?

(7) To what extent are the entries in the "Parameters Dictionary" for the AALM sufficiently clear and accurate in explaining important elements of the AALM? How might the Parameters Dictionary be improved?

(8) Are there any other comments or advice that the AALM Panel wishes to provide with regard to ways that the AALM, its software, and other associated materials can be improved to help to facilitate its application and enhance the usefulness of its results?

(9) Does the AALM follow the Agency's Regulatory Environmental Model Guidance found at URL: http://cfpub.epa.gov/crem.

Appendix B

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