



EPA600/R-19/011
May 2019

Technical Support Document for the All Ages Lead Model (AALM) – Parameters, Equations, and Evaluations

Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC 20460

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ACRONYMS AND ABBREVIATIONS

AALM	All Ages Lead Model
AALM-LE	ACSL implementation of Leggett model
AALM-OF	ACSL implementation of O’Flaherty model
ABLOOD	amount of Pb in blood
ABONE	amount of Pb in bone
ACSL	Advanced Continuous Simulation Language
AF	absorption fraction
AKIDNEY	amount of Pb in kidney
ALIVER	amount of Pb in liver
ALM	Adult Lead Methodology
ASOFT	amount of Pb in soft tissue
ATSDR	Agency for Toxic Substances and Disease Registry
AMTBLD	Leggett model blood volume
BLDHCT	age-dependent hematocrit
BLL	blood lead level
CB	O’Flaherty model blood Pb concentration
CF	AALM adjustment factor for Pb deposition into RBCs
CIHAR	AALM fraction of inhaled Pb transferred to stomach
CSFII	continuing survey of food intakes
CSV	comma-delimited text file
DF	deposition fractions
EFH	Exposure Factors Handbook
EPA	Environmental Protection Agency
EVF	extravascular fluid
FRX	O’Flaherty model Pb excretory clearance
GI	gastrointestinal
GIT	gastrointestinal tract
GFR	glomerular filtration rate
GM	geometric mean
GSD	geometric standard deviation
HCTA	adult hematocrit
HRTM	Human Respiratory Tract Model
ICR	Information Collection Request
ICRP	International Commission on Radiological Protection
IEUBK	Integrated Exposure Uptake Biokinetics
IVBA	validated in vitro bioaccessibility
LFM	Leggett Fortran Model
LLIC	lower large intestine contents
NCEA	National Center for Environmental Assessment
NHANES	National Health and Nutrition Examination Survey
NHEXAS	National Human Exposure Assessment Survey
NSLAH	National Survey of Lead and Allergens
NTIS	National Technical Information Service
OCSPP	Office of Chemical Safety and Pollution Prevention
OEHHA	Office of Environmental Health Hazard Assessment
OLEM	Office of Land and Emergency Management
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
OSWER	Office of Solid Waste and Emergency Response

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Pb	lead
PK	O'Flaherty model plasma-kidney partition coefficient
PL	O'Flaherty model plasma-liver partition coefficient
PP	O'Flaherty model plasma-poorly perfused tissue partition coefficient
PW	O'Flaherty model plasma-well perfused tissue partition coefficient
RBA	relative bioavailability
RBC	red blood cell
RBCONC	red blood cell Pb concentration
RRBC	rate transfer of Pb from red blood cells to diffusible plasma
RT	respiratory tract
SAB	Science Advisory Board
SOF	Other Soft Tissues
SSC	standardized sensitivity coefficient
ST	soft tissue
ULIC	upper large intestine contents
VBLC	blood volume fraction of body weight
VBONE	bone volume
VK	kidney volume
VL	liver volume
VR	ventilation rate
XRF	X-ray fluorescence
WBODY	body weight
WBONE	bone weight

1 CHAPTER 1. INTRODUCTION AND HISTORY OF ALL AGES LEAD MODEL

2 1.1. INTRODUCTION

3 The All Ages Lead Model (AALM) is a tool for quantitatively relating lead (Pb) exposures from
4 environmental media that occur over the life time to Pb levels and concentrations in blood, other body
5 tissues, and excreta. The primary intended use of the model is for computational Pb toxicology and risk
6 assessment. The AALM represents an extension of research and regulatory models previously developed
7 by EPA such as the Integrated Exposure Uptake Biokinetics (IEUBK) Model for Pb in Children which
8 simulates exposure-blood Pb concentration relationships occurring from birth to age 7 years ([Hogan et al.,](#)
9 [1998](#); [White et al., 1998](#); [Zaragoza and Hogan, 1998](#)). The AALM also incorporates Pb modeling
10 concepts explored in models developed in other research efforts, including those of Leggett ([Pounds and](#)
11 [Leggett, 1998](#); [Leggett, 1993](#); [Leggett et al., 1993](#)), O'Flaherty ([O'Flaherty et al., 1998](#); [O'Flaherty, 1998,](#)
12 [1995, 1993, 1991a, b, c](#)) and others ([U.S. EPA, 2006](#); [Maddaloni et al., 2005](#)).

13 As discussed in Section 1.2, the AALM has been implemented in several platforms over the course of its
14 development. The AALM was first developed and implemented in Visual C+ (AALM.C) by U.S. EPA's
15 Office of Research and Development (ORD). Subsequently, ORD implemented the AALM in Advance
16 Continuous Simulation Language, ACSL[®], a.k.a. acsIX, (AALM.CLS) to further develop and evaluate the
17 model. In a parallel effort, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) was
18 developing a biokinetic Fortran model (ICRPv005.FOR) with similar capabilities to the AALM.CLS
19 being developed by ORD. Since 2015, EPA's ORD and OCSPP have coordinated efforts to advance Pb
20 biokinetic modeling and produced the current version of the AALM software implemented in Fortran
21 (AALM.FOR) with a Microsoft Excel user interface.

22 This document, in Chapter 2, describes in detail the conceptual and computational structure of the current
23 Fortran version of the AALM (AALM.FOR), including an inventory and explanation of all parameters,
24 variables, and expressions used in the model to calculate Pb intakes and Pb tissue and excreta levels
25 and/or concentrations. Chapter 2 has two primary subsections. The initial primary section (exposure
26 model) describes components of the AALM.FOR that relate environmental and diet Pb exposures to rates
27 of Pb intake. This is followed by a section that provides a detailed description of model components that
28 relate Pb intakes to Pb levels and concentrations in body tissues and excreta. Appendices A and B
29 provide a complete listing of equations and parameters used in the model, respectively, that are directly
30 pertinent to calculations of Pb intakes and Pb levels and concentrations in body tissues and excreta.
31 Appendices C and D provide a complete list of parameter names and default values used in the model.

32 Chapter 3 describes the development and evaluation of AALM.FOR. This chapter describes the process
33 of harmonizing two model versions [AALM.CLS and OCSPP's biokinetic model in Fortran
34 (ICRPv005.FOR)], evaluating the differing biokinetics for the two versions against available human data,
35 and selection of final model parameters for use in AALM.FOR. The side-by-side comparisons of
36 AALM.CLS and AALM.FOR provided a quality assurance opportunity to ensure code was implemented
37 and operating as expected, i.e., the mathematical relationships posited by the model were correctly
38 translated into computer code and its operation was free of numerical errors. Model parameter
39 optimization and sensitivity analyses discussed in Chapter 4 provides the basis for parameters in
40 AALM.CLS that were ultimately used in AALM.FOR. These analyses were not repeated using
41 AALM.FOR since it provides identical predictions to AALM.CLS. Model evaluations in Chapter 3

1 compare AALM.CLS and AALM.FOR against the same datasets used in Chapter 4 as well as some
2 additional datasets for striking workers and children.

3 Chapter 4 describes the ORD development and evaluation of AALM.CLS. The AALM.CLS version
4 implemented both the Leggett model ([Leggett, 1993](#)) and O’Flaherty model ([O’Flaherty, 1995, 1993](#)).
5 The chapter begins with a comparison of the Leggett and O’Flaherty model structures and then provides a
6 comparison of predicted blood and bone concentrations of Pb between the models. Sensitivity analyses
7 are subsequently provided that were utilized to determine the most influential biokinetic parameters in the
8 models. An evaluation and optimization biokinetics models against observations is provided. A
9 biokinetic parameter controlling Pb binding to red blood cells Pb concentrations was adjusted to align the
10 AALM.CLS results more closely with the IEUBK model for children without adversely affecting the
11 good model agreement and predictive capability for infants or adults.

12 **1.1.1. Quality Assurance and Peer Review**

13 The use of quality assurance (QA) and peer review helps ensure that EPA conducts high-quality science
14 that can be used to inform policymakers, industry, and the public. Quality assurance activities performed
15 by EPA ensure that the Agency’s environmental data are of sufficient quantity and quality to support the
16 Agency’s intended use. Detailed QA Project Plans (QAPPs) have been developed as a requirement for
17 contracted technical support during the development of the AALM. The AALM is classified as providing
18 Influential Scientific Information (ISI), which is defined by the Office of Management and Budget
19 (OMB) as scientific information the agency reasonably can determine will have or does have a clear and
20 substantial impact on important public policies or private sector decisions ([OMB, 2004](#)). OMB requires
21 the Agency to subject ISI to be peer review prior to dissemination. To meet this requirement, EPA often
22 engages the Scientific Advisory Board (SAB) as an independent federal advisory committee to conduct
23 peer reviews. The SAB released a call for peer review panel nominations on November 1, 2018
24 (83FR54923). Panel members were chosen to create a balanced review panel based on factors such as
25 technical expertise, knowledge, experience, and absence of any real or perceived conflicts of interest.
26 Both peer review comments provided by the SAB panel and public comments submitted to the panel
27 during their deliberations about the external review draft will be considered in the development of a final
28 version of the AALM.

29 **1.2. HISTORY OF THE AALM**

30 The AALM was developed as a computational tool for predicting blood Pb concentrations associated with
31 multimedia exposures to Pb that occur from birth through adulthood. The model is a substantial
32 conceptual extension of an earlier IEUBK model developed by EPA to predict blood Pb concentrations in
33 children, the IEUBK model ([Hogan et al., 1998](#); [White et al., 1998](#); [Zaragoza and Hogan, 1998](#); [U.S.
34 EPA, 1994a, c, 1989](#)). The IEUBK model has been widely used at Superfund sites to develop remedial
35 objectives.

36 **1.2.1. AALM.C**

37 Development of the AALM implemented in Visual C (AALM.C) by the EPA National Center for
38 Environmental Assessment (NCEA) began in 1999 to extend Pb exposure and biokinetics modeling
39 capability of the IEUBK model to address a wider range of model applications in computational Pb
40 toxicology and risk assessment; these include:

- 1 • Simulation of Pb biokinetics associated with multimedia exposures occurring within any age
- 2 range from birth through adulthood (the IEUBK model is limited to birth to age 84 months);
- 3 • Simulation of Pb biokinetics in blood, bone, soft tissues, and excreta (in the IEUBK model,
- 4 Pb levels in tissues and excreta are intermediary variables used to support the blood Pb
- 5 simulation, and are not output variables);
- 6 • Simulation of Pb biokinetics in response to changes in Pb exposure that occur over periods of
- 7 days (the IEUBK model exposure averaging time is typically ≥ 1 year and predicts quasi-
- 8 steady state blood Pb concentrations); and
- 9 • Expansion of the exposure model to include multiple sources of exposure from air, drinking
- 10 water, food, and indoor dust and soil.

11 Over the intervening years between initiation of the development of the IEUBK model in 1989 and its
12 release for regulatory ([U.S. EPA, 1994b](#)), several modeling approaches were reported for simulating Pb
13 biokinetics of ages extending beyond early childhood. Two models in particular were influential in
14 developing the structure of the AALM. The first was the Leggett model ([Pounds and Leggett, 1998](#);
15 [Leggett, 1993](#)), based on a biokinetic model originally developed for the International Commission on
16 Radiological Protection (ICRP) that calculated radiation doses from environmentally important bone-
17 seeking radionuclides, including radioisotopes of Pb ([Leggett, 1992a, b, 1985](#)). The original model was
18 used to develop cancer risk coefficients for internal radiation exposures to Pb and other alkaline earth
19 elements that have biokinetics similar to those of calcium ([U.S. EPA, 1998](#); [ICRP, 1993](#)). The
20 compartment structure, Pb transfer coefficients, and numerical integration method of the Leggett model
21 were adopted in the early versions of the AALM. The second model was the O’Flaherty model that
22 simulates Pb exposure, uptake, and disposition in humans, from birth through adulthood ([O’Flaherty,](#)
23 [2000](#); [O’Flaherty et al., 1998](#); [O’Flaherty, 1998, 1995, 1993, 1991a, b, c](#)). Important features that
24 distinguish the O’Flaherty model from the Leggett model are simulation of growth (the Leggett model
25 simulates growth of blood volume only), bone formation, and resorption (the Leggett model simulates the
26 “effects” of bone growth and resorption on Pb kinetics, but does not simulate bone growth and resorption
27 explicitly). Uptake and release of Pb from trabecular bone and metabolically active cortical bone are
28 functions of bone formation and resorption rates, respectively, and are simulated in the O’Flaherty model;
29 this establishes a relationship between the age-dependence and the Pb kinetics in and out of bone, and
30 allows for explicit simulation of the effects of bone formation (e.g., growth and loss, changes in bone
31 volume, and bone maturation) on Pb uptake and release from bone. In contrast, the Leggett model
32 represents age-dependence of bone Pb kinetics as age-dependent rate coefficients for transfer of Pb into
33 and out of bone. Although the O’Flaherty model had a more physiologically accurate representation of
34 bone growth and resorption, the Leggett model configuration for growth of the blood volume and bone Pb
35 kinetics was used for early versions of the AALM.

36 In October of 2005, the EPA Science Advisory Board (SAB) reviewed a Visual C implementation of the
37 AALM (AALMv1.05.C) and highlighted the need for expanded documentation and further evaluation of
38 the model ([U.S. EPA, 2007](#)). The SAB also identified a number of deficiencies, and suggested potential
39 improvements. EPA expanded the documentation and evaluation of the AALM to include the following:
40 (1) a Guidance Manual for the AALM that describes the conceptual basis and structure of the model
41 (including all equations, parameters, and parameter values) ([SRC, 2008](#)); (2) review and evaluation of
42 evidence supporting further extension and/or refinement of the model ([SRC, 2009a](#)); and (3) a
43 comparative review of alternative modeling approaches ([SRC, 2009b](#)).

1 **1.2.2. AALM.CSL**

2 Research initiated by EPA NCEA in early 2013 expanded the AALM further to address deficiencies
3 identified by the SAB and re-evaluated performance of the model. The AALM was migrated to acslX
4 which removed the need to develop and maintain computer code for the numerical integration solution of
5 the AALM biokinetics model, and made use of existing acslX code to implement the Leggett and
6 O’Flaherty models ([Lorenzana et al., 2005](#)). An exposure model was developed in Excel which removed
7 the need to develop *de novo* computer code for the exposure model, and allowed development of
8 exposure scenarios in Excel without the requirement for a license or knowledge of acslX. Development
9 of the acslX version of the AALM is described in Chapter 4. The latest version of the model is
10 AALMv4.2.CSL (July 2015).

11 AALM.CSL included the user option to link the exposure model to either the Leggett or O’Flaherty
12 biokinetics models. It also introduced several changes to both the Leggett and O’Flaherty biokinetics
13 models including some new parameters and as well as revised parameter values. Some of these data used
14 in the optimization were not available at the time the original models were developed. Optimization
15 against a common set of data resulted in general convergence of AALM-LG.CSL and AALM-OF.CSL
16 predictions for blood, bone, and soft tissue, and agreement with blood Pb predictions for children from
17 the IEUBK model (Chapter 4).

18 **1.2.3. AALM.FOR**

19 In 2014, the EPA Office of Pollution Prevention and Toxics (OPPT) developed an implementation of the
20 Leggett model ([Pounds and Leggett, 1998](#); [Leggett, 1993](#)) biokinetics model to support the Agency’s
21 *Approach for Estimating Exposures and Incremental Health Effects from Lead Due to Renovation,*
22 *Repair, and Painting Activities in Public and Commercial Buildings* ([U.S. EPA, 2014b](#)). The latest
23 released version of the model, ICRPv005.FOR, has the capability of simulating Pb levels in body tissues
24 (e.g., blood, bone, brain) and excreta at resulting from acute or chronic exposures to inorganic Pb that
25 occur from birth through adulthood.

26 In developing ICRPv005.FOR, several changes were made to Leggett biokinetics model (see Table 3-1 in
27 Chapter 3); however, up to ICRPv004.FOR, the biokinetics model was unchanged from [Leggett \(1993\)](#).
28 The major changes included (1) age-dependent blood and tissue masses, adjustments to RBC uptake
29 parameters, and adjustment of bone-to-plasma transfer rates. Collectively, updates made to
30 ICRPv004.FOR to create ICRPv005.FOR resulted in lower predicted blood Pb concentrations for a given
31 Pb intake in children, that more closely agreed with predictions from the IEUBK model ([see Figure M-4](#)
32 [in, U.S. EPA, 2014a](#)); and lower blood and bone Pb concentrations in adults ([see Figure M-6 in, U.S.](#)
33 [EPA, 2014a](#)). ICRPv005.FOR was evaluated against data on blood and bone Pb levels in occupationally
34 exposed adults reported in [Nie et al. \(2005\)](#), although some of these data have not been published. The
35 conclusion from these evaluations was that the model tended to predict lower cortical bone Pb
36 concentrations than observed and higher blood Pb concentrations ([see Figures M-5 and M-6 in, U.S. EPA,](#)
37 [2014a](#)).

38 External peer review of the Approach for Estimating Exposures and Incremental Health Effects from
39 Lead Due to Renovation, Repair, and Painting Activities in Public and Commercial Buildings ([U.S. EPA,](#)
40 [2014b](#)) resulted in several recommendations ([Post-Meeting Peer Review Summary Report, Versar, 2015](#)),
41 including the need for further evaluation of ICRPv005.FOR. Based on these evaluations, ICRPv005.FOR

1 was revised and parameter values updated to create AALM.FOR (Chapter 3). In the development of
2 AALM.FOR, the model was evaluated with a larger set of observations in children and adults, including
3 some data that had not been used in previous evaluations of ICRPv005.FOR, including all datasets used
4 in the evaluation and development of the AALM.CSL (Chapter 4). AALM.FOR utilizes the same
5 exposure and biokinetic parameter values as the AALM.CSL and, as a result, both models predict the
6 same blood and tissue Pb levels when the same exposure inputs are used in both models. Similar to the
7 AALM.CSL, AALM.FOR utilizes a spreadsheet graphical user interface for setting exposure and
8 biokinetics parameter model inputs and processing output. The major difference between the general
9 architecture of the two models is that the biokinetics model of the AALM.FOR is implemented in Fortran,
10 whereas, the biokinetics model of the AALM.CSL is implemented in acsIX.

CHAPTER 2. THEORETICAL FRAMEWORK, PARAMETERS, AND EQUATIONS

2.1. OVERVIEW OF AALM.FOR STRUCTURE

The AALM.FOR consists of two major submodels that simulate Pb exposure and Pb biokinetics, respectively. The exposure model described in Section 2.2 calculates rates of Pb intake ($\mu\text{g Pb/day}$) from ingestion or inhalation based on inputs for exposure concentrations in air, indoor dust, soil and water; and Pb intakes ($\mu\text{g/day}$) from food or other sources. The exposure model simulates a hypothetical individual (subject), defined in terms of age, sex and rates of contact with environmental media (e.g., drinking water or indoor dust or soil ingestion rates).

The AALM.FOR biokinetics model described in Section 2.3 simulates kinetics of absorption of Pb into a central (diffusible blood plasma) compartment, transfers of Pb between the central compartment and various tissues, and transfers of Pb to excreta. Absorption of Pb from the respiratory tract is simulated as a first-order process governed by rate coefficients (d^{-1}) for absorption from each of four respiratory tract compartments. Absorption from the gastrointestinal tract is simulated as a first-order process governed by age-dependent absorption fractions and first-order rate coefficients for transfers of Pb within the gastrointestinal tract. Rates of absorption from inhaled and ingested Pb are summed to yield a total rate of transfer ($\mu\text{g Pb/day}$) to the central plasma compartment; these rates include Pb absorbed from intakes from exposures as well as Pb transferred to the gastrointestinal tract from the respiratory tract (i.e., mucocilliary clearance), and from the liver (i.e., biliary secretion). Biokinetics model output variables are tissue Pb masses and concentrations, and Pb masses in excreta corresponding to the exposure and absorption scenarios constructed in the exposure and absorption models. Tissues represented in the model include red blood cells and blood plasma (including a pool of Pb in plasma that is bound to proteins), brain, cortical and trabecular bone, kidney, liver, and other soft tissues. Distinct excretory pathways represented in the model include feces, urine, sweat, and other routes (e.g., hair and nails, exfoliated skin). Transfers of Pb between compartments are simulated as first-order processes governed by first-order rate coefficients (d^{-1}) that are scaled for age.

The AALM.FOR architecture consists of two components: (1) a macro-enabled Excel workbook (*AALM Fortan.xlsm*) that implements the exposure model and provides user access to all exposure and biokinetics parameters in the AALM.FOR; (2) a Fortran program that implements the biokinetics model. Input parameter values are selected by the user in *AALM Fortran.xlsm*. Macros in the *AALM Fortran.xlsm* file pass the input parameter values to a comma-delimited (CSV) text file (*AALM_LG_INPUTDATA.DAT*) which are imported into the AALM Fortran program. Output variables from the simulation are passed to a CSV file (*AALM_LG_OUTPUTDATA.DAT*) and are read into the *AALM.Fortran.xlsm* file with Excel macros.

AALM.FOR inputs and outputs are controlled and recorded in *AALM Fortan.xlsm* workbook. This workbook has several functions: (1) allows setting of input parameter values for AALM.FOR simulations; (2) macros in this workbook are used to pass data to and from Fortran; (3) allows plotting of AALM.FOR output data; and (4) provides a complete record of input values and results of each AALM.FOR simulation. Worksheets in *AALM Fortran.xlsm* allow the user to set exposure scenarios for Pb in air (*Air*), food (*Food*), indoor dust, (*Dust*), soil (*Soil*), drinking water (*Water*), and/or other ingestion intakes (*other*). Exposures can be discrete (i.e., a series of exposures at selected ages), and/or pulsed in a repeating frequency (e.g., 2 days/week for 3 months/year, for a selected age range). The AALM.FOR

1 uses inputs from all exposure media when it creates biokinetics simulations. This allows construction of
 2 complex multi-pathway exposure scenarios having varying temporal patterns. Worksheets in *AALM*
 3 *Fortran.xlsx* also allow the user to set values for parameters that control Pb absorption and relative
 4 bioavailability in individual exposure media (*RBA*), and biokinetics (*Lung, Systemic, Sex*). All settings
 5 are recorded in the *AALM Fortran.xlsx* workbook and can be recalled to re-run the simulation.

6 **2.2. EXPOSURE MODEL**

7 **2.2.1. General Structure of the Exposure Model**

8 The exposure model of the AALM.FOR calculates rates of Pb intake from ingestion and inhalation
 9 pathways, for a hypothetical individual (subject) based on inputs for exposure to Pb in air, food, indoor
 10 dust, soil, water, and from miscellaneous ingestion intakes (designated in the model as *other*). Intakes
 11 ($\mu\text{g Pb/day}$) derived from the exposure model are passed to the biokinetics model and provide the bases
 12 for calculating Pb masses in tissues and excreta for each age day simulated. Calculations of Pb intakes
 13 are controlled by model parameters that can specify two major categories of exposure parameters:
 14 (1) parameters that define the individual (e.g., age, sex); and (2) parameters that define Pb intake rates. A
 15 list of all equations used in the AALM.FOR to calculate Pb intakes as they appear in the AALM.FOR
 16 code is provided in Appendix A of this chapter, and parameters used in these equations are defined in
 17 Appendix C.

18 An AALM.FOR simulation progresses through a series of exposure time steps representing age-days. A
 19 simulation begins at birth and progresses to a terminal age for the simulation (e.g., 32,850 days for a
 20 simulation of approximately 90 years). As a simulation progresses, Pb intakes ($\mu\text{g Pb/day}$) are calculated
 21 for each day based on values specified for Pb concentrations in exposure media (e.g., $\mu\text{g Pb/g dust}$) and
 22 rates of media intakes (e.g., $\mu\text{g dust ingested/day}$); or based on inputted Pb intake rates ($\mu\text{g Pb/day}$) for
 23 ingestion of Pb in food or in *other* media. The exposure time step of one day is independent of the
 24 numerical integration time step described in Section 2.3.1 (setting one has no effect on the other). Lead
 25 intakes passed to the biokinetics model are in units of $\mu\text{g/day}$ and are adjusted (along with other time-
 26 dependent parameters and variables) in biokinetics differential equations to agree with the integration
 27 time step used at every point in the simulation. Lead intakes calculated from the exposure model are
 28 accessible as output to the *AALM Fortran.xlsx* file.

29 Lead intakes resulting from exposures to Pb in air, indoor dust, soil, or water are calculated from inputs of
 30 Pb concentrations. The general form of the equations for calculating Pb intakes from Pb concentrations is
 31 given in Equation 2.2-1:

32

$$33 \quad IN_{medium} = \sum_{i=1}^n (Pb_{medium_i} \cdot f_{medium_i}) \cdot IR_{medium} \cdot RBA_{medium} \quad \text{Eq. (2.2-1)}$$

34

35 where IN_{medium} is the Pb intake rate ($\mu\text{g Pb/day}$) for a specific environmental medium (e.g.,
 36 water), Pb_{medium_i} is the exposure concentration (e.g., $\mu\text{g Pb/L water}$) in that medium for a given
 37 exposure setting i , f_{medium_i} is the fraction of total intake of the medium that occurs in setting i , IR_{medium}
 38 is the intake rate of the medium (e.g., L water/day), and RBA_{medium} is the relative bioavailability of Pb
 39 in the exposure medium (relative to completely water-soluble Pb). Parameter values in Equation 2.2-1
 40 representing exposure concentrations, media intakes, and fractional media intakes for each setting can be

1 assigned age-dependent values; whereas, the value assigned to RBA represents the entire age range
 2 simulated. The application of RBA as an adjustment to Pb intake rather than an adjustment to the
 3 gastrointestinal absorption fraction is a simplification that results in an underprediction of fecal excretion
 4 of unabsorbed Pb and negative mass balance ($\text{intake} > \text{body burden} + \text{excreted}$) when $\text{RBA} < 1$.

5 Lead intakes resulting from exposures to Pb in food and *other* media are calculated from inputs of Pb
 6 intake rate (e.g. $\mu\text{g Pb/day}$) using equations of the following general form (Equation 2.2-2):

$$7 \quad 8 \quad IN_{\text{medium}} = \sum_{i=1}^n (Pb_{\text{intake}_i}) \cdot RBA_{\text{medium}} \quad \text{Eq. (2.2-2)}$$

9
 10 where Pb_{intake_i} is the rate of Pb intake ($\mu\text{g/day}$) entered for the medium for exposure setting i .

11
 12 Lead exposure concentrations (air, indoor dust, soil, water) or intakes (food, *other*) can be entered into the
 13 AALM.FOR as discrete values representing specific ages, or as pulse trains in which the exposure Pb
 14 concentration or Pb intake is turned on or off at specific ages. The AALM User Guide should be
 15 consulted for specific examples of how this functionality is implemented in the Excel User Interface.
 16 Pulse train intakes or exposure concentrations are fixed as constant over periods specified by users. Users
 17 can select whether discrete exposure concentrations or intakes are constant (stepwise) or interpolated
 18 between ages specified in the discrete time series. Selection of stepwise or interpolation will be applied to
 19 all discrete media concentrations or intakes. In the discrete mode, exposure settings for each exposure
 20 medium are simulated as a time (age-day) series of exposure concentrations (air, indoor dust, soil, water)
 21 or Pb intakes (food, *other*) and weighting factors for exposure concentrations that represent the
 22 percentage of exposure contributed by each setting, each day, at each age. The exposure setting functions
 23 allow the user to simulate exposure scenarios in which exposure to a Pb in a specific medium may occur
 24 from different sources, or at different locations (e.g., home, school, work) within a day. Concentrations
 25 of Pb in air, water, indoor dust or soil, at each specified age, are calculated as the weighted average of
 26 contributions from all exposure settings represented in the simulation that contribute to that particular
 27 exposure medium (Equation 2.2-3).

$$28 \quad 29 \quad Pb_{\text{medium}_{\text{weighted}}} = \sum_{i=1}^n (Pb_{\text{medium}_i} \cdot f_{\text{medium}_i}) \quad \text{Eq. (2.2-3)}$$

30 where f_{medium_i} is the fraction contributed by exposure setting i . Intakes of Pb in food and *other*
 31 at each specified age are calculated as the sum intakes for exposure settings represented in the simulation
 32 that contribute to that particular exposure medium (Equation 2.2-4).

$$33 \quad 34 \quad IN_{\text{medium}_{\text{sum}}} = \sum_{i=1}^n (IN_{\text{medium}_i}) \quad \text{Eq. (2.2-4)}$$

35
 36 The exposure model allows inputs of up to three different exposure settings for each medium ($n = 3$ in
 37 Equations 2.2-3 and 2.2-4) and setting discrete exposures for up to 50 ages.

1 The pulse train functions can be used to represent episodic exposures or intakes that occur at fixed
 2 frequency (pulse period) and duration (pulse width) schedule (e.g., 2 days per 7 days), over a given age
 3 range (pulse start, pulse stop) above a user-inputted baseline Pb concentration or intake. The exposure
 4 model allows the user to specify up to two overlapping pulse trains, which can be used to simulate more
 5 complex intermittent exposure patterns (e.g., 2 days per 7 days; 3 months per 12 months). A combination
 6 of discrete and pulsed exposures can be simulated by assigning a value of <1 to the parameter f_{pulse} . This
 7 parameter apportions the relative contributions of the discrete and pulsed Pb intakes according to the
 8 fraction of total assigned to the pulse (Equation 2.2-5)

$$10 \quad IN_{medium_{Total}} = IN_{medium_{discrete}} \cdot (1 - f_{pulse}) + IN_{medium_{pulse}} \cdot f_{pulse} \quad \text{Eq. (2.2-5)}$$

11
 12 Equations used in the AALM.FOR to calculate Pb inhalation and ingestion intakes concentrations in
 13 tissues are presented in Tables 2-1 and 2-2 and in Appendix A of this chapter and parameters are defined
 14 in Appendix B. The main differences between these two presentations of the equations are that: (1)
 15 equations in Appendix A use the exact nomenclature for parameters as they appear in the AALM.FOR
 16 code (Appendix B), whereas, nomenclature in Table 2-1 has been modified for simplicity; and (2) the
 17 equations in Appendix A are presented in their integrated forms as used in the AALM.FOR numerical
 18 integration routine, whereas, the differential equations are shown in Table 2-1. For readability, tables and
 19 appendices are provide at the end of this chapter.

20 **2.2.2. Parameters That Define a Hypothetical Individual**

21 *Age:* Each step in the simulation represents a day of age, beginning at birth (age = 0).

22 *Sex:* The sex specification links the subject to an appropriate sex-specific growth algorithm ([O'Flaherty,](#)
 23 [1995, 1993](#)) described in Section 3.5.2.

24 *Fetal Exposure:* The AALM.FOR simulation begins at birth with the neonatal tissue Pb masses assigned
 25 values based on the user-designated maternal blood Pb, described in Section 2.3.11.

26 **2.2.3. Exposure Media Intakes and Lead Concentrations**

27 It should be noted that for ingested Pb, the adjustment for RBA is applied to Pb intake rather than an
 28 adjustment to the gastrointestinal absorption fraction (Section 2.3.3.2) is a simplification that results in an
 29 underprediction of fecal excretion of unabsorbed Pb and negative mass balance (intake > body burden +
 30 excreted) when RBA < 1.

31 **2.2.3.1. Air Pb Exposure**

32 Air Pb intakes ($\mu\text{g Pb/day}$) are calculated as the product of air Pb concentration ($\mu\text{g Pb/m}^3$) and
 33 ventilation rates ($\text{m}^3 \text{ air/day}$) that are specified for a given age range (Equation 2.2-6).

$$35 \quad IN_{air} = Pb_{air} \cdot VR \quad \text{Eq. (2.2-6)}$$

1 where VR is the ventilation rate (m^3/day). The values assigned to ventilation rates represent the
 2 average daily values for specific age ranges. These values can be modified to represent specific activity
 3 levels (e.g., ventilation during periods of rest, moderate activity, strenuous activity, etc.). Values for VR
 4 are interpolated between inputted ages. Air Pb intakes ($\mu g Pb/day$) are passed to the biokinetics model
 5 where they represent values for rates of deposition of Pb in the respiratory tract (see *BRETH* in Section
 6 2.3.3.1).

7
 8 The discrete mode allows the user to specify exposures to multiple (i.e., $n = 3$) sources; for example,
 9 indoor air, outdoor air, or air at different locations (e.g., home, school, work). In the discrete mode, the
 10 $PbAir$ term in Equation 2.2-6 is the weighted average from all exposure settings (Equation 2.2-7):

$$11 \quad Pbair_{discrete\ weighted} = \sum_{i=1}^n (Pbair_i \cdot fair_i) \quad \text{Eq. (2.2-7)}$$

12
 13
 14 where $Pbair_i$ is the air concentration for exposure setting i at a given age and $fair_i$ is the fraction
 15 of total daily exposure assigned to setting i .

16 The pulse mode allows the user to represent episodic exposures to air Pb that occur at fixed frequency
 17 (pulse period) and duration (pulse width) schedule. In the pulse mode, air Pb concentration is specified
 18 with values for a baseline concentration ($\mu g Pb/m^3$), a pulsed concentration, the start and ending ages of
 19 the pulse train (day), the width of each pulse (days) and the period of each pulse (the number of days
 20 between pulses). During each pulse, air Pb concentration is calculated as the sum of the baseline and
 21 pulsed concentrations (Equation 2.2-8):

$$22 \quad Pbair_{pulse\ sum} = Pbair_{baseline} + Pbair_{pulse} \quad \text{Eq. (2.2-8)}$$

23
 24
 25 Air Pb intakes calculated for discrete and pulse train inputs are summed to calculate total Pb intake
 26 associated with exposures to Pb in air (Equation 2.2-9):

$$27 \quad INair_{Total} = INair_{discrete} \cdot (1 - F_{pulse}) + INair_{pulse} \cdot F_{pulse} \quad \text{Eq. (2.2-9)}$$

28 2.2.3.2. Indoor Dust Pb Exposure

29
 30
 31 Ingestion intakes resulting from contact with Pb in indoor dusts (e.g., adherence on hand-to-mouth) from
 32 all sources are simulated by specifying values for dust exposure parameters. Dust Pb intakes ($\mu g Pb/day$)
 33 are calculated as the product of Pb concentration ($\mu g Pb/g$) and ingestion rate (g dust/day, Equation 2.2-
 34 10):

$$35 \quad INdust = Pb_{dust} \cdot IR_{dust} \cdot RBA_{dust} \quad \text{Eq. (2.2-10)}$$

1

2 where $INDust$ is the intake of dust Pb ($\mu\text{g Pb/day}$), $Pbdust$ is the Pb concentration in dust (μg
 3 Pb/g), $IRdust$ is the intake rate of dust from all sources (g dust/day) and RBA_{dust} is the relative
 4 bioavailability of Pb in dust, relative to water-soluble Pb. Values for $IRdust$ are interpolated between
 5 inputted ages. The model accepts a single inputted value for RBA which represents dust from all sources,
 6 in all exposure settings. Dust Pb intakes ($\mu\text{g Pb/day}$) are summed with other ingestion intakes (i.e., soil,
 7 food, water, *other*) and passed to the biokinetics model as rates of intake Pb to the stomach compartment
 8 of the gastrointestinal tract (see Section 2.3.3.2).

9 The discrete mode allows the user to specify exposures to multiple (i.e., $n = 3$) sources; for example,
 10 indoor dusts at different locations (e.g., home, school, playground). In the discrete mode, the $Pbdust$ term
 11 in Equation 2.2-10 is the weighted concentration for all exposure settings (Equation 2.2-11):

12

$$13 \quad Pbdust_{discrete\ weighted} = \sum_{i=1}^n (Pbdust_i \cdot fdust_i) \quad \text{Eq. (2.2-11)}$$

14

15 where $Pbdust_i$ is the soil or dust Pb concentration for exposure setting i at a given age and $fdust_i$ is
 16 the fraction of total daily exposure assigned to setting i .

17 The pulse mode allows the user to simulate episodic exposures to dust Pb that occur at fixed frequency
 18 (pulse period) and duration (pulse width) schedule. In the pulse mode, dust Pb concentration is specified
 19 with values for a baseline concentration ($\mu\text{g Pb/g}$), a pulsed concentration, the start and ending ages of the
 20 pulse train (day), the width of each pulse (days) and the period of each pulse (the number of days between
 21 pulses). During each pulse, dust Pb concentration is calculated as the sum of the baseline and pulsed
 22 concentrations (Equation 2.2-12):

23

$$24 \quad Pbdust_{pulse\ sum} = Pbdust_{baseline} + Pbdust_{pulse} \quad \text{Eq. (2.2-12)}$$

25

26 Dust Pb intakes calculated for discrete and pulse train inputs are summed to calculate total Pb intake
 27 associated with exposures to Pb in dust (Equation 2.2-13):

28

$$29 \quad INDust_{Total} = INDust_{discrete} \cdot (1 - f_{pulse}) + INDust_{pulse} \cdot f_{pulse} \quad \text{Eq. (2.2-13)}$$

30

31 **2.2.3.3. Soil Pb Exposure**

32 Ingestion intakes resulting from contact with Pb in soil (e.g., adherence on hand-to-mouth) from all
 33 sources are simulated by specifying values for soil exposure parameters. Exposure to soil could include
 34 hand-to-mouth contact with soil transported from surficial soil to other surfaces (e.g., indoor), or direct
 35 hand-to-mouth contact with surficial soil. Ingestion of bulk soil (e.g. pica) can also be simulated as a
 36 pathway separate from dust (i.e., *other*). The main consideration for including exposures to soil in the
 37 soil pathway rather than simulating the soil exposures in the *other* pathway is the determination of

1 whether or not parameter values for soil ingestion rate (IR_{soil} , Equation 2.2-14) apply to the soil
2 exposure.

3 Soil Pb intakes ($\mu\text{g Pb/day}$) are calculated as the product of Pb concentration ($\mu\text{g Pb/g}$) and ingestion rate
4 (g dust/day , Equation 2.2-14):

$$5 \quad IN_{soil} = Pb_{soil} \cdot IR_{soil} \cdot RBA_{soil} \quad \text{Eq. (2.2-14)}$$

7
8 where IN_{soil} is the intake of soil Pb ($\mu\text{g Pb/day}$), Pb_{soil} is the Pb concentration in soil ($\mu\text{g Pb/g}$),
9 IR_{soil} is the intake rate of soil from all sources (g soil/day) and RBA_{soil} is the relative bioavailability of
10 Pb in soil, relative to water-soluble Pb. Values for IR_{soil} are interpolated between inputted ages. The
11 model accepts a single inputted value for RBA which represents soil from all sources, in all exposure
12 settings. Soil Pb intakes ($\mu\text{g Pb/day}$) are summed with other ingestion intakes (i.e., dust, food, water,
13 *other*) and passed to the biokinetics model as rates of intake Pb to the stomach compartment of the
14 gastrointestinal tract (see Section 2.3.3.2).

15 The discrete mode allows the user to specify exposures to multiple (i.e., $n = 3$) sources; for example, soils
16 at different locations (e.g., home, school, playground). In the discrete mode, the Pb_{soil} term in Equation
17 2.2-14 is the weighted concentration for all exposure settings (Equation 2.2-15):

$$18 \quad Pb_{soil}_{discrete\ weighted} = \sum_{i=1}^n (Pb_{soil}_i \cdot f_{soil}_i) \quad \text{Eq. (2.2-15)}$$

20
21 where Pb_{soil}_i is the soil or soil Pb concentration for exposure setting i at a given age and f_{soil}_i is
22 the fraction of total daily exposure assigned to setting i .

23 The pulse mode allows the user to simulate episodic exposures to soil Pb that occur at fixed frequency
24 (pulse period) and duration (pulse width) schedule. In the pulse mode, soil Pb concentration is specified
25 with values for a baseline concentration ($\mu\text{g Pb/g}$), a pulsed concentration, the start and ending ages of the
26 pulse train (day), the width of each pulse (days) and the period of each pulse (the number of days between
27 pulses). During each pulse, soil Pb concentration is calculated as the sum of the baseline and pulsed
28 concentrations (Equation 2.2-16):

$$29 \quad Pb_{soil}_{pulse\ sum} = Pb_{soil}_{baseline} + Pb_{soil}_{pulse} \quad \text{Eq. (2.2-16)}$$

31
32 Soil Pb intakes calculated for discrete and pulse train inputs are summed to calculate total Pb intake
33 associated with exposures to Pb in soil (Equation 2.2-17):

$$34 \quad IN_{soil}_{Total} = IN_{soil}_{discrete} \cdot (1 - f_{pulse}) + IN_{soil}_{pulse} \cdot f_{pulse} \quad \text{Eq. (2.2-17)}$$

35

1 2.2.3.4. Water Pb Exposure

2 Lead intakes from ingestion of water ($\mu\text{g Pb/day}$) are calculated as the product of Pb concentration (μg
3 Pb/L) and ingestion rate (L/day , Equation 2.2-18):

$$4 \quad IN_{water} = Pb_{water} \cdot IR_{water} \cdot RBA_{water} \quad \text{Eq. (2.2-18)}$$

7 where IN_{water} is the intake of Pb in water ($\mu\text{g Pb/day}$), Pb_{water} is the Pb concentration in water
8 ($\mu\text{g Pb/L}$), IR_{water} is the rate ingestion of water (L/day) and RBA_{water} is the relative bioavailability of
9 Pb in water and dust, relative to water-soluble Pb. Values for IR_{water} are interpolated between inputted
10 ages. The model accepts a single inputted value for RBA which represents both water, in all exposure
11 settings. Lead dissolved in water would, by definition, have $RBA = 1$; however, the RBA parameter
12 could be used in scenarios in which ingestion exposures include Pb-bearing particulates suspended in
13 water for which the RBA may be <1 . Water Pb intakes ($\mu\text{g Pb/day}$) are summed with other ingestion
14 intakes (i.e., food, dust, soil, *other*) and passed to the biokinetics model as rates of intake Pb to the
15 stomach compartment of the gastrointestinal tract (see Section 2.3.3.2).

16 The discrete mode allows the user to specify exposures to multiple (i.e., $n = 3$) sources of water Pb; for
17 example, first-draw, flushed, bottled; or water consumed different locations (e.g., home, school, work).
18 In the discrete mode, the Pb_{water} term in Equation 2.2-18 is the weighted concentration for all exposure
19 settings (Equation 2.2-19):

$$21 \quad Pb_{water_{weighted}} = \sum_{i=1}^n (Pb_{water_i} \cdot f_{water_i}) \quad \text{Eq. (2.2-19)}$$

23 where Pb_{water_i} is the water Pb concentration for exposure setting i at a given age and f_{water_i} is
24 the fraction of total daily exposure assigned to setting i .

25 The pulse mode allows the user to simulate episodic exposure to water Pb that occur at fixed frequency
26 (pulse period) and duration (pulse width) schedule. In the pulse mode, water Pb concentration is specified
27 with values for a baseline concentration ($\mu\text{g Pb/L}$), a pulsed concentration, the start and ending ages of the
28 pulse train (day), the width of each pulse (days) and the period of each pulse (the number of days between
29 pulses). During each pulse, dust Pb concentration is calculated as the sum of the baseline and pulsed
30 concentrations (Equation 2.2-20):

$$32 \quad Pb_{water_{pulse\ sum}} = Pb_{water_{baseline}} + Pb_{water_{pulse}} \quad \text{Eq. (2.2-20)}$$

34 Intakes assigned to discrete and pulse train inputs are summed to calculate total Pb intake associated with
35 exposures to Pb in water (Equation 2.2-21):

$$37 \quad IN_{water_{Total}} = IN_{water_{discrete}} \cdot (1 - f_{pulse}) + IN_{water_{pulse}} \cdot f_{pulse} \quad \text{Eq. (2.2-21)}$$

1

2 **2.2.3.5. Food Pb Exposure**

3 Food Pb exposures are inputted as Pb intakes from ingestion of food ($\mu\text{g Pb/day}$) and are adjusted by
4 RBA (Equation 2.2-22):

$$5 \quad IN_{food} = IN_{food \text{ input}} \cdot RBA_{food} \quad \text{Eq. (2.2-22)}$$

6

7 Inputted food Pb intakes represent the total Pb intakes from all foods consumed and included in the
8 simulation. The model does not calculate food Pb intakes from inputted data on Pb concentrations in
9 foods and food consumption rates. Lead intakes from food are summed with other ingestion intakes (i.e.,
10 water, dust, soil, *other*) and passed to the biokinetics model as rates of Pb transferred to the stomach
11 compartment of the gastrointestinal tract (see Section 2.3.3.2).

12 The discrete mode allows the user to specify exposures to multiple (i.e., $n = 3$) sources of food Pb (e.g.
13 market basket, home grown produce, local fish or game). In the discrete mode, the $Pb_{food \text{ input}}$ term in
14 Equation 2.2-22 is the sum of Pb intakes from all exposure settings (Equation 2.2-23):

15

$$16 \quad IN_{food \text{ discrete sum}} = \sum_{i=1}^n (IN_{food_i}) \cdot RBA_{food} \quad \text{Eq. (2.2-23)}$$

17

18 where IN_{food_i} is the food Pb intake for exposure setting i at a given age, and RBA_{food} is the
19 relative bioavailability of Pb in food, relative to water-soluble Pb. The model accepts a single inputted
20 value for RBA which represents food in all exposure settings.

21 The pulse mode allows the user to simulate episodic food Pb intakes that occur at fixed frequency (pulse
22 period) and duration (pulse width) schedule. In the pulse mode, food intake is specified with values for a
23 baseline Pb intake ($\mu\text{g/day}$), a pulsed Pb intake ($\mu\text{g/day}$), the start and ending ages of the pulse train (day),
24 the width of each pulse (days) and the period of each pulse (the number of days between pulses). During
25 each pulse, Pb intake is calculated as the sum of the baseline and pulsed intakes (Equation 2.2-24):

26

$$27 \quad IN_{food \text{ pulse sum}} = IN_{food \text{ baseline}} + IN_{food \text{ pulse}} \quad \text{Eq. (2.2-24)}$$

28

29 Intakes assigned to discrete and pulse train inputs are summed to calculate total Pb intake from ingestion
30 of food (Equation 2.2-25):

31

$$32 \quad IN_{food \text{ Total}} = IN_{food \text{ discrete}} \cdot (1 - f_{\text{pulse}}) + IN_{food \text{ pulse}} \cdot f_{\text{pulse}} \quad \text{Eq. (2.2-25)}$$

33

1 2.2.3.6. Other Exposure Media

2 The *other* ingestion category is a placeholder for miscellaneous exposures that are not accounted for by
 3 other media (e.g., paint, pica). The *other* ingestion category may also be used to establish a baseline
 4 blood Pb concentration such as based on National Health and Nutrition Examination Survey (NHANES)
 5 above which the contribution from soil or other media may be determined. *Other* Pb exposures are
 6 inputted as Pb intakes ($\mu\text{g Pb/day}$) and are adjusted by RBA (Equation 2.2-26):

$$7 \quad 8 \quad INother = INother_{input} \cdot RBA_{other} \quad \text{Eq. (2.2-26)}$$

9
 10 *Other* Pb intakes are summed with other ingestion intakes (i.e., water, dust, soil, water) and passed to the
 11 biokinetics model as rates of Pb transferred to the stomach compartment of the gastrointestinal tract (see
 12 Section 2.3.3.2).

13 The discrete mode allows the user to specify exposures to multiple (i.e., $n = 3$) sources of other Pb (e.g.
 14 home, school, work). In the discrete mode, the $INother_{input}$ term in Equation 2.2-26 is the sum of Pb
 15 intakes from all exposure settings (Equation 2.2-27):

$$16 \quad 17 \quad INother_{sum} = \sum_{i=1}^n (INother_i) \cdot RBA_{other} \quad \text{Eq. (2.2-27)}$$

18
 19 where $INother_i$ is the Pb intake for exposure setting i at a given age, F_i is the fraction of total
 20 daily *other* Pb intake assigned to setting i , and RBA_{other} is the relative bioavailability of Pb in the *other*
 21 medium, relative to water-soluble Pb. The model accepts a single inputted value for RBA_{other} which
 22 represents Pb in all *other* exposure settings.

23 The pulse mode allows the user to simulate episodic *other* Pb intakes that occur at fixed frequency (pulse
 24 period) and duration (pulse width) schedule. In the pulse mode, *other* intake is specified with values for a
 25 baseline Pb intake ($\mu\text{g/day}$), a pulsed Pb intake ($\mu\text{g/day}$), the start and ending ages of the pulse train (day),
 26 the width of each pulse (days) and the period of each pulse (the number of days between pulses). During
 27 each pulse, Pb intake is calculated as the sum of the baseline and pulsed intakes (Equation 2.2-28):

$$28 \quad 29 \quad INother_{pulse\ sum} = INother_{baseline} + INother_{pulse} \quad \text{Eq. (2.2-28)}$$

30
 31 Intakes assigned to discrete and pulse train inputs are summed to calculate total Pb intake (Equation 2.2-
 32 29):

$$33 \quad 34 \quad INother_{Total} = INother_{discrete} \cdot (1 - f_{pulse}) + INother_{pulse} \cdot f_{pulse} \quad \text{Eq. (2.2-29)}$$

35

1 2.3. BIOKINETICS

2 2.3.1. Computational Structure of the Aalm.For Biokinetics Model

3 The AALM.FOR computes Pb masses (μg) in tissues and excreta for each age day simulated (e.g.,
 4 assuming 365 days/year, a simulation extending to age 90 years would include 32,850 days). These
 5 masses are used to calculate secondary variables such as blood Pb concentration. Lead masses calculated
 6 for each age day are based on Pb intake rates ($\mu\text{g Pb/day}$) calculated in the exposure model and passed to
 7 the biokinetics model. Lead intakes contribute to rates of entry of Pb into the central plasma compartment
 8 (i.e., Pb absorption, $\mu\text{g Pb/day}$), along with transfers to the central compartment resulting from Pb
 9 exchanges with other tissues. Lead masses in each biokinetics compartment are computed by numerical
 10 integration applied to a series of differential equations that represent the rate of change in Pb mass in each
 11 compartment. The general form of the differential equations used in the biokinetics model is as follows
 12 (Equation 2.3-1):

$$14 \quad \frac{dY_j}{dt} = -R_j \cdot Y_j + P_j \quad \text{Eq. (2.3-1)}$$

15

16 where dY_j/dt is the change in Pb mass (μg) in compartment j over time t , R_j is the rate coefficient
 17 for transfer of Pb out of compartment j over time t (t^{-1}), and P_j is the rate of transfer of Pb into
 18 compartment j ($\mu\text{g Pb/t}$). Starting values for compartment Pb masses are inputs to the model, allowing
 19 the user to start simulations with pre-existing Pb masses (*starting values for compartment Pb masses are*
 20 *set to zero in the current version of AALM.FOR and can be modified in the Fortran input file,*
 21 *POUNDS_GUI.DAT*). The fundamental unit of time in the biokinetics model is day (i.e., rates used in
 22 differential equations are in units of $\mu\text{g Pb/day}$ or d^{-1}). Equation 2.3-2 is solved for each state variable
 23 (e.g., compartment) using the following numerical approximation for small time steps, Δt ([Leggett, 1993](#);
 24 [Leggett et al., 1993](#)) as follows (Equations 2.3-2 to 2.3-4):

25

$$26 \quad Y_{t+\Delta t} = \left(Y_t - \frac{P_t}{R_t} \right) \cdot e^{-R_t \Delta t} + \frac{P_t}{R_t} \quad \text{Eq. (2.3-2)}$$

27

28 where $Y_{t+\Delta t}$ is the Pb mass at the end of each integration time step. The time-integrated Pb mass
 29 in each compartment ($YINT$) at each time step is computed as follows (Equation 2.3-3):

30

$$31 \quad YINT_{t+\Delta t} = \left(Y_t - \frac{P_t}{R_t} \right) \cdot \frac{1 - e^{-R_t \Delta t}}{R_t} + \frac{P_t \Delta t}{R_t} \quad \text{Eq. (2.3-3)}$$

32

33 The rate of inflow of Pb into each compartment is a function of the time-integrated Pb masses in
 34 contributing compartments (Equation 2.3-4):

35

$$P_j = \frac{R_{i \rightarrow j} \cdot YINT_i}{\Delta t} \quad \text{Eq. (2.3-4)}$$

where, P_j is the inflow rate of Pb into compartment j , $R_{i \rightarrow j}$ is the rate coefficient for transfer of Pb from compartment i to j , and $YINT_i$ is the time-integrated Pb mass in compartment i . The above numerical integration approach can be expected to achieve numerical integration errors that do not exceed a 0.5% if the integration step size (10^{-N}) is selected such that (Equation 2.3-5):

$$10^{-(N+1)} < \frac{\ln(2)}{R_{max}} \quad \text{Eq. (2.3-5)}$$

where R_{max} is largest rate coefficient in the model, and N is an integer value ([Leggett et al., 1993](#)). In the AALM.FOR, the largest rate coefficient is 1000 d^{-1} , for transfer of Pb from the plasma to the extravascular compartment and the corresponding integration step size (10^{-N}) that satisfies Equation 2.3-5 is 0.001 day (i.e., $N = 3$). At a fixed time step, integration error will be more pronounced in the early parts of a simulation, when Pb masses are changing in compartments with fast turnover rates (high R values), and will decrease as the simulation progresses and steady states are achieved in these compartments. In the AALM.FOR, the integration time step can be varied during the simulation by assigning values to the step length at different points in the simulation. This allows for relatively short time steps in the early phases of the simulation to minimize error in integration of fast compartments, and use of longer steps (requiring less computation time) in later phases of the simulation. An integration scheme recommended by [Leggett et al. \(1993\)](#) to minimize error in the early phases of the simulation and achieve computational speed in the later phases is as follows:

Step Length (day)	Integration Cycles	Simulation Day
0.001	1–1000	0–1
0.01	1000–1900	1–10
0.1	1900–2800	10–100
1	>2800	>100

In this scheme, the first 1000 integration cycles (an integration cycle is completed when all state variables have been integrated over a given time step) are computed using a step length of 0.001 day, at the conclusion of which the first age day of the simulation is concluded. The next 900 cycles are computed using a step length of 0.01 days, concluding at age day 10. The next 900 cycles are computed using a step length of 0.1 day, and the remaining cycles are computed with a step length of 1 day. While step length is a user-defined model input, the recommended step length for AALM.FOR is a constant step length of 0.1 to 1 days, which should result in acceptable integration error for anticipated applications of the model, including intermittent exposures. Adequacy of the step length can be determined by evaluating the sensitivity of the output to changes in step length. When using the pulse train function for a brief exposure (e.g., 1-2 days), it is recommended that a step length of ≤ 0.01 day be used. Varying the step within a simulation (i.e., using different lengths at different times) is not recommended.

1 **2.3.2. Compartment Structure of the AALM.FOR Biokinetics Model**

2 The structure of the AALM.FOR biokinetics model is based on the [Leggett \(1993\)](#) model. The model
 3 includes a central exchange compartment, 15 peripheral body compartments, and 3 elimination pools
 4 (Figure 2-1). The central exchange compartment is the *diffusible* Pb in plasma distinguished from a
 5 *bound* pool in plasma representing Pb bound to plasma proteins. Lead is absorbed from the
 6 gastrointestinal tract, respiratory tract into the diffusible plasma compartment. Lead in diffusible plasma
 7 exchanges with Pb in bone, brain, kidney, liver, red blood cells (RBC), and other soft tissues. Absorbed
 8 Pb is excreted in urine, sweat, and in a combined pathway representing hair, nails, and exfoliated skin.
 9 Unabsorbed ingested Pb is excreted in feces along with a fraction of absorbed Pb transferred to the
 10 gastrointestinal tract from diffusible plasma and liver (i.e., bile pathway). The application of RBA as an
 11 adjustment to Pb intake rather than an adjustment to the gastrointestinal absorption fraction is a
 12 simplification that results in an underprediction of fecal excretion of unabsorbed Pb and negative mass
 13 balance (intake > body burden + excreted) when RBA < 1.

14 Transfers of Pb between compartments are assumed to follow first-order kinetics governed by rate
 15 coefficients (d^{-1}), where each rate coefficient represents a fraction of Pb mass (μg) in the compartment
 16 that is transferred per day. Lead masses (μg) in compartments are computed by numerical integration of
 17 linear differential equations representing the rates of change of Pb mass in each compartment (see section
 18 2.3.1). The computed Pb masses in tissues and tissue masses (g) and/or volumes (dL) are used to
 19 calculate Pb concentrations in tissues. A conceptual representation of equations used in the AALM.FOR
 20 to calculate Pb masses and concentrations in tissues are presented in Table 2-2. A more comprehensive
 21 and accurate presentation of the equations as they appear in the AALM.FOR code is presented in
 22 Appendix A of this chapter and parameters are defined in Appendix B. The main differences between
 23 these two presentations of the equations are that: (1) equations in Appendix A use the exact nomenclature
 24 for parameters as they appear in the AALM.FOR code (Appendix B), whereas, nomenclature in Table 2-2
 25 has been modified for simplicity; and (2) the equations in Appendix A are presented in their integrated
 26 forms as used in the AALM.FOR numerical integration routine, whereas, the differential equations are
 27 shown in Table 2-2. General concepts that underlie equations used in the AALM.FOR for calculating Pb
 28 masses and concentrations are presented in the sections that follow. For readability, tables and
 29 appendixes are provide at the end of this chapter.

30 **2.3.2.1. Rate Equations for Pb Transfers**

31 Transfers of Pb between compartments are assumed to follow first-order kinetics governed by rate
 32 coefficients (d^{-1}) and described by first-order rate equations having the following general form (Equations
 33 2.3-6 to 2.3-8):

$$34 \quad \frac{dY_j}{dt} = INFLOW_j - OUTFLOW_j \quad \text{Eq. (2.3-6)}$$

$$35 \quad INFLOW_j = \sum_{i=1}^n (R_{i \rightarrow j} \cdot Y_i) \quad \text{Eq. (2.3-7)}$$

$$36 \quad OUTFLOW_j = \sum_{i=1}^n (-R_{j \rightarrow i} \cdot Y_j) \quad \text{Eq. (2.3-8)}$$

39

1 where dY_j/dt is the change in Pb mass in compartment j over time t , $INFLOW_i$ is the sum of all
 2 transfers into compartment j (Equation 2.3-7), $OUTFLOW_j$ is the sum of all transfers out of compartment
 3 j (Equation 2.3-8), $R_{j \rightarrow i}$ is the rate coefficient for transfer of Pb out of compartment j to compartment i
 4 over time t (t^{-1}), Y_j is the Pb mass in compartment j (μg), $R_{i \rightarrow j}$ is the rate coefficient for transfer of Pb from
 5 compartment i to compartment j , and Y_i is the Pb mass in compartment i . The current version of the
 6 AALM.FOR uses values for rate coefficients that are based on [Leggett \(1993\)](#) and updated based on more
 7 recent evaluations of the model (Chapter 3); these values are presented in Table 2-3 located at the end of
 8 this chapter.

9 The AALM.FOR uses two approaches to assigning values to INFLOW and OUTFLOW rate coefficients:
 10 (1) rate coefficients representing transfers of Pb out of individual compartments are assigned values for
 11 specific, user-designated, age ranges in the simulation and are designated in rate equations with the prefix
 12 R (e.g., $RLVI$ for the rate coefficient for transfer of Pb from liver compartment 1 to diffusible plasma);
 13 (2) rate coefficients representing transfers of Pb from the diffusible plasma compartment to tissues are
 14 variables computed from expressions relating deposition fractions to each tissue and a rate coefficient for
 15 transfer of Pb from the diffusible plasma compartment to all receiving compartments. Deposition
 16 fractions are designated with the prefix T (e.g., $TLVRI$ for the deposition fraction from diffusible plasma
 17 to liver compartment 1). Deposition fractions represent the instantaneous fractional outflow of Pb from
 18 diffusible plasma and are used in the AALM.FOR to establish corresponding rate coefficients.

19 2.3.2.2. Deposition Fractions

20 As a means to ensure mass balance of transfers between tissues and the diffusible plasma compartment,
 21 transfer rates from the central compartment are expressed as fractions of the combined rate of transfer
 22 from the central compartment to all compartments (Equation 2.3-9):

$$24 \quad R_{PLAS \rightarrow j} = T_{PLAS \rightarrow j} \cdot RPLAS \quad \text{Eq. (2.3-9)}$$

25
 26 where $R_{PLAS \rightarrow j}$ is the rate coefficient for transfer of Pb from diffusible plasma to compartment j (d^{-1})
 27 ¹), $T_{PLAS \rightarrow j}$ is the deposition fraction for transfer of Pb from diffusible plasma to compartment j , and
 28 $RPLAS$ is the rate coefficient for transfer of Pb from diffusible plasma to all receiving compartments
 29 (2000 d^{-1}). The sum of all deposition fractions from diffusible plasma must equal one to ensure mass
 30 balance. The product of the sum of all age-adjusted deposition fractions and the Pb mass in the diffusible
 31 plasma compartment is the rate of Pb transfer out of the diffusible plasma to all receiving compartments,
 32 and is designated in the AALM.FOR as $BTEMP$ (Equations 2.3-10 and 2.3-11):

$$34 \quad RPLS = \sum_j^n T_{PLAS \rightarrow j} \cdot RPLAS \quad \text{Eq. (2.3-10)}$$

$$36 \quad BTEMP = RPLS \cdot YPLS \quad \text{Eq. (2.3-11)}$$

1 where $RPLS$ is the age-adjusted rate coefficient for or transfer of Pb from the diffusible plasma to
 2 all receiving compartments (d^{-1}), and $YPLS$ is the mass of Pb (μg) in the diffusible plasma compartment.

3 **2.3.2.3. Scaling of Rate Coefficients and Deposition Fractions**

4 Values for deposition fractions and rate coefficients are age-dependent and are assigned values for
 5 specific ages. Values between ages are interpolated. The input values for deposition fractions from
 6 diffusible plasma (designated with the prefix TO; e.g., TOBONE) are scaled in the biokinetics model to
 7 account for two factors: (1) growth of bone surface area and resulting age-dependence of deposition of Pb
 8 to bone surface, which changes the deposition fractions to other tissues; and (2) non-linear uptake of Pb
 9 from diffusible plasma to RBCs, which changes the RBC deposition fraction as the RBC Pb concentration
 10 increases. Scaled deposition fractions designated with the prefix T (e.g., TBONE). The scaling
 11 adjustment for bone surface takes the form (Equations 2.3-12 and 2.3-13):

$$13 \quad AGESCL = \frac{1-TEVF-TBONE}{1-TEVF-TBONEL} \quad \text{Eq. (2.3-12)}$$

$$15 \quad T_{PLAS \rightarrow j} = AGESCL \cdot TO_{PLAS \rightarrow j} \quad \text{Eq. (2.3-13)}$$

16
 17 where $TEVF$ is the deposition fraction to the extravascular fluid (see description of central
 18 compartment and bone Pb kinetics), $TBONE$ is the deposition fraction to bone surface, $TBONEL$ is the
 19 limiting adult value for the bone deposition fraction, and $TO_{PLAS \rightarrow j}$ is the input value for the deposition
 20 fraction from diffusible plasma to compartment j , before adjustment for bone surface area.

21 Uptake of Pb into RBCs is simulated as a capacity-limited process, in which the deposition fraction to
 22 RBCs ($TRBC$) decreases with increasing RBC Pb concentration above a limiting threshold (see
 23 description of RBC compartment in Section 2.3.4.3). The decrease in RBC deposition fraction as the
 24 RBC concentration approaches the limiting value results in greater Pb available for deposition to other
 25 tissues. This change is accounted for in the model by adjusting the deposition fractions to other tissues by
 26 the factor CF (Equation 2.3-14):

$$28 \quad CF = \frac{1-TOORBC}{1-TRBC} \quad \text{Eq. (2.3-14)}$$

29
 30 where $TRBC$ is the deposition fraction to RBCs below the limiting RBC Pb concentration, and
 31 $TOORBC$ is the deposition fraction to RBCs above the limiting RBC Pb concentration. The adjustment
 32 factor, CF , increases as the RBC Pb concentration approaches saturation, and deposition fractions to other
 33 tissues ($TO_{PLAS \rightarrow j}$) are proportionately increased.

34
 35 Equations 2.3-9 to 2.3-14 yield rate equations for the change in Pb mass with time (i.e., integration time
 36 step) of the following typical form, for example for liver compartment 1 (Equation 2.3-15):

1

$$\frac{dy_{LVR1}}{dt} = TLVR1 \cdot CF \cdot BTEMP - RLVR1 \cdot YLVR1 \quad \text{Eq. (2.3-15)}$$

3

2.3.2.4. Growth of Blood and Tissues for Calculation of Pb Concentrations

5 The AALM.FOR biokinetics equations are used to compute Pb masses in each tissue compartment.
6 Concentrations of Pb in selected tissues are calculated as the quotient of Pb mass and tissue volumes (e.g.,
7 dL blood) or masses (e.g., g kidney, cortical bone, trabecular bone, skeleton). Tissue volumes and masses
8 are calculated based on growth equations and parameters from O'Flaherty's studies ([O'Flaherty, 1995,](#)
9 [1993](#)) (see Table 2-2 Equations N1–N17). Tissue volumes and masses are functions of body weight
10 (Equation 2.3-16):

11

$$WBODY = WBIRTH + \frac{WCHILD \cdot AGEYEAR}{HALF + AGEYEAR} + \frac{WADULT}{1 + KAPPA \cdot e^{-LAMBDA \cdot WADULT \cdot AGEYEAR}} \quad \text{Eq. (2.3-16)}$$

13 In the AALM.FOR code, the variable *AGEYEAR* in Equation 2.3-16 is replaced with the variable
14 *HOWOLD*. Equation 2.3-16 calculates body weight as the sum of three growth phases: (1) pre-natal
15 which achieves birth weight; (2) rapid (hyperbolic) post-natal growth that occurs before age 10 years; and
16 (3) logistic growth beginning at puberty and continuing into early adulthood. *WBODY* is the body weight
17 at any given age (*AGEYEAR*), *WBIRTH* is the body weight at birth, *WCHILD* is the maximum body
18 weight achieved during early hyperbolic growth phase, *HALF* is the age at which body weight is one half
19 of *WCHILD*, *WADULT* is the maximum adult body weight, and *KAPPA* and *LAMBDA* are empirically
20 derived logistic parameters. The body weight parameters enable simulation of different growth patterns,
21 including distinct patterns for males and females. The current default growth simulations are show in in
22 Figure 2-2.

23 Volume growth of blood (*AMTBLD*) is a linear function of body weight (Equation 2.3-17):

24

$$AMTBLD = VBLC \cdot WBODY \cdot 10 \quad \text{Eq. (2.3-17)}$$

26

27 where *VBLC* is the blood volume expressed as a fraction of body weight (*WBODY*). Plasma and
28 RBC volumes are functions of blood volume and age-dependent hematocrit (*BLDHCT*), which increases
29 during the first 4 days post-natal from approximately 0.52 to 0.66 (default value), and then decreases to
30 0.46 (default value) by age 1 year (Equations 2.3-18 and 2.3-19):

31

$$BLDHCT_{AGEYEAR \leq 0.01} = 0.52 + AGEYEAR \cdot 14 \quad \text{Eq. (2.3-18)}$$

$$BLDHCT_{AGEYEAR > 0.01} = HCTA \cdot (1 + (0.66 - HCTA) \cdot e^{-(AGEYEAR - 0.01) \cdot 13.9}) \quad \text{Eq. (2.3-19)}$$

34

35 where HCTA is the adult hematocrit (default = 0.46).

1 Volume growth of kidney (VK) and liver (VL) are power functions of body weight (Equations 2.3-20 and
2 2.3-21).

3

$$4 \quad VK = 1000 \cdot VKC \cdot (WBIRTH + WADULT + WCHILD) \cdot \left(\frac{WBODY}{WBIRTH + WADULT + WCHILD} \right)^{0.84}$$

5 Eq. (2.3-20)

6

$$7 \quad VL = 1000 \cdot VLC \cdot (WBIRTH + WADULT + WCHILD) \cdot \left(\frac{WBODY}{WBIRTH + WADULT + WCHILD} \right)^{0.85}$$

8 Eq. (2.3-21)

9

10 where VKC and VLC are fractions of body weight ($WBODY$). Kidney and liver are weights
11 ($KIDWT$, $LIVWT$) are calculated from tissue density (Equations 2.3-22 and 2.3-23):

12

$$13 \quad KIDWT = VK \cdot 1.05$$

Eq. (2.3-22)

$$14 \quad LIVWT = VL \cdot 1.05$$

Eq. (2.3-23)

15

16 The growth of bone volume ($VBONE$) and weight ($WBONE$) are calculated as a power functions of body
17 weight, with cortical bone volume ($CVBONE$) assigned 0.8 of total bone volume ($VBONE$, Equations
18 2.3-24 to 2.3-26):

19

$$20 \quad WBONE = 1000 \cdot 0.0290 \cdot WBODY^{1.21}$$

Eq. (2.3-24)

$$21 \quad VBONE = 1000 \cdot 0.0168 \cdot WBODY^{1.188}$$

Eq. (2.3-25)

$$22 \quad CVBONE = 0.8 \cdot VBONE$$

Eq. (2.3-26)

23

24 **2.3.2.5. Age Dependencies of Parameter Values**

25 Biokinetics parameters that are assumed to change with age are assigned values for specific ages. These
26 assignments are made as arrays of parameter values and corresponding ages (year), beginning with birth
27 (age = 0 years). Parameter values between age designations are calculated by linear interpolation.

28 **2.3.3. Absorption**

29 The AALM.FOR model simulates Pb absorption from inhalation, ingestion, or dermal contact with
30 surface dust. In the AALM.FOR, absorption represents the transfer of Pb intake ($\mu\text{g Pb intake/day}$),
31 computed in the exposure model, to a rate of entry of Pb into the diffusible plasma compartment of the

1 biokinetics model ($\mu\text{g Pb absorbed/day}$). Absorption from each exposure pathway is simulated as a first-
2 order processes governed by absorption fractions and/or first-order rate coefficients (d^{-1}).

3 **2.3.3.1. Absorption from the Respiratory Tract**

4 In the AALM.FOR, the respiratory tract is simulated as four compartments into which inhaled Pb (IN_{AIR} ,
5 $\mu\text{g Pb/day}$) is deposited and from which Pb is absorbed into the diffusible plasma compartment. Division
6 of the respiratory tract into four compartments provides a means for simulating multi-phase absorption
7 kinetics of inhaled Pb observed in studies of human exposures to Pb particulates ([Leggett, 1993](#)). The
8 four compartments are intended to represent the intrathoracic, bronchiolar, bronchiole, and alveolar
9 regions of the respiratory tract. In the current version of the AALM.FOR, Pb deposition and absorption
10 are assigned the following values (half-times, $t_{1/2}$, are estimated as $\ln(2)/BR$):

11

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

12

13 The above deposition fractions correspond to the regional distribution of deposited Pb from the [Leggett](#)
14 [\(1993\)](#) model partitioned to have 40% total deposition of inhaled Pb in the respiratory tract. Of the total
15 amount of Pb initially deposited, 4% (0.016 of deposited Pb, i.e., 0.04×0.4) is transferred to the stomach
16 (i.e., mucociliary clearance). The above parameter values reflect the data on which the model was based,
17 which were derived from studies in which human subjects inhaled submicron Pb-bearing particles
18 ([Morrow et al., 1980](#); [Chamberlain et al., 1978](#); [Wells et al., 1977](#); [Hursh and Mercer, 1970](#); [Hursh et al.,](#)
19 [1969](#)). These assumptions would not necessarily apply for exposures to larger or less soluble airborne
20 particles.

21 Rate equations describing the rates of change of Pb mass (μg) in the respiratory tract are presented in
22 Table 2-2 (Equations C1–C10). In these equations, the parameter *BRETH* (Equation G1 in Table 2-1)
23 represents the total intake of Pb from exposure to Pb in air ($\mu\text{g Pb/day}$, equivalent to $IN_{AIR_{TOTAL}}$ from
24 Equation A4 in Table 2-1). The mucociliary clearance fraction, designated *CILIAR*, appears in the rate
25 equations for diffusible plasma (Table 2-2, Equation E2), in which the rates for transfer of Pb from all
26 respiratory tract compartments to diffusible plasma are factored by the value $1 - CILIAR$ (e.g., Equation
27 2.3-27):

28

$$29 \quad UPTAKERT = (1 - CILIAR) \cdot \sum_{i=1}^4 (BR_i \cdot YR_i) \quad \text{Eq. (2.3-27)}$$

30

31 where *UPTAKERT* is the rate of absorptive transfer of Pb from the respiratory tract to diffusible
32 plasma, *CILIAR* is the fraction of inhaled Pb transferred to the stomach, BR_i is the fraction of inhaled Pb
33 deposited in respiratory tract compartment i , and YR_i is the Pb mass (μg) in respiratory tract compartment
34 i .

1 2.3.3.2. Absorption from the Gastrointestinal Tract

2 In the AALM.FOR, the gastrointestinal tract contents (i.e., Pb masses in the lumen of the gastrointestinal
3 tract) is simulated as four compartments representing: (1) stomach contents (STMC); (2) small intestine
4 contents (SIC); (3) upper large intestine contents (ULIC); and (4) lower large intestine contents (LLIC).
5 Total intake of Pb from ingestion (see Equation G2 in Table 2-1) enters the stomach and is passed, in
6 series, to the small intestine, upper large intestine, lower large intestine, and feces at rates represented by
7 first-order rate coefficients. Absorption of Pb from the gastrointestinal tract is assumed to occur in the
8 small intestine, and is represented by an absorption fraction (*AFI*), representing the fraction of Pb mass in
9 the small intestine that is transferred to the diffusible plasma compartment. The absorption fraction given
10 by Equation 2.3-28 is age-dependent, and calculated based on an expression from O’Flaherty’s studies
11 ([O’Flaherty, 1995, 1993](#)):

$$13 \quad AF_{AGEYEAR} = AF_{C1} - \frac{AF_{C2}}{1+30 \cdot e^{-AGEYEAR}} \quad \text{Eq. (2.3-28)}$$

14 Values for AF_{C1} and AF_{C2} were assigned values of 0.4 and 0.28, respectively based on fitting simulations
15 to data on blood Pb concentration in children ([Sherlock and Quinn, 1986](#); [Ryu et al., 1983](#)) and adults
16 ([Rabinowitz et al., 1976](#)) who ingested Pb in formula or food, respectively, as described in Chapter 4.
17 These parameter values produce a decrease in the absorption fraction from a value of 0.39 at birth to a
18 value of 0.12 at age 8 years (Figure 2-3), which aligns with the fractional gastrointestinal tract absorption
19 for adults in the Adult Lead Methodology ([U.S. EPA, 2003](#)). This age pattern of higher absorption
20 fraction in infants and children is generally consistent with observations made in mass balance studies in
21 infants and children ([Ziegler et al., 1978](#); [Alexander et al., 1974](#)) and in isotope studies of Pb absorption
22 in adults ([Watson et al., 1986](#); [James et al., 1985](#); [Heard and Chamberlain, 1982](#); [Rabinowitz et al., 1980](#)).

23 Rate equations describing the rates of change of Pb mass (μg) in gastrointestinal tract contents are
24 presented in Table 2-2 (Equations D1–D10). Values of rate coefficients for movement of Pb through the
25 gastrointestinal tract are derived from [Leggett \(1993\)](#); the approximate half-times in adults are assumed to
26 be 0.69, 2.8, 9.0, and 17 hours, respectively. These rate coefficients are scaled for age (GSCAL), relative
27 to adult values:

AGE	0	100 d	1 yr	5 yr	10 yr	15	≥25
GSCAL	1.67	1.67	1.67	1.67	1.33	1.33	1.00

29 In addition to intake of Pb from ingestion of environmental media, the stomach also receives Pb from the
30 respiratory tract (i.e., mucociliary clearance). The rate equation describing stomach inflow of Pb to
31 stomach contents (Table 2-2 Equation D1) includes this mucociliary contribution (Equation 2.3-29):

$$34 \quad IN_{STMC} = EATCRN + CILIAR \cdot \sum_{i=1}^4 (BR_i \cdot YR_i) \quad \text{Eq. (2.3-29)}$$

35

1 where $EATCRN$ is the sum of Pb intakes from all ingestion pathways ($\mu\text{g}/\text{day}$), $CILIAR$ is the
 2 fraction of inhaled Pb transferred to the stomach, BR_i is the fraction of inhaled Pb deposited in respiratory
 3 tract compartment i , and YR_i is the Pb mass (μg) in respiratory tract compartment i .

4
 5 The small intestine receives Pb from the stomach as well as from liver (i.e., biliary secretion) and
 6 diffusible plasma (Table 2-2 Equation D3). Transfer from the liver to the small intestine is represented in
 7 Equation D3 as (Equation 2.3-30):

$$8 \quad IN_{LVR1 \rightarrow SIC} = HITOSI \cdot RLVRI \cdot YLVR1 \quad \text{Eq. (2.3-30)}$$

10
 11 where $HITOSI$ is the fraction of Pb in liver compartment 1 (LVR1) that goes to the small
 12 intestine, $RLVRI$ is the rate coefficient for transfer of Pb out of liver compartment 1 (d^{-1}), and $YLVR1$ is
 13 the Pb mass in the fast liver compartment (μg).

14 Transfer of Pb from the diffusible plasma to the small intestine is represented as (Equation 2.3-31):

$$15 \quad IN_{PLAS \rightarrow SIC} = TFECE \cdot CF \cdot BTEMP \quad \text{Eq. (2.3-31)}$$

16
 17 where $TFECE$ is the scaled deposition fraction from plasma to small intestine; CF is an
 18 adjustment factor for deposition fractions from diffusible plasma to account for non-linear uptake of Pb
 19 into RBCs (Equation 2.3-14) and $BTEMP$ is the rate transfer of Pb from plasma to all receiving
 20 compartments ($\mu\text{g Pb}/\text{day}$, Equation 2.3-11).

21
 22 Although absorption occurs from the small intestine, it is accounted for in the equations for inflow of Pb
 23 to the upper large intestine (Table 2-2 Equation D6) and into diffusible plasma (Table 2-2, Equation E1
 24 and E2). All inflows of Pb to the small intestine, including from liver and diffusible plasma, are subject
 25 to absorption; as a result, inflow of Pb to the upper large intestine is equivalent to the $1-AF1$ fraction
 26 (where $AF1$ is the absorption fraction) of the total rate of transfer from the small intestine (Equation 2.3-
 27 32), and inflow from the small intestine to the diffusible plasma includes the corresponding $AF1$ fraction
 28 (Equation 2.3-33):

$$29 \quad IN_{SIC \rightarrow ULIC} = (1 - AF1) \cdot GSCAL \cdot RSIC \cdot YSIC \quad \text{Eq. (2.3-32)}$$

$$30 \quad IN_{SIC \rightarrow PLAS} = AF1 \cdot GSCAL \cdot RSIC \cdot YSIC \quad \text{Eq. (2.3-33)}$$

31
 32 where $IN_{SIC \rightarrow PLAS}$ is the absorption rate ($ABSORBG1$), $AF1$ is the absorption fraction, $GSCAL$ is
 33 the age adjustment factor for movement of Pb through the gastrointestinal tract, $RSIC$ is the rate
 34 coefficient for transfer of Pb from small intestine contents to upper large intestine contents (d^{-1}), and $YSIC$
 35 is the Pb mass in the small intestine contents (μg). Relative bioavailability (RBA) of ingested Pb (e.g., in
 36
 37

1 dust) is considered in the exposure model (see Sections 2.2.1 and 2.2.3). The application of RBA as an
 2 adjustment to Pb intake rather than an adjustment to the gastrointestinal absorption fraction is a
 3 simplification that results in an underprediction of fecal excretion of unabsorbed Pb and negative mass
 4 balance (intake > body burden + excreted) when RBA < 1.

5 **2.3.4. Vascular and Extravascular Fluid**

6 **2.3.4.1. Diffusible Plasma**

7 The AALM.FOR represents Pb in the vasculature as three compartments: (1) diffusible plasma; (2) bound
 8 plasma; and (3) RBCs. The diffusible plasma compartment receives Pb from all absorption pathways and
 9 exchanges with Pb bound to plasma protein, Pb in RBCs, Pb in an extravascular fluid compartment, and
 10 Pb in extravascular tissues (bone, brain, kidney, liver, and other soft tissues). Lead is also transferred
 11 from diffusible plasma to the small intestine, where it can contribute to fecal elimination of absorbed Pb.
 12 The rate coefficient for transfer of Pb from diffusible plasma to all receiving compartments (*RPLS*) is
 13 2000 day^{-1} ($t_{1/2} \approx 0.5 \text{ min}$; $\ln(2)/\text{rate constant}$). This rate constant is subdivided into deposition fractions
 14 that represent the fractions of the total transfer assigned to each receiving compartment. Deposition
 15 fractions appear in all rate equations that include inflows of Pb from diffusible plasma to any
 16 compartment, and appear as the product of the deposition fraction (TC_i), an adjustment factor for variable
 17 deposition fraction to RBCs (CF , from Equation 2.3-14), and the rate of total outflow of Pb from
 18 diffusible plasma (*BTEMP*, from Equations 2.3-10 and 2.3-11) (Equation 2.3-34):

19

$$20 \quad IN_{PLAS \rightarrow C} = TC_i \cdot CF_i \cdot BTEMP \quad \text{Eq. (2.3-34)}$$

21

22 Values of corresponding rate coefficients for transfers from diffusible plasma to receiving compartments
 23 (i.e., $TC_i \cdot RPLS$), based on [Leggett \(1993\)](#), are presented in Table 2-2. The highest rates are for transfers
 24 to the extravascular fluid compartment, RBCs, and bone surface.

25 **2.3.4.2. Bound Pb in Plasma**

26 Lead in the bound plasma compartment represents Pb reversibly bound to plasma proteins. Bound Pb in
 27 plasma is confined to the vascular fluid. Reversible binding is simulated as first-order transfers between
 28 compartments, with no maximum capacity for binding (Table 2-2, Equation E8). The transfer rate ratio
 29 establishes the equilibrium for binding. Based on [Leggett \(1993\)](#), these values for adults are 0.8 day^{-1}
 30 ($t_{1/2} = 0.9 \text{ day}$) for transfer to the bound compartment and 0.139 day^{-1} ($t_{1/2} = 5.0 \text{ day}$) for transfer from the
 31 bound compartment, providing an equilibrium ratio (bound/free) of approximately 6. Values for children
 32 are similar, but transfer to the bound compartment is slightly slower.

33 **2.3.4.3. Red Blood Cells**

34 Lead in diffusible plasma exchanges with Pb in RBCs (Table 2-2, Equation E13) and is governed by a
 35 deposition fraction and corresponding rate coefficient for uptake (*TOORBC*) and return from the RBC
 36 (*RRBC*). Uptake of Pb in RBCs is assumed to be limited by a maximum capacity, represented in the
 37 AALM.FOR by a maximum Pb concentration in RBCs (*SATRAT*, $\mu\text{g Pb/dL RBC volume}$). Above a
 38 threshold concentration in red blood cells (*RBCNL*, $\mu\text{g Pb/dL RBC volume}$), the deposition fraction (and
 39 corresponding rate coefficient) for transfer from diffusible plasma to RBCs (*TOORBC*) declines

1 (Equation 2.3-35) and deposition fractions to all other tissues increase proportionally by the factor CF
 2 (from Equation 2.3-14).

3

$$4 \quad TOORBC = 1 - \left(\frac{RBCONC - RBCNL}{SATRAT - RBCNL} \right)^{1.5} \quad \text{Eq. (2.3-35)}$$

5 Values for rate coefficients for transfer in and out of the RBC, $SATRAT$ (350 $\mu\text{g Pb/dL RBC}$) and $RBCNL$
 6 (20 $\mu\text{g Pb/dL RBC}$) result in rapid uptake of Pb into RBCs (adult $t_{1/2} \approx 2$ min in adults, 2-3 min in children)
 7 and replicate the non-linear relationship between plasma and red blood observed in adults ([Smith et al.,](#)
 8 [2002](#); [Manton et al., 2001](#); [Bergdahl et al., 1999](#); [Bergdahl et al., 1998](#); [Bergdahl et al., 1997](#)). The values
 9 for $RBCNL$ and $RRBC$ in Equations D-12 and 13 of Table 2-2 were adjusted upward from the values
 10 assigned in [Leggett \(1993\)](#) to provide improved fit to plasma-whole blood Pb relationships in adults and
 11 to harmonize blood Pb predictions in young children with the IEUBK model at the ages of 1, 5, and 10
 12 years (see Chapter 4).

13 **2.3.4.4. Extravascular Fluid**

14 Lead in diffusible plasma exchanges with Pb in an extravascular fluid (EVF) compartment (Table 2-2
 15 Equation F1). The conceptual basis for including the EVF compartment is to allow simulation of the
 16 dynamics of Pb in plasma of efflux of Pb from plasma and return to the plasma during the first minutes
 17 following intravenous injection of Pb that has been observed following intravenous injection of Pb, as
 18 summarized in [Leggett \(1993\)](#) based on various experimental studies ([Heard and Chamberlain, 1984](#);
 19 [Booker et al., 1969](#); [Hursh and Suomela, 1968](#); [Stover, 1959](#)). Efflux of Pb from the plasma is assumed
 20 to occur immediately after its entrance into plasma and prior to binding of binding of Pb to plasma
 21 proteins ($t_{1/2} \approx 1$ day, adults) and uptake into RBCs (adult $t_{1/2} \approx 2$ min, adults). Uptake of Pb into RBCs
 22 subsequently provides a driving force for return of Pb to the plasma. These dynamics are simulated as
 23 rapid exchanges of Pb between the diffusible plasma and EVF compartments. For all ages, rate
 24 coefficients for transfers to and from the EVF, based on [Leggett \(1993\)](#), are 1000 day^{-1} ($t_{1/2} \approx 1$ min) and
 25 333 day^{-1} ($t_{1/2} \approx 3$ min). These values produce a rapid efflux of Pb to the EVF compartment and return to
 26 diffusible plasma, with an equilibrium ratio for EVF/diffusible plasma Pb mass of approximately 3. The
 27 corresponding volume of distribution for the rapidly exchanging EVF compartment of three times
 28 diffusible plasma is consistent with observations made for the distribution of calcium, summarized in
 29 [Leggett \(1993\)](#) based on [Harrison et al. \(1967\)](#) and ([Hart and Spencer, 1976](#)).

30 **2.3.5. Skeleton**

31 **2.3.5.1. General Structure of Bone Model**

32 A major concept underlying the AALM.FOR simulation of bone Pb kinetics is that Pb kinetics behavior
 33 in bone is similar to that of calcium and other bone accumulating elements that mimic calcium (e.g.,
 34 strontium). Observations that formed the bases for the [Leggett \(1993\)](#) bone Pb model included
 35 experimental studies of the kinetics of Pb, calcium, and strontium in humans, non-human primates, and
 36 dogs (e.g., [Heard and Chamberlain, 1984](#); [Lloyd et al., 1975](#); [Cohen et al., 1970](#)). The AALM.FOR
 37 simulates Pb biokinetics in bone as a combination of three processes: (1) relatively rapid exchange of Pb
 38 between diffusible plasma and surfaces of cortical and trabecular bone; (2) slower exchange of Pb at bone
 39 surfaces with an *exchangeable* Pb pool in bone volume; and (3) slow transfer of a portion of Pb in bone

1 volume to a *non-exchangeable* pool that is released from bone to diffusible plasma only when bone is
 2 resorbed (Figure 2-4). These features are represented in the AALM.FOR as six bone subcompartments;
 3 three separate compartments for cortical and trabecular bone, each, representing bone surface,
 4 exchangeable Pb in bone volume, and non-exchangeable Pb in bone volume. Cortical and trabecular
 5 bone volume are assumed to account for 80% and 20% of total bone volume, respectively ([Leggett,
 6 1993](#)). Transfers of Pb in and out of the bone surface compartment are assumed to be relatively rapid:
 7 values for $t_{1/2}$ are approximately 0.01 day for transfer from plasma-to-bone surface; and 1.4 days for
 8 return from bone surface to plasma and transfer from bone surface to exchangeable bone volume
 9 ([Leggett, 1993](#)). Transfer from bone surface is faster in children ($t_{1/2} \approx 1.1$ days). Return of Pb from the
 10 exchangeable bone volume to bone surface is slower ($t_{1/2} \approx 37$ days); however, the dominant transfer
 11 processes determining long-term accrual of bone Pb burden ($\approx 90\%$ of body burden) are the slower rate
 12 coefficients for transfer of Pb from the non-exchangeable compartments of trabecular and cortical bone to
 13 diffusible plasma (adult $t_{1/2} \approx 1.9$ and 12 years, respectively). Bone transfer coefficients vary with age
 14 (faster in children) to reflect age-dependence of bone turnover. The slow, non-exchangeable, bone
 15 volume compartment is assumed to be much more labile in infants and children than in adults (e.g.,
 16 cortical $t_{1/2} \approx 42$ days at birth, 677 days at 15 years, and 4220 days at ≥ 25 years; trabecular $t_{1/2} \approx 42$ days at
 17 birth, 363 days at 15 years, and 703 days at ≥ 25 years). Other physiological states that affect bone
 18 turnover and, therefore, bone Pb kinetics, such as pregnancy and menopause, could be accommodated
 19 with adjustments to tissue (e.g., bone) transfer coefficients.

20 **2.3.5.2. Cortical and Trabecular Bone Surface**

21 Cortical and trabecular bone surfaces exchange Pb with diffusible plasma and the exchangeable
 22 compartment of bone volume (Table 2-2, Equations G5 and G11). Bone *surfaces*, in this context,
 23 represent surfaces of bone in contact with the plasma (e.g., Haversian and Volkmann canals) and/or
 24 involved in bone production and resorption (e.g., endosteal and periosteal surfaces for cortical bone,
 25 resorption cavities, surfaces of trabecular bone). Deposition of Pb in bone surface is considered to reflect
 26 (and be in proportion to) rates of incorporation of calcium in bone that occur during growth, modeling,
 27 and remodeling of bone. Rates change with age, reflecting periods of more intense growth (e.g., infancy,
 28 pre-adolescence). In the AALM.FOR, bone Pb kinetics have the following three general characteristics.
 29 First, transfers are relatively rapid: adult $t_{1/2} \approx 0.01$ day for plasma-to-bone surface, adult $t_{1/2} \approx 1.4$ days for
 30 bone surface to plasma. Second, rates of transfer are age-dependent with highest rates during infancy (0–
 31 1 years) and adolescence (10–15 years), during periods of rapid bone growth. In infancy, transfer of Pb to
 32 bone surface accounts for approximately 24% of total flow of Pb out of the diffusible plasma (8% in
 33 adults). And third, relative fractions of transfer from diffusible plasma to cortical and trabecular bone is
 34 also age-dependent, decreasing from 80% of total transfer going to cortical bone during infancy, to
 35 approximately 44% in adults.

36 **2.3.5.3. Cortical and Trabecular Bone Volume**

37 Bone volume compartments are subdivided into cortical (80%) and trabecular bone (20%), with each
 38 further subdivided into *exchangeable* and *non-exchangeable* subcompartments (Table 2-2, Equations G7,
 39 G9, G13, and G15). Exchangeable and non-exchangeable compartments represent Pb pools in bone
 40 volume having different rates and mechanisms of turnover. Lead in the exchangeable compartment is
 41 assumed to be subject to heteroionic exchange with other bone minerals (e.g., calcium) and/or diffusion of
 42 Pb into osteons ([Leggett, 1993](#)). Lead that enters the non-exchangeable compartment remains there,

1 unless subject to bone resorption. Turnover of Pb in the non-exchangeable compartment reflects bone
2 turnover rates.

3 Lead enters bone volume from bone surface. In the AALM.FOR, exchanges of Pb between bone surface
4 and bone volume have the following three characteristics. First, the transfer to bone volume is faster
5 (adult $t_{1/2} \approx 1.4$ days) compared to return to bone surface (adult $t_{1/2} \approx 37$ days), resulting in accumulation of
6 Pb in bone volume, relative to bone surface. Second, transfer rates from bone surface to bone volume are
7 constant ($t_{1/2} \approx 2$ days) up through adolescence, and slower than in adults ($t_{1/2} \approx 1.4$ days). And third,
8 transfer rates between bone volume and bone surface are assumed to be similar for cortical and trabecular
9 bone.

10 A portion of the Pb that enters bone from bone surface becomes associated with deep bone mineral
11 deposits that can be mobilized during periods of bone resorption (including that which occurs during bone
12 modeling associated with growth). In the AALM.FOR, kinetics of Pb in this non-exchangeable pool have
13 the following six characteristics. First, transfer of Pb from the exchangeable compartment to the non-
14 exchangeable compartment is relatively faster ($t_{1/2} \approx 30$ days) than transfer to surface bone ($t_{1/2} \approx 37$ days).
15 Second, the transfer rate to the non-exchangeable compartment is independent of age. Third, transfer to
16 the non-exchangeable compartments of cortical and trabecular bone occur at the same rates. Fourth,
17 transfer of Pb out of the non-exchangeable compartment returns Pb directly to the diffusible plasma.
18 Fifth, rates of transfer from the non-exchangeable compartment reflect bone turnover rate and are
19 relatively slow (adult $t_{1/2} \approx 12$ years for cortical bone, adult $t_{1/2} \approx 1.9$ years for trabecular bone) compared to
20 rates of removal of Pb from the exchangeable compartment. And sixth, age-dependent changes in bone
21 turnover rates give rise to movement of Pb out of the non-exchangeable compartments that declines with
22 increasing age:

23

AGE	100 d	1 yr	5 yr	10 yr	15 yr	≥ 25
Cortical $t_{1/2}$ (yr)	0.12	0.33	0.62	1.1	1.9	12
Trabecular $t_{1/2}$ (yr)	0.12	0.33	0.52	0.72	1.0	1.9

24

25 Discussed in Chapter 4, values for *RCORT* and *RTRAB* in Equations G9 and G15 of Table 2-2, and
26 *FLONG* (Equation G1-G4) were adjusted to improve agreement between predicted and observed
27 elimination kinetics of Pb from bone in adults ([Nilsson et al., 1991](#)).

28 **2.3.6. Liver**

29 The AALM.FOR simulates Pb kinetics in liver as the combination of three properties. First, there is
30 relatively rapid exchange between Pb in diffusible plasma and a *fast* compartment in liver (LVR1).
31 Second, slower transfer of Pb from the *fast* liver compartment to a *slow* compartment in liver (LVR2),
32 which can release Pb to the diffusible plasma. And third, there is transfer of Pb from the fast liver
33 compartment to the small intestine (i.e., biliary secretion). This configuration gives rise to Pb kinetics
34 following a single absorbed dose that result in a relatively rapid initial uptake of Pb in liver, followed by a
35 slow decline in liver Pb burden, consistent with experimental studies conducted in humans, non-human
36 primate, and dogs ([Leggett, 1993](#)), based on several studies ([Heard and Chamberlain, 1984](#); [Lloyd et al.,](#)

1 [1975; Cohen et al., 1970](#)). With chronic dosing, liver Pb levels increase to approximately 10% of total
2 body burden in early childhood and decline to 2% by age 40 years.

3 Rate equations for transfers of Pb in and out of liver are presented in Table 2-2 (Equations J1 and J3). In
4 the AALM.FOR, kinetics of Pb in liver have the following four general characteristics. First, transfer to
5 the fast liver compartment (LVR1) from diffusible plasma is relatively rapid (adult $t_{1/2} \approx 0.01$ day) and
6 accounts for approximately 4% of total transfer of Pb from diffusible plasma. Second, transfers from the
7 LVR1 to diffusible plasma and to the small intestine are assumed to occur at approximately the same rate
8 ($t_{1/2} \approx 22$ days) and is slower than uptake from diffusible plasma, resulting in Pb accumulates in the fast
9 pool. Third, Pb in the fast liver compartment is slowly transferred to the slow liver pool (LVR2, $t_{1/2} \approx 100$
10 day). Fourth, rates of return of Pb from the slow compartment to diffusible plasma are age-dependent,
11 with half-times decreasing from $t_{1/2} \approx 1000$ days at birth to 500 days at age 5 years, increasing to
12 approximately 1200 days at age ≥ 10 years. This results in increasing rate of accumulation of Pb in the
13 slow compartment with age, with chronic dosing. As discussed in Chapter 4, the value for *RLIV2* in
14 Equation J3 of Table 2-2 was adjusted from the value reported in [Leggett \(1993\)](#) to improve agreement
15 between predicted and observed soft tissue-bone Pb ratios ([Barry, 1975](#)).

16 Biliary secretion of Pb is simulated as transfer of Pb from the fast liver compartment (LVR1) to the small
17 intestine (Table 2-2, Equation D3). The biliary contribution to the small intestine Pb contents is given by
18 Equation 2.3-36:

19

$$20 \quad IN_{LVR1 \rightarrow SIC} = HITOSI \cdot RLVR1 \cdot YLVR1 \quad \text{Eq. (2.3-36)}$$

21

22 where *HITOSI* is the fraction of Pb in LVR1 that goes to the small intestine, *RLVR1* is the rate
23 coefficient for transfer of Pb out of LVR1 (day^{-1}), and *YLVR1* is the Pb mass in LVR1 (μg). A value of
24 0.45 is assumed for *HITOSI*. This value is the rate constant from LVR1 to the small intestine divided by
25 the sum of rate constants for movement from LVR1 to the small intestine, plasma, and LVR2 ([Leggett,](#)
26 [1993](#)).

27 **2.3.7. Kidney**

28 Similar to liver, kidney Pb kinetics exhibit multiple components that include an initial phase of rapid
29 uptake of Pb following a single dose of Pb, followed by a slow decline in kidney Pb burden, with long-
30 term retention of <1% of the body burden during chronic dosing. The AALM.FOR simulates Pb kinetics
31 in kidney as the combination of two parallel processes: (1) relatively rapid transfer between Pb from
32 diffusible plasma to a *fast* compartment in kidney (KDN1), a portion of which is excreted in urine
33 (*urinary path*); and (2) slower exchange Pb between diffusible plasma and a *slow* compartment in kidney
34 (KDN2). This configuration gives rise to Pb kinetics following a single absorbed dose that result in a
35 relatively rapid initial uptake of Pb in kidney, followed by a slow decline in kidney Pb burden. With
36 chronic dosing, kidney Pb levels increase to approximately 2% of total body burden in early childhood
37 and decline progressively 0.2–0.3% after age 40 years.

38 Rate equations for transfers of Pb in and out of kidney are presented in Table 2-2 (Equations I1 and I3).
39 In the AALM.FOR, kinetics of Pb in kidney have the following four general characteristics. First,
40 transfer from the diffusible plasma to the fast (urinary path) kidney compartment (KDN1) is relatively

1 rapid ($t_{1/2} \approx 0.02$ day) and accounts for approximately 2.5% of total transfer of Pb from diffusible plasma.
2 Second, transfer from the fast compartment of kidney (KDN1) to bladder urine is slower than uptake from
3 diffusible plasma ($t_{1/2} \approx 5$ days). As a result, Pb accumulates in the fast compartment. Third, transfer of Pb
4 from diffusible plasma to the slow kidney compartment (KDN2) is approximately 100 times slower than
5 that to the fast compartment (adult $t_{1/2} \approx 2$ days), receiving approximately 0.04% of the total transfer out of
6 the diffusible plasma). and fourth, rates of return of Pb from the slow compartment (KDN2) to diffusible
7 plasma are age-dependent, with half-times increasing from $t_{1/2} \approx 1000$ days until age 5 years and to 3648
8 days at age ≥ 10 years. This results in increasing rate of accumulation of Pb in the slow compartment with
9 age, with chronic dosing.

10 The value for *TKDNI* in Equation I1 of Table 2-2 was adjusted (see Chapter 4) from the value reported in
11 [Leggett \(1993\)](#) to improve agreement between predicted and observed plasma-to-urine clearance in adults
12 ([Araki et al., 1986](#); [Manton and Cook, 1984](#); [Manton and Malloy, 1983](#); [Chamberlain et al., 1978](#)). The
13 value for *RKDN2* in Equation I3 of Table 2-2 was adjusted (see Chapter 4) from the value reported in
14 [Leggett \(1993\)](#) to improve agreement between predicted and observed soft tissue-bone Pb ratios reported
15 by [Barry \(1975\)](#).

16 **2.3.8. Brain**

17 In the AALM.FOR, the brain is treated as a homogenous compartment (Table 2-2, Equations H1, H2).
18 This assumption is a gross simplification of more complex, non-uniform distribution of Pb in brain
19 tissues. Nevertheless, the simplification has little consequence of overall kinetics of Pb, since brain
20 constitutes a relatively small site of deposition. In the AALM.FOR, the brain is assumed to receive
21 approximately 0.05% total outflow of Pb from the diffusible plasma up to age 1 year and 0.015% at ages
22 ≥ 5 years. Transfer rates into brain (adult $t_{1/2} \approx 2.3$ day) and from brain to diffusible plasma ($t_{1/2} \approx 730$ day)
23 result in brain Pb burdens that are 0.1–0.2% of body burden, with chronic dosing. Transfer rates into
24 brain are age-dependent, and are highest during the first year ($t_{1/2} \approx 1$ day) and decrease ($t_{1/2} \approx 2-3$ days) at
25 ages ≥ 5 years. The age-dependence in transfer rates contribute to a peak in the Pb mass in brain ($\approx 0.8\%$
26 of body burden) between ages 3–4 years, with chronic exposure.

27 **2.3.9. Other Soft Tissues**

28 In the AALM.FOR, soft tissues not explicitly simulated as distinct compartments (e.g., muscle, skin, etc.)
29 are lumped into a single compartment (Other Soft Tissue, SOF). This compartment is assumed to
30 comprise three subcompartments that are characterized with relatively *fast*, *intermediate*, or *slow*
31 exchange kinetics with diffusible plasma (Table 2-2, Equations K1, K3, and K5), and no exchanges
32 between subcompartments. The fast compartment (*SOF0*) receives approximately 8-9% of the outflow of
33 Pb from diffusible plasma (adult $t_{1/2} \approx 0.004$ day, child $t_{1/2}$ 0.5-1 day), with slower return of Pb to the
34 diffusible plasma ($t_{1/2} \approx 0.33$ day). The intermediate compartment (*SOF1*) receives approximately 0.5-1%
35 of the outflow from diffusible plasma (adult $t_{1/2} \approx 0.07$ day, child $t_{1/2}$ 0.04-0.06 day), with slower return
36 kinetics (adult $t_{1/2} \approx 167$ day). The slow compartment (*SOF2*) receives approximately 0.1% of the total
37 outflow of Pb from diffusible plasma (adult $t_{1/2} \approx 0.35$ day, child $t_{1/2}$ 0.400.6 day), with slower return
38 ($t_{1/2} \approx 1800$ day). This configuration results in approximately 9% of the Pb body burden residing in the
39 combined subcompartments that comprise the other soft tissue compartment during early childhood
40 followed by a decrease to approximately 3% by age 40 years. A pathway for elimination of Pb to hair,

1 nails, and exfoliated skin is assigned to the intermediate soft tissue compartment (Table 2-2, Equation
2 L9).

3 **2.3.10. Excretion**

4 The AALM.FOR simulates excretion of absorbed Pb as five separate pathways representing urine,
5 secretion from liver to small intestine (e.g., biliary), secretion from diffusible plasma to small intestine,
6 sweat, and other routes (e.g., hair, nails, exfoliated skin as described in Section 2.3.9). The urinary
7 pathway includes excretion of Pb deposited from the diffusible plasma into the fast kidney compartment
8 (KDN1, Table 2-2, Equation L1). This pathway contributes approximately 2.5% of total outflow of Pb
9 from the diffusible plasma. The corresponding plasma clearance (L plasma/day) is approximately 2.4
10 L/day at age 1 year and 20 L/day at age ≥ 25 years, and blood clearance (L blood/day) is approximately
11 0.05 L/day at age 1 year and 0.07 L/day at age ≥ 25 years. The urinary pathway contributes approximately
12 45% of total excretion of absorbed Pb in adults and approximately 80% up to ages ≤ 12 years. The
13 AALM.FOR also includes rate coefficient for direct transfer of Pb from plasma to urine (*TURIN* in
14 Equation L1 of Table 2-2). Improved agreement between predicted and observed plasma-to-urine
15 clearance in adults was achieved with adjustments to the parameter *TKDNI* (Equation I1 of Table 2-2).
16 Because values assigned to *TURIN* did not improve the fit to observations, the direct excretion pathway
17 was nulled by setting *TURIN* to zero.

18 The fecal excretion pathway in the AALM.FOR includes the unabsorbed fraction of Pb that enters the
19 small intestine from three sources (Table 2-2 Equation L5): (1) ingestion; (2) transfer from the liver
20 (biliary secretion, Table 2-2 Equation D3); and (3) transfer from diffusible plasma. Biliary secretion
21 contributes approximately 32% of total excretion of absorbed Pb in adults (55% up to age 12 years) and
22 transfer from plasma contributes approximately 11% (18% at age ≤ 12 years).

23 Sweat is simulated as a direct transfer out of diffusible plasma and accounts for approximately 6% in of
24 total excretion of absorbed Pb in adults and approximately 11% at ages ≤ 12 years (Table 2-2, Equation
25 L7). All other pathways of Pb excretion, not simulated with specific pathways, are accounted for in
26 transfer of Pb from the intermediate soft tissue compartment (SOF1; Table 2-2 Equation L9). These
27 pathways include losses to hair, nails, and exfoliated skin and, combined, account for approximately 6%
28 of total excretion of absorbed Pb in adults and 12% at ages ≤ 12 years.

29 **2.3.11. Fetus**

30 Lead masses in all compartments at birth are assigned values based on a value for maternal blood Pb
31 concentration (Table 2-2, Equations A1–A7). The general equation for the fetal distribution of Pb masses
32 is in the form (Equation 2.3-37):

$$33 \quad Y_i = \frac{YF_i \cdot PbB_M \cdot PbB_{F/M} \cdot 3}{YF_{RBC}} \quad \text{Eq. (2.3-37)}$$

34
35
36 where Y_i is the Pb mass (μg) in tissue i at birth, YF_i is the fraction of total body burden in tissue i
37 at birth, PbB_M is the maternal blood Pb concentration ($\mu\text{g/dL}$), $PbB_{F/M}$ is the fetal/maternal blood Pb
38 concentration ratio, YF_{RBC} is the fraction of body burden in RBCs at birth and Y_{blood} is the blood volume at
39 birth (assumed to be 3 liters). The value 3 in the numerator represents the assumed blood volume(dL) at

1 birth. Tissue compartments assigned values at birth include: brain, kidney (*KDN2*), liver (*LVR2*), RBC,
2 soft tissue (*SOF0*), and non-exchangeable bone volume (80% cortical, 20% trabecular).

3 **2.3.12. Chelation**

4 The AALM.FOR includes parameters to simulate of the effect of chelation therapy on internal Pb
5 kinetics. The chelation simulation decreases transfer of Pb from diffusible plasma and increases transfer
6 from diffusible plasma to urine. Chelation parameters include the beginning and end age (days) of
7 chelation (*CHELI*, *CHEL2*) and a parameter that adjusts the deposition fractions of Pb transfer from
8 diffusible plasma to tissues (*CHLEFE*). The adjustment of the deposition fraction takes the following
9 general form (Equation 2.3-38):

10

$$11 \quad TBONE = (1 - CHLEFE) \cdot TBONE \quad \text{Eq. (2.3-38)}$$

12

13 where *TBONE* is the deposition fraction for transfer from diffusible plasma to bone. The same
14 adjustment is made to the deposition fractions for all tissue and excretory compartments, except urine
15 (*TURIN*). During the chelation period, the deposition fraction from diffusible plasma to urine is
16 calculated as follows (Equation 2.3-39):

$$17 \quad TURIN = \sum_{i=1}^n (1 - T_i) \quad \text{Eq. (2.3-39)}$$

18 where T_i represents the deposition fraction for a given tissue.

19

1 TABLE 2-1. EXPOSURE EQUATIONS OF AALM.FOR

No.	Equation
A	Pb Intakes from Inhaled Air
A 1	$IN_{air} = Pb_{Air} \cdot VR$
A 2	$Pb_{Air}_{discrete\ weighted} = \sum_{i=1}^n (Pb_{Air}_i \cdot f_i)$
A 3	$Pb_{Air}_{pulse\ sum} = Pb_{Air}_{baseline} + Pb_{Air}_{pulse}$
A 4	$IN_{air}_{Total} = IN_{air}_{discrete} \cdot (1 - f_{pulse}) + IN_{air}_{pulse} \cdot f_{pulse}$
B	Pb Intakes from Ingested Indoor Dust
B 1	$IN_{dust} = Pb_{Dust} \cdot IR_{dust} \cdot RBA$
B 2	$IR_{dust} = IR_{SD} \cdot f_{IR_{soil}}$
B 3	$Pb_{Dust}_{discrete\ weighted} = \sum_{i=1}^n (Pb_{Dust}_i \cdot f)$
B 4	$Pb_{Dust}_{pulse\ sum} = Pb_{Dust}_{baseline} + Pb_{Dust}_{pulse}$
B 5	$IN_{dust}_{Total} = IN_{dust}_{discrete} \cdot (1 - f_{pulse}) + IN_{dust}_{pulse} \cdot f_{pulse}$
C	Pb Intakes from Ingested Soil
C 1	$IN_{soil} = Pb_{Soil} \cdot IR_{soil} \cdot RBA$
C 2	$IR_{soil} = IR_{SD} \cdot (1 - f_{IR_{soil}})$
C 3	$Pb_{Soil}_{discrete\ weighted} = \sum_{i=1}^n (Pb_{soil}_i \cdot f)$
C 4	$Pb_{Soil}_{pulse\ sum} = Pb_{Soil}_{baseline} + Pb_{Soil}_{pulse}$
C 5	$IN_{soil}_{Total} = IN_{soil}_{discrete} \cdot (1 - f_{pulse}) + IN_{soil}_{pulse} \cdot f_{pulse}$
D	Pb Intakes from Ingested Water
D 1	$IN_{water} = Pb_{Water} \cdot IR_{water} \cdot RBA$
D 2	$Pb_{Water}_{discrete\ weighted} = \sum_{i=1}^n (Pb_{Water}_i \cdot f)$
D 3	$Pb_{Water}_{pulse\ sum} = Pb_{Water}_{baseline} + Pb_{Water}_{pulse}$
D 4	$IN_{water}_{Total} = IN_{water}_{discrete} \cdot (1 - f_{pulse}) + IN_{water}_{pulse} \cdot f_{pulse}$
E	Pb Intakes from Ingested Food
E 1	$IN_{food} = IN_{food\ input} \cdot RBA$
E 2	$IN_{food}_{discrete\ sum} = \sum_{i=1}^n (IN_{food}_i) \cdot RBA$
E 3	$IN_{food}_{pulse\ sum} = IN_{food}_{baseline} + IN_{food}_{pulse}$
E 4	$IN_{food}_{Total} = IN_{food}_{discrete} \cdot (1 - f_{pulse}) + IN_{food}_{pulse} \cdot f_{pulse}$
F	Pb Intakes from Ingested Other Media

No.		Equation
F	1	$IN_{other} = IN_{other_{input}} \cdot RBA$
F	2	$IN_{other_{discrete\ sum}} = \sum_{i=1}^n (IN_{other_i}) \cdot RBA$
F	3	$IN_{other_{pulse\ sum}} = IN_{other_{baseline}} + IN_{other_{pulse}}$
F	4	$IN_{other_{Total}} = IN_{other_{discrete}} \cdot (1 - f_{pulse}) + IN_{other_{pulse}} \cdot f_{pulse}$
G		Pb Intakes from All Exposure Pathways
G	1	$BRETH = IN_{air_{total}}$
G	2	$IN_{ingestion_{total}} = IN_{water} + IN_{dust} + IN_{food} + IN_{other}$
G	3	$EAT = IN_{ingestion_{total}}$

See text (Section 2.2.1) for explanation of parameter names. The prefix *IN* refers to Pb intake ($\mu\text{g}/\text{day}$) and the prefix *Pb* refers to Pb concentration (e.g. $\mu\text{g}/\text{L}$, $\mu\text{g}/\text{g}$).

1 TABLE 2-2. BIOKINETICS EQUATIONS OF AALM.FOR

No.	Equation
A	Pb Masses at Birth
A 1	$YBRAN = \frac{BRANIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
A 2	$YCVOL = \frac{0.8 \cdot BONIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
A 3	$YKDN2 = \frac{RENIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
A 4	$YLVR2 = \frac{HEPIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
A 5	$YRBC = \frac{RBCIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
A 6	$YSOF = \frac{SOFIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
A 7	$YTVOL = \frac{0.2 \cdot BONIN \cdot BLDMOT \cdot BRATIO \cdot 3}{RBCIN}$
B	Age-scaling of Diffusible Plasma-to-tissue Deposition Fractions
B 1	$AGSCL = \frac{1 - TEVF - TBONE}{1 - TEVF - TBONEL}$
B 2	$TBRAN = AGESCL \cdot TOBRAN$
B 3	$TFECE = AGESCL \cdot TOFECE$
B 4	$TKDN1 = AGESCL \cdot TOKDN1$
B 5	$TKDN2 = AGESCL \cdot TOKDN2$
B 6	$TLVR1 = AGESCL \cdot TOLVR1$
B 7	$TPROT = AGESCL \cdot TOPROT$
B 8	$TRBC = AGESCL \cdot TORBC$
B 9	$TSOF0 = AGESCL \cdot TOSOF0$
B 10	$TSOF1 = AGESCL \cdot TOSOF1$
B 12	$TSOF2 = AGESCL \cdot TOSOF2$
B 13	$TSWET = AGESCL \cdot TOSWET$
B 14	$TURIN = AGESCL \cdot TOURIN$

No.	Equation
C	Respiratory Tract (RT)
C 1	$\frac{dR1}{dt} = R1 \cdot BRTCRN - BR1 \cdot YR1$
C 2	$YR1 = \int_0^T \frac{dR1}{dt} dt$
C 3	$\frac{dR2}{dt} = R2 \cdot INHALE - BR2 \cdot YR2$
C 4	$YR2 = \int_0^T \frac{dR2}{dt} dt$
C 5	$\frac{dR3}{dt} = R3 \cdot INHALE - BR3 \cdot YR3$
C 6	$YR3 = \int_0^T \frac{dR3}{dt} dt$
C 7	$\frac{dR4}{dt} = R4 \cdot INHALE - BR4 \cdot YR4$
C 8	$YR4 = \int_0^T \frac{dR4}{dt} dt$
C 9	$YLUNG = YR1 + YR2 + YR3 + YR4$
C	Rate of Pb Absorption from RI
C 10	$UPTAKERI = \frac{(1 - CILIAR) \cdot (BR1 \cdot YR1 + BR2 \cdot YR2 + BR3 \cdot YR3 + BR4 \cdot YR4)}{dt}$
D	Gastrointestinal Tract (GIT) – Stomach (STMC)
D 1	$\frac{dSTMC}{dt} = EATCRN \cdot CILIAR \cdot (BR1 \cdot YR1 + BR2 \cdot YR2 + BR3 \cdot YR3 + BR4 \cdot YR4) - GSCAL \cdot RSTMC \cdot YSTMC$
D 2	$YSTMC = \int_0^T \frac{dSTMC}{dt} dt$
D	Gastrointestinal Tract (GIT) – Small Intestine (SI)
D 3	$\frac{dSIC}{dt} = GSCAL \cdot RSTMC \cdot YSTMC + H1TOSI \cdot RLVR1 \cdot YLVR1 + TFECE \cdot CF \cdot BTEMP - GSCAL \cdot RSIC \cdot YSIC$

No.	Equation
D 4	$YSIC = \int_0^T \frac{dSIC}{dt} dt$
D	Gastrointestinal Tract (GIT) – Upper Large Intestine (ULI)
D 5	$F_1 = AF_{C1} - \frac{AF_{C2}}{1 + 30 * e^{-AGEYEAR}}$
D 6	$\frac{dULIC}{dt} = (1 - F_1) \cdot GSCAL \cdot RSIC \cdot YSIC - GSCAL \cdot RULI \cdot YULIC$
D 7	$YULIC = \int_0^T \frac{dULIC}{dt} dt$
D	Gastrointestinal Tract (GIT) – Lower Large Intestine (LLI)
D 8	$\frac{dLLIC}{dt} = GSCAL \cdot RULI \cdot YULIC - GSCAL \cdot RLLI \cdot YLLIC$
D 9	$YLLIC = \int_0^T \frac{dLLIC}{dt} dt$
D	Rate of Absorption from Gastrointestinal Tract (GI)
D 10	$UPTAKEGI = \frac{F_1 \cdot GSCALE \cdot RSIC \cdot YSIC}{dt}$
E	Blood – Plasma (Diffusible)
E 1	$PP1 = RPROT \cdot YPROT + RRBC \cdot YRBC + REVF \cdot YEVF + RSOF0 \cdot YSOF0 + (1 - S2HAIR) \cdot RSOF1 \cdot YSOF1 + RSOF2 \cdot YSOF2 + H1TOBL \cdot RLVR1 \cdot YLVR1 + RLVR2 \cdot YLVR2 + RKDN2 \cdot YKDN2 + RCS2B \cdot YCSUR + RTS2B \cdot YTSUR + RCORT \cdot YCVOL + RTRAB \cdot YTVOL + RBRAN \cdot YBRAN + F_1 \cdot GSCAL \cdot RSIC \cdot YSIC$
E 2	$\frac{dPLS}{dt} = PP1 + (1 - CILIAR) \cdot (BR1 \cdot YR1 + BR2 \cdot YR2 + BR3 \cdot YR3 + BR4 \cdot YR4) - RPLS \cdot YPLS$
E 3	$YPLS = \int_0^T \frac{dPLS}{dt} dt$
E 4	$RPLS = TSUM \cdot RPLAS$
E 5	$TSUM = TOORBC + TEVF + TPROT + TBONE + TURIN + TFECE + TSWET + TLIVR1 + TKDN1 + TKDN2 + TSOFO + TSOF1 + TSOF2 + TBRAN$
E 6	$BTEMP = RPLS \cdot YPLS$

No.	Equation
E 7	$CF = \frac{1 - TOORBC}{1 - TRBC}$
E	Blood – Plasma – Protein Bound
E 8	$\frac{dPROT}{dt} = TPROT \cdot CF \cdot BTEMP - RPROT \cdot YPROT$
E 9	$YPROT = \int_0^T \frac{dPROT}{dt} dt$
E	Blood – Total Pb in Plasma (Diffusible, Protein Bound)
E 10	$YPLAS = YPLS + YPROT$
E	Blood – Red Blood Cell (RBC)
E 11	$RBCONC \leq RBCNL :$ $TOORBC = TRBC$
E 12	$RBCONC > RBCNL :$ $TOORBC = TRBC \cdot \left(1 - \frac{RBCONC - RBCNL}{SATRAT - RBCNL} \right)^{1.5}$
E 13	$\frac{dRBC}{dt} = TOORBC \cdot BTEMP - RRBC \cdot YRBC$
E 14	$YRBC = \int_0^T \frac{dRBC}{dt} dt$
E	Blood – Total Pb in Blood
E 15	$YBLUD = YPLAS + YRBC$
E	Blood – Concentrations and Clearance
E 16	$BLCONC = \frac{YBLUD}{AMTBLD}$
E 17	$RBCONC = \frac{YRBC}{BLDHCT \cdot AMTBLD}$
E 18	$PCENT = \frac{100 \cdot YPLAS}{YBLUD}$
E 19	$CLEAR = \frac{100 \cdot URIN}{DEL T \cdot YPLAS}$
E 20	$BCLEAR = \frac{100 \cdot URIN}{DEL T \cdot YBLUD}$

No.	Equation
F	Extravascular Fluid
F 1	$\frac{dEVF}{dt} = TEVF \cdot CF \cdot BTEMP - REVF \cdot YEVF$
F 2	$REVF = TEVF \cdot \frac{RPLS}{SIZEVF}$
F 3	$YEVF = \int_0^T \frac{dEVF}{dt} dt$
G	Bone – Transfer Rates within Bone
G 1	$RDF2CS = (1 - FLONG) \cdot RDIFF$
G 2	$RDF2TS = (1 - FLONG) \cdot RDIFF$
G 3	$RDF2DC = (FLONG) \cdot RDIFF$
G 4	$RDF2DT = (FLONG) \cdot RDIFF$
G	Bone – Cortical Bone Surface
G 5	$\frac{dCSUR}{dt} = TBONE \cdot (1 - TFRAC) \cdot CF \cdot BTEMP + RDF2CS \cdot YCDIF - (RCS2B + RCS2DF) \cdot YCSUR$
G 6	$YCSUR = \int_0^T \frac{dCSUR}{dt} dt$
G	Bone – Exchangeable Cortical Bone
G 7	$\frac{dCDIF}{dt} = RCS2DF \cdot YCSUR - (RDF2CS + RDF2DC) \cdot YCDIF$
G 8	$YCDIF = \int_0^T \frac{dCDIF}{dt} dt$
G	Bone – Non-Exchangeable Cortical Bone Volume
G 9	$\frac{dCVOL}{dt} = RDF2DC \cdot YCDIF - RCORT \cdot YCVOL$
G 10	$YCVOL = \int_0^T \frac{dCVOL}{dt} dt$
G	Bone – Trabecular Bone Surface
G 11	$\frac{dTSUR}{dt} = TBONE \cdot TFRAC \cdot CF \cdot BTEMP + RDF2TS \cdot YTDIF - (RTS2B + RTS2DF) \cdot YTSUR$

No.	Equation	
G	12	$YTSUR = \int_0^T \frac{dTSUR}{dt} dt$
G	Bone – Exchangeable Trabecular Bone	
G	13	$\frac{dTDIF}{dt} = RTS2DF \cdot YTSUR - (RDF2TS + RDF2DT) \cdot YTDIF$
G	14	$YTDIF = \int_0^T \frac{dTDIF}{dt} dt$
G	Bone – Non-Exchangeable Trabecular Bone	
G	15	$\frac{dTVOL}{dt} = RDF2DT \cdot YTDIF - RTRAB \cdot YTVOL$
G	16	$YTVOL = \int_0^T \frac{dTVOL}{dt} dt$
G	Total Pb in Cortical, Trabecular, and Total Bone	
G	17	$YCORT = YCVOL + YCDIF + YCSUR$
G	18	$YTRAB = YTVOL + YTDIF + YTSUR$
G	19	$YSKEL = YCVOL + YTVOL + YCDIF + YTDIF + YCSUR + YTSUR$
G	Bone – Pb Concentration	
G	20	$CRTCON = \frac{YCORT}{CORTWT}$
G	21	$CRTCONBM = \frac{CRTCON}{0.55}$
G	22	$TRBCON = \frac{YTRAB}{TRBWT}$
G	23	$TRBCONBM = \frac{TRABCON}{0.50}$
G	24	$ASHCON = \frac{YSKEL}{TSKELWT}$
H	Brain	
H	1	$\frac{dBRAN}{dt} = TBRAN \cdot CF \cdot BTEMP - RBRAN \cdot YBRAN$

No.	Equation
H 2	$YBRAN = \int_0^T \frac{dBRAN}{dt} dt$
I	Kidney – Compartments 1 (fast, urinary path) and 2 (slow)
I 1	$\frac{dKDN1}{dt} = TKDN1 \cdot CF \cdot BTEMP - RKDN1 \cdot YKDN1$
I 2	$YKDN1 = \int_0^T \frac{dKDN1}{dt} dt$
I 3	$\frac{dKDN2}{dt} = TKDN2 \cdot CF \cdot BTEMP - RKDN2 \cdot YKDN2$
I 4	$YKDN2 = \int_0^T \frac{dKDN2}{dt} dt$
I	Kidney – Total Pb in Kidney
I 5	$YKDNE = YKDN1 + YKDN2$
I	Kidney – Pb Concentration in Kidney
I 6	$RENCON - \frac{YKDNE}{KIDWT}$
J	Liver – Fast Compartment 1
J 1	$\frac{dLVR1}{dt} = TLVR1 \cdot CF \cdot BTEMP - RLVR1 \cdot YLVR1$
J 2	$YLVR1 = \int_0^T \frac{dLVR1}{dt} dt$
J	Liver – Slow Compartment 2
J 3	$\frac{dLVR2}{dt} = H1TOH2 \cdot RLVR1 \cdot YLVR1 - RLVR2 \cdot YLVR2$
J 4	$YLVR2 = \int_0^T \frac{dLVR2}{dt} dt$
J	Liver – Total Pb in Liver
J 5	$YLIVR = YLVR1 + YLVR2$
J	Liver – Pb Concentration in Liver
J 6	$LIVCON - \frac{YLIVR}{LIVWT}$

No.	Equation
K	Soft Tissue – Compartments 0 (fast), 1 (intermediate), and 2 (slow)
K 1	$\frac{dSOFO}{dt} = TSOFO \cdot CF \cdot BTEMP - RSOFO \cdot YSOFO$
K 2	$YSOFO = \int_0^T \frac{dSOFO}{dt} dt$
K 3	$\frac{dSOF1}{dt} = TSOF1 \cdot CF \cdot BTEMP - RSOF1 \cdot YSOF1$
K 4	$YSOF1 = \int_0^T \frac{dSOF1}{dt} dt$
K 5	$\frac{dSOF2}{dt} = TSOF2 \cdot CF \cdot BTEMP - RSOF2 \cdot YSOF2$
K 6	$YSOF2 = \int_0^T \frac{dSOF2}{dt} dt$
K	Soft Tissue – Total Pb in Soft Tissue
K 7	$YSOFT = YSOFO + YSOF1 + YSOF2$
L	Excretion – Urinary Bladder
L 1	$\frac{dBLAD}{dt} = TURIN \cdot CF \cdot BTEMP + RKDN1 \cdot YKDN1 - RBLAD \cdot YBLAD$
L 2	$YBLAD = \int_0^T \frac{dBLAD}{dt} dt$
L	Excretion – Urine
L 3	$\frac{dURIN}{dt} = RBLAD \cdot YBLAD$
L 4	$YURIN = \int_0^T \frac{dURIN}{dt} dt$
L	Excretion – Feces
L 5	$\frac{dFECE}{dT} = GSCAL \cdot RLLI \cdot YLLIC$
L 6	$YFECE = \int_0^T \frac{dFECE}{dT} dt$
L	Excretion – Sweat

No.		Equation
L	7	$\frac{dSWET}{dt} = TSWET \cdot CF \cdot BTEMP$
L	8	$YSWET = \int_0^T \frac{dSWET}{dt} dt$
L		Excretion – Other (e.g., hair, nails, desquamated skin)
L	9	$\frac{dHAIR}{dt} = S2HAIR \cdot RSOF1 \cdot YSOF1$
L	10	$YHAIR = \int_0^T \frac{dHAIR}{dt} dt$
M		Lead Body Burden and Distribution
M	1	$SIGMA = YPLAS + YRBC + YEVF + YSOF0 + YSOF1 + YSOF2 + YBRAN + YCVOL + YTVOL + YCSUR + YTSUR + YCDIF + YTDIF + YKDN1 + YKDN2 + YBLAD + YLVR1 + YLVR2 + YR1 + YR2 + YR3 + YR4 + YSTMC + YSIC + YULIC + YLLIC + YURIN + YFECE + YSWET + YHAIR$
M	2	$TBODY1 = YPLAS + YRBC + YEVF + YSOF0 + YSOF1 + YSOF2 + YBRAN + YCVOL + YTVOL + YCSUR + YTSUR + YCDIF + YTDIF + YKDN1 + YKDN2 + YLVR1 + YLVR2$
M	3	$TBODY2 = YPLAS + YRBC + YEVF + YSOF0 + YSOF1 + YSOF2 + YBRAN + YCVOL + YTVOL + YCSUR + YTSUR + YCDIF + YTDIF + YKDN1 + YKDN2 + YBLAD + YLVR1 + YLVR2 + YR1 + YR2 + YR3 + YR4 + YSTMC + YSIC + YULIC + YLLIC$
M	4	$TSOFTALL = YSOFT + YKDNE + YLIVR + YBRAN + YBLUD + YEVF$
M	5	$BLDFRC = \frac{YBLUD}{TBODY1}$
M	6	$BONFRC = \frac{YSKEL}{TBODY1}$
M	7	$BRNFRC = \frac{YBRAN}{TBODY1}$
M	8	$HEPFRC = \frac{YLIVR}{TBODY1}$
M	9	$RENFRC = \frac{YKDNE}{TBODY1}$

No.	Equation
M 10	$OTHFRC = \frac{YSOFT}{TBODY1}$
N	Growth and Tissue Volumes and Masses
N 1	$WBODY = WBIRTH + \frac{WCHILD \cdot AGEYEAR}{HALF + AGEYEAR} + \frac{WADULT}{1 + KAPPA \cdot e^{-LAMBDA \cdot WADULT \cdot AGEYEAR}}$
N 2	$AMTBLD = VBLC \cdot WBODY \cdot 10$
N 3	$PLSVOL = AMTBLD \cdot (1 - BLDHCT)$
N 4	$RBCVOL = AMTBLD \cdot (BLDHCT)$
N 5	$BLDHCT_{AGEYEAR \leq 0.01} = 0.52 + AGEYEAR \cdot 14$ $BLDHCT_{AGEYEAR > 0.01} = HCTA \cdot (1 + (0.66 - HCTA) \cdot e^{-(AGEYEAR - 0.01) \cdot 13.9})$
N 6	$VK = 1000 \cdot VKC \cdot (WBIRTH + WADULT + WCHILD) \cdot \left(\frac{WBODY}{WBIRTH + WADULT + WCHILD} \right)^{0.84}$
N 7	$KIDWT = VK \cdot 1.05$
N 8	$VL = 1000 \cdot VLC \cdot (WBIRTH + WADULT + WCHILD) \cdot \left(\frac{WBODY}{WBIRTH + WADULT + WCHILD} \right)^{0.85}$
N 9	$LIVWT = VL \cdot 1.05$
N 10	$VK = 1000 \cdot VKC \cdot (WBIRTH + WADULT + WCHILD) \cdot \left(\frac{WBODY}{WBIRTH + WADULT + WCHILD} \right)^{0.84}$
N 11	$TSKELWT = 1000 \cdot 0.058 \cdot WBODY^{1.21}$
N 12	$WBONE = 1000 \cdot 0.0290 \cdot WBODY^{1.21}$
N 13	$VBONE = 1000 \cdot 0.0168 \cdot WBODY^{1.188}$
N 14	$CVBONE = 0.8 \cdot VBONE$
N 15	$TVBONE = VBONE - CVBONE$
N 16	$CORTWT = \frac{WBONE \cdot CVBONE}{VBONE}$
N 17	$TRABWT = \frac{WBONE \cdot TVBONE}{VBONE}$

No.	Equation
-----	----------

See Appendix B for parameter name definitions and descriptions. Generally, prefix R indicates a rate constant from a compartment, prefix T indicates deposition fractions from plasma into a compartment, and prefix Y indicates mass in a compartment. Also see text (Section 2.3) for discussion of equations.

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1 **TABLE 2-3. RATE COEFFICIENTS FOR PB TRANSFERS IN AALM**

Pathway	100 days	1 year	5 years	10 years	15 years	≥25 years
Plasma-D to EVF	1000	1000	1000	1000	1000	1000
Plasma-D to RBCs	297.1	406.9	425.1	366.9	300.6	480.0
Plasma-D to Plasma-B	0.495	0.678	0.709	0.611	0.501	0.800
Plasma-D to Urinary Bladder	0	0	0	0	0	0
Plasma-D to Small Intestine	7.429	10.171	10.629	9.171	7.514	12.000
Plasma-D to Trab Surf	96.00	57.60	56.83	89.50	132.25	88.96
Plasma-D to Cort Surf	384.0	230.4	199.2	268.5	341.8	71.0
Plasma-D to Liver 1	49.52	67.81	70.86	61.14	50.10	80.00
Plasma-D to Kidney 1	31.0	42.4	44.3	38.2	31.3	50.0
Plasma-D to Kidney 2	0.496	0.678	0.708	0.612	0.500	0.800
Plasma-D to ST0	103.3	141.5	148.4	128.0	104.9	177.5
Plasma-D to ST1	12.38	16.95	17.71	15.29	12.52	10.00
Plasma-D to ST2	1.238	1.695	1.771	1.529	1.252	2.000
Plasma-D to Brain	0.557	0.763	0.266	0.229	0.188	0.300
Plasma-D to Sweat	4.333	5.933	6.200	5.350	4.383	7.000
RBCs to Plasma-D	0.4620	0.7854	0.4986	0.1946	0.1390	0.1390
EVF to Plasma-D	333.3	333.3	333.3	333.3	333.3	333.3
Plasma-B to Plasma-D	0.139	0.139	0.139	0.139	0.139	0.139
Cort Surf to Plasma-D	0.65	0.65	0.65	0.65	0.65	0.50
Trab Surf to Plasma-D	0.65	0.65	0.65	0.65	0.65	0.50
Cort Surf to Exch Vol	0.35	0.35	0.35	0.35	0.35	0.50
Trab Surf to Exch Vol	0.35	0.35	0.35	0.35	0.35	0.50
Cort Exch Vol to Surf	0.0185	0.0185	0.0185	0.0185	0.0185	0.0185
Trab Exch Vol to Surf	0.0185	0.0185	0.0185	0.0185	0.0185	0.0185
Cort Exch Vol to Nonexch Vol	0.02311	0.02311	0.02311	0.02311	0.02311	0.02311
Trab Exch Vol to Nonexch Vol	0.02311	0.02311	0.02311	0.02311	0.02311	0.02311
Cort Nonexch Vol to Plasma-D	0.01644	0.00576	0.00308	0.00178	0.00102	0.00016

Pathway	100 days	1 year	5 years	10 years	15 years	≥25 years
Trab Nonexch Vol to Plasma-D	0.01644	0.00576	0.00362	0.00264	0.00191	0.00099
Liver 1 to Plasma-D	0.0312	0.0312	0.0312	0.0312	0.0312	0.0312
Liver 1 to Small Intestine	0.0312	0.0312	0.0312	0.0312	0.0312	0.0312
Liver 1 to Liver 2	0.00693	0.00693	0.00693	0.00693	0.00693	0.00693
Liver 2 to Plasma-D	0.000693	0.000693	0.001386	0.000570	0.000570	0.000570
Kidney 1 to Urinary Bladder	0.139	0.139	0.139	0.139	0.139	0.139
Kidney 2 to Plasma-D	0.000693	0.000693	0.000693	0.000190	0.000190	0.000190
ST0 to Plasma-D	2.079	2.079	2.079	2.079	2.079	2.079
ST1 to Plasma-D	0.00416	0.00416	0.00416	0.00416	0.00416	0.00416
ST1 to Excreta	0.00277	0.00277	0.00277	0.00277	0.00277	0.00277
ST2 to Plasma-D	0.00038	0.00038	0.00038	0.00038	0.00038	0.00038
Brain to Plasma-D	0.00095	0.00095	0.00095	0.00095	0.00095	0.00095

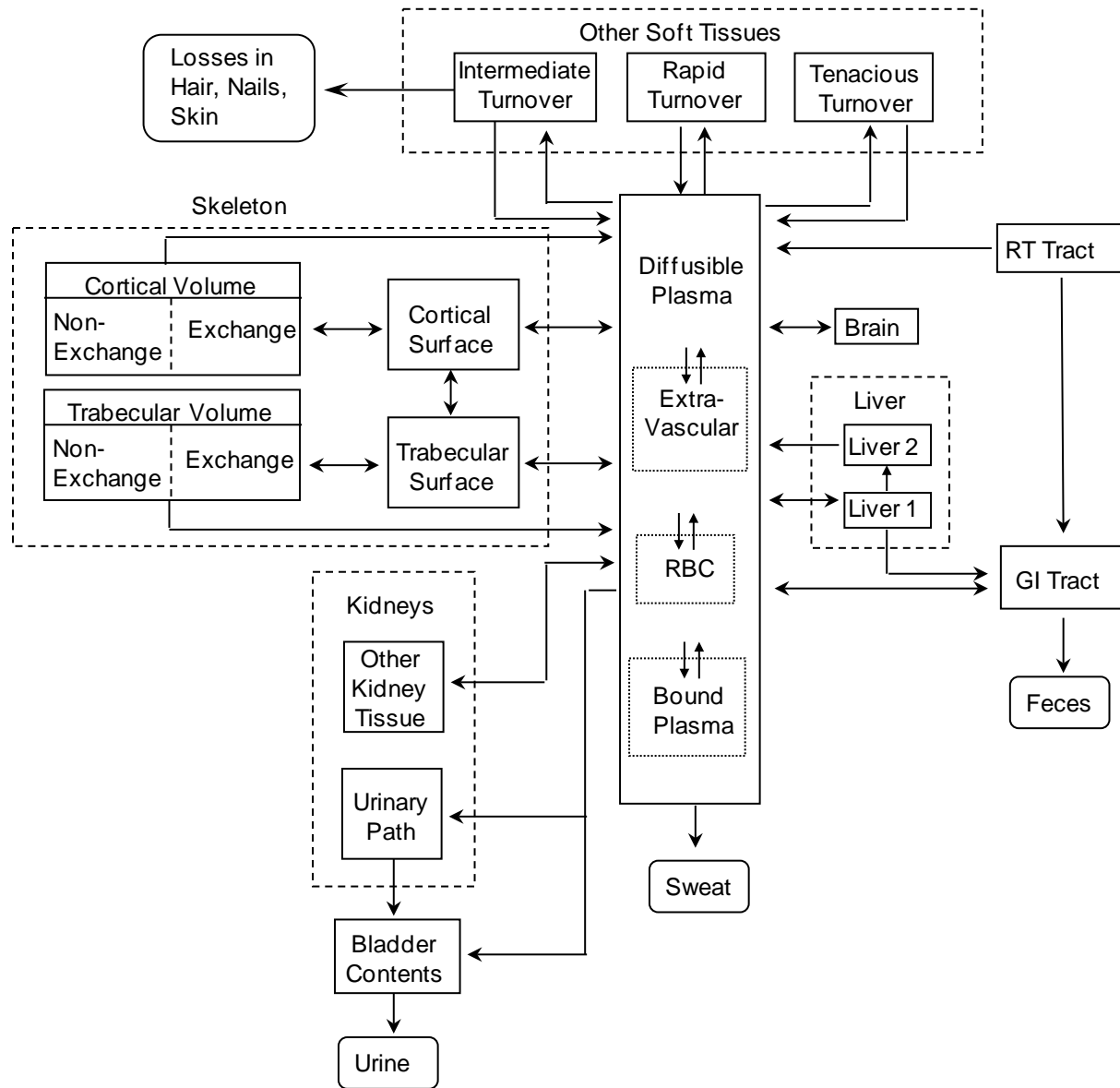
Coefficients are in units of d^{-1} . Coefficients from diffusible plasma (Plasma-D) are derived from the product of scaled deposition fractions and the rate coefficient for transfer from the diffusible plasma to all receiving compartments (RPLS, $2000 d^{-1}$), from Equation 2.3-9.

Cort, cortical bone; Exch, exchangeable; EVF, extravascular fluid; Nonexch, nonexchangeable; Plasma-D, diffusible plasma; Plasma-B, Pb-bound plasma RBC, red blood cell; Surf, surface; ST0, ST1, and ST2, soft tissues with fast, moderate, and slow exchange rates, respectively, Trab, trabecular bone; vol, volume.

1

2

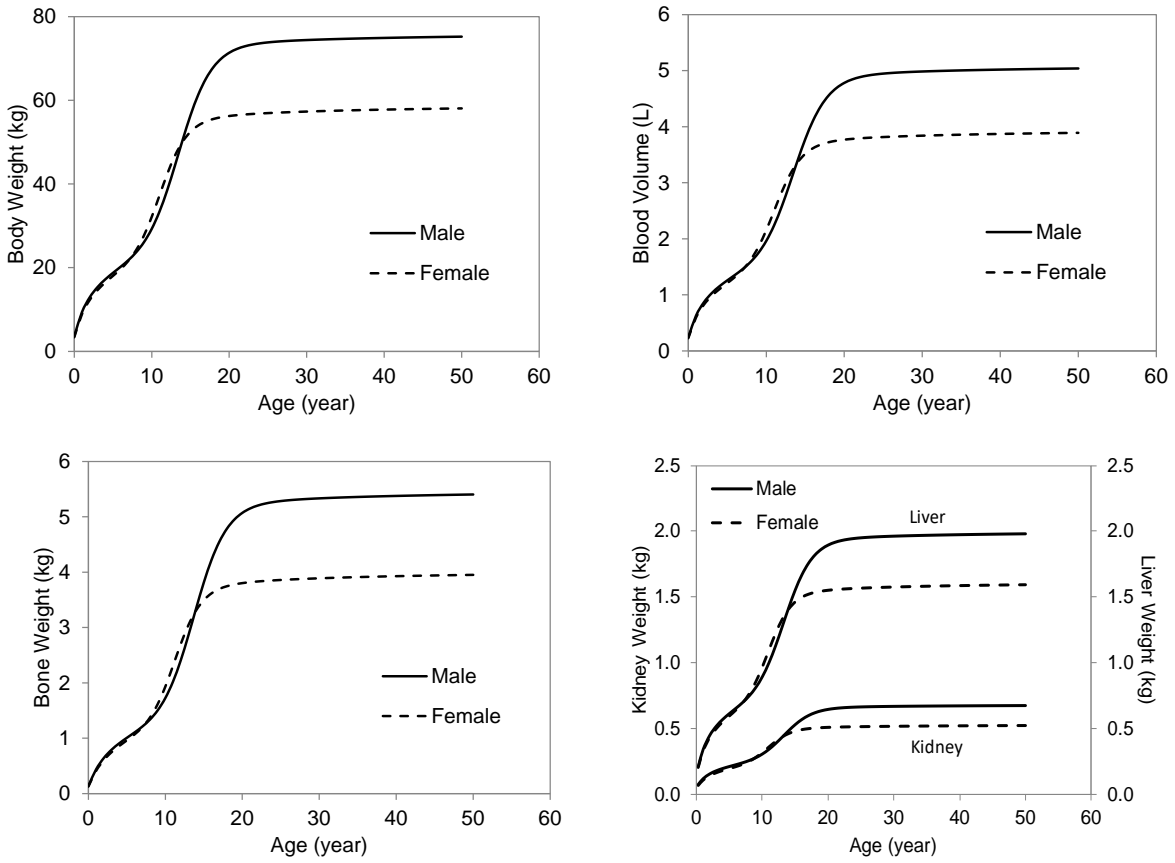
1 **FIGURE 2-1. STRUCTURE OF AALM.FOR BIKINETICS MODEL.**



2

3 Based on [Leggett \(1993\)](#). Lines with arrows represent Pb transfers.

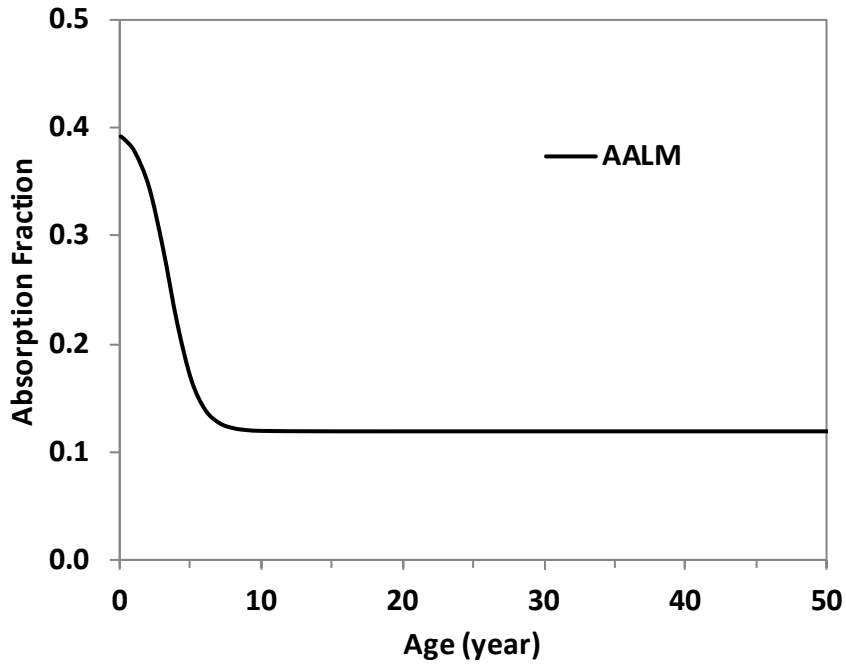
1 **FIGURE 2-2. BODY AND TISSUE GROWTH IN THE AALM.FOR.**



2

3

1 **FIGURE 2-3. GASTROINTESTINAL ABSORPTION OF PB AS OPTIMIZED IN AALM.FOR.**



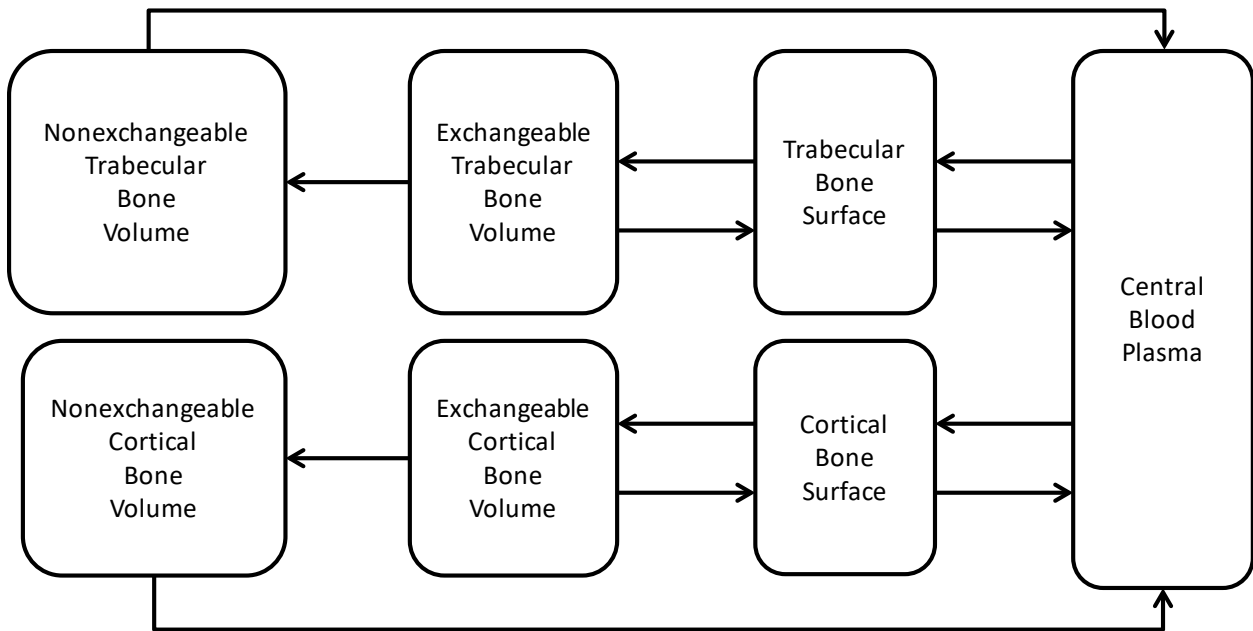
2

3 Optimization based on [Ryu et al. \(1983\)](#), [Sherlock and Quinn \(1986\)](#), [Rabinowitz et al. \(1976\)](#) and
4 [Maddaloni et al. \(2005\)](#).

5

1 **FIGURE 2-4. STRUCTURE OF AALM.FOR BONE MODEL.**

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5 This figure is based on [Leggett \(1993\)](#).

6

1 CHAPTER 3. EVALUATION AND DEVELOPMENT OF AALM.FOR

2 3.1. INTRODUCTION AND OBJECTIVES OF THIS ANALYSIS

3 In 2014, EPA released the report Framework for Identifying and Evaluating Lead-Based Paint Hazards
4 from Renovation, Repair, and Painting Activities in Public and Commercial Buildings ([U.S. EPA, 2014c](#))
5 which described how EPA could identify and evaluate hazards in public and commercial buildings. The
6 framework report was followed by a more detailed Approach for Estimating Exposures and Incremental
7 Health Effects due to Lead During Renovation, Repair and Painting Activities in Public and Commercial
8 Buildings ([U.S. EPA, 2014b](#)) and appendices ([U.S. EPA, 2014a](#)). The latter report describes in greater
9 detail an approach to estimating potential environmental concentrations, Pb body burdens, and
10 incremental health effects related to exposure to Pb from renovations of public and commercial buildings.
11 A key element in the approach was a Monte Carlo Analysis of Pb exposure scenarios and predicted blood
12 and bone Pb concentrations in children and adults. Blood and bone Pb were predicted using an
13 implementation of the Leggett ([Pounds and Leggett, 1998](#); [Leggett, 1993](#)) biokinetics model (Leggett
14 Fortran Model, LFM). Several modifications were made to the LFM to improve its performance and
15 facilitate the Monte Carlo Analysis. The results of these modifications produced ICRPv005.FOR, also
16 referred to as Leggett Model Version 5 ([https://www.epa.gov/lead/approach-estimating-exposures-and-](https://www.epa.gov/lead/approach-estimating-exposures-and-incremental-health-effects-lead-due-renovation-repair-and)
17 [incremental-health-effects-lead-due-renovation-repair-and](https://www.epa.gov/lead/approach-estimating-exposures-and-incremental-health-effects-lead-due-renovation-repair-and)). In developing ICRPv005.FOR, several
18 changes were made to the Leggett biokinetics model (Table 3-1). ICRPv005.FOR performed well when
19 evaluated using the NHANES data for children and occupational Pb smelter data for adults, indicating
20 good agreement with both these measured data sources and IEUBK model estimates. As part of the
21 response to peer review comments on the approach, EPA undertook the analyses described in another
22 report ([Post-Meeting Peer Review Summary Report, Versar, 2015](#)).

23 In the months following EPA OPPT's release of the Approach for Estimating Exposures and Incremental
24 Health Effects due to Lead During Renovation, Repair and Painting Activities in Public and Commercial
25 Buildings document, EPA ORD NCEA completed a beta test version of the All Ages Lead Model
26 (AALM.CLS; v. 4.2, July 2015) which also implemented an updated and expanded version of the Leggett
27 model ([Pounds and Leggett, 1998](#); [Leggett, 1993](#)) in Advanced Continuous Simulation Language (ACSL;
28 a.k.a. acsIX). The development of AALM.CSL included calibration and evaluation of model performance
29 that are described in Chapter 4 using several data sets that were of potential value for further evaluations
30 of the ICRPv005.FOR model. EPA was also interested in exploring differences in the structures and
31 predictions of blood and bone Pb from the two models. In part, to determine if one or the other model
32 might offer advantages for applications in predicting Pb body burdens related to public and commercial
33 building renovations as well as other potential research and regulatory applications of the models for
34 predicting exposure-body burden relationships.

35 This chapter summarizes results of analyses undertaken by EPA to explore differences in the structures
36 and predictions of blood and bone Pb between AALM.CSL and ICRPv005.FOR. The specific objectives
37 of these analyses were as follows:

- 38 • Conduct further evaluations of ICRPv005.FOR and AALM.CSL;
- 39 • Modify the models as needed, based on the outcome of these evaluations; and
- 40 • Harmonize the two models so that the models predict similar blood and bone Pb levels for similar
41 exposure inputs.

1 A detailed description of the structure of the AALM.FOR is provided in Chapter 2.

2 Within this chapter, Section 3.2 compares predictions of blood and bone Pb concentrations obtained from
3 the models. Section 3.3 describes the outcomes of comparisons of model predictions to observations.

4 Section 3.4 discusses data needs for potential further refinement and evaluation of the models. Section 3.5
5 summarizes conclusions from the model comparisons, model harmonization and responses to peer review
6 comments on approaches to blood and bone Pb modeling.

7 **3.2. MODEL PREDICTIONS OF BLOOD AND BONE PB**

8 Differences in the parameter values used in ICRPv005.FOR and AALM.CSL biokinetics models (Table
9 3-2) resulted in different predictions of blood and tissue Pb levels for similar Pb exposure assumptions.
10 Ultimately it was decided to harmonize the two models and a Fortran version (AALM.FOR) of
11 AALM.CSL was created. Thus, Table 3-2 essentially provides the changes in ICRPv005.FOR that were
12 required to create AALM.FOR. The AALM.FOR and AALM.CSL implementations are structurally
13 identical and have only few differences in parameter values and computational schemes that do not affect
14 simulations of blood and bone Pb concentrations (Table 3-3). The most important changes made to
15 ICRPv005.FOR to create AALM.FOR include the following: (1) Growth parameters from [O'Flaherty
16 \(1995, 1993\)](#) were adopted in AALM.FOR, this results in identical age profiles for blood volumes and
17 tissue masses between the models (see Chapter 2, Figure 2-2); and (2) GI absorption parameters from
18 AALM.CSL were adopted in AALM.FOR (see Section 4.7.1 and Figure 4-13). The GI absorption
19 fraction is 0.39 at birth and decreases to 0.12 at age 8 years (Figure 3-1). All other parameter values (e.g.
20 transfer rates and deposition fractions) from AALM.CSL were adopted in AALM.FOR.

21 Two types of comparisons were made of ICRPv005.FOR and AALM: (1) age profiles for blood and
22 tissue Pb levels following an exposure to a constant Pb intake ($\mu\text{g}/\text{day}$) were simulated and compared;
23 and (2) dose-response relationships between ingested dose and Pb levels were compared by simulating a
24 series of increasing Pb intakes. In either type of simulation, parameters that control Pb absorption and
25 growth were set to the same values, so that differences in blood and tissue Pb levels could be attributed
26 entirely to differences in the simulation of systemic (post-absorption) biokinetics.

27 **3.2.1. Constant Pb Intake**

28 Figures 3-2 and 3-3 show simulations of the accrual and elimination of Pb in blood and bone,
29 respectively, in children and adults. Exposures were simulated as a constant baseline Pb intake (5
30 $\mu\text{g}/\text{day}$) with a period of elevated intake (40 $\mu\text{g}/\text{day}$ in children and 105 $\mu\text{g}/\text{day}$ in adults). This exposure
31 results in predicted blood Pb concentrations $\leq 5 \mu\text{g}/\text{dL}$, which is well below the concentration at which
32 saturation of uptake into RBCs significantly affects blood Pb levels. Several differences are evident from
33 these comparisons:

- 34 • The harmonized AALM.FOR and AALM.CSL produce identical predictions of blood and bone
35 Pb concentrations.
- 36 • The AALM predicts higher blood and bone Pb concentrations than ICRPv005.FOR. The
37 difference is more pronounced in the adult simulation (Figure 3-2).
- 38 • The AALM predicts a slower approach to a quasi-state state blood Pb concentration than
39 ICRPv005.FOR and slower elimination and return to baseline (Figure 3-2). The difference is

1 more pronounced in the adult simulation. The AALM predicts a return to baseline over a period
2 of decades in adults; whereas, ICRPv005.FOR predicts a return to baseline within one year.

- 3 • The pattern of decline in blood Pb concentration following an abrupt decrease in Pb intake is also
4 different in the AALM and ICRPv005.FOR. Both models predict multi-phasic elimination of Pb
5 from blood in children (Figure 3-2A); however, the AALM predicts an early rapid phase,
6 followed by a slower phase; whereas, ICRPv005.FOR predicts a slower early phase, followed by
7 more rapid phase.
- 8 • The AALM predicts similar cortical and trabecular bone Pb concentrations in children; whereas,
9 ICRPv005.FOR predicts trabecular bone Pb concentrations that are approximately 25% of
10 cortical bone (Figure 3-3A, 8C).
- 11 • The AALM and ICRPv005.FOR predict higher Pb concentrations in adult trabecular bone,
12 compared to cortical bone, and slower accrual and elimination kinetics in cortical bone (Figure 3-
13 3 B, D).
- 14 • The AALM predicts faster elimination of Pb from adult cortical bone compared to
15 ICRPv005.FOR (Figure 3-3B).

16 **3.2.2. Dose-Response for Blood and Bone Pb**

17 Although both the AALM and ICRPv005.FOR model are mathematically linear models (i.e., all
18 compartment Pb masses are defined with linear differential equations), they predict curvilinear dose-
19 response relationships for blood Pb resulting from a saturable capacity of RBCs to take up Pb. Dose-
20 response relationships predicted from AALM.CSL, AALM.FOR and ICRPv005.FOR are shown in
21 Figures 3-4 for blood and 3-5 for bone, in children (age 2 years) and adults (age 30 years). In the AALM,
22 curvature in the intake-blood Pb relationship is negligible at blood Pb concentrations <10 µg/dL. Both
23 models predict linear dose-response relationships for bone Pb.

24 **3.3. COMPARISONS OF MODEL PREDICTIONS TO OBSERVATIONS**

25 Peer reviewers of Approach for Estimating Exposures and Incremental Health Effects due to Lead During
26 Renovation, Repair and Painting Activities in Public and Commercial Buildings ([U.S. EPA, 2014b](#))
27 suggested that data be used to evaluate blood and bone Pb predictions in adults from [Hattis \(1981\)](#) and
28 [Nie et al. \(2005\)](#), including additional unpublished Nie et al. data.

29 Data that were available from the Nie study consisted of three longitudinal blood and bone XRF
30 measurements for 209 adult Pb workers. The measurements were made in 1991, 1999 and 2008. This
31 period included a nine-month strike (July 1990 to May 1991), during which exposures at the plant were
32 interrupted. The available data also included birth dates and dates of hire. There were no data on actual
33 exposures at the plant. Although attempts were made to reconstruct exposures so that blood and bone Pb
34 concentrations could be predicted and compared to observations, ultimately, it was concluded that the
35 data were not suitable for model evaluations because of the uncertainty in the exposures that preceded the
36 blood and bone Pb measurements and that occurred during the measurement period. Exposures prior to
37 1991, including the period of the strike, had to be reconstructed with no basis for verification other than
38 the observed blood and bone Pb measurements. In one reconstruction attempted, each subject was
39 assumed to have an age-intake profile that predicted an age-blood Pb profile that was similar to the

1 central estimates from the NHANES survey that corresponded to the subject's age date. Added to this
 2 background intake was a constant occupational intake (except during the strike) that was calibrated to
 3 achieve a good fit to the weighted MSE for observed bone Pb (tibia and calcaneus) and blood Pb (relative
 4 weights: cortical bone 3, trabecular bone 2, blood 1). This fitting procedure resulted in good agreement
 5 between cortical and trabecular bone Pb predicted from ICRPv005.FOR and corresponding observations
 6 ($r^2 > 0.8$). However, a good fit to the observations could be expected for a wide range biokinetics
 7 parameter settings; therefore, these data would not allow a determination of whether ICRPv005.FOR or
 8 the AALM would perform better at predicting the observations.

9 Data that were available from the Hattis study were much more suitable for model evaluation. These data
 10 included blood Pb concentrations in 57 workers at hire and prior to and following a nine-month strike.
 11 Although pre-hire exposures were unknown, it was possible to calibrate the post-hire and pre-strike
 12 exposures to achieve agreement with blood Pb concentrations at the time of hire and just prior to the
 13 strike, and then predict without further calibration the post-strike blood Pb. Agreement between post-
 14 strike observations and predictions would be sensitive to biokinetics parameter settings that control blood
 15 Pb elimination rates. Therefore, these data were used to compare performance of ICRPv005.FOR and
 16 AALM. The outcome of this comparison indicated that the AALM performed better at predicting the
 17 Hattis observations than ICRPv005.FOR (described in detail in Section 3.3.1). Based on these
 18 evaluations, a Fortran version of the AALM (AALM.FOR) was developed and additional evaluations of
 19 AALM.FOR and AALM.CSL were conducted. These evaluations are described in Sections 3.3.2 to 3.3-
 20 10.

21 Goodness of fit of model predictions to observations were evaluated three approaches: (1) visual
 22 inspection of observed and predicted values; (2) inspection of standardized residuals (Equation 3-1); and
 23 (3) r^2 for the least-squares linear regression of observed and predicted values.

$$24 \quad \text{Standardized Residual} = \frac{\text{Predicted} - \text{Observed}}{\text{Standard Deviation of Observed Mean}} \quad \text{Eq. (3-1)}$$

25 Standardized residuals $\leq \pm 2$ and $r^2 > 0.70$ were considered acceptable fit to the observations.

26 **3.3.1. Pb Elimination Kinetics in Workers with Dose Reconstruction (Hattis Data)**

27 The Hattis data set used in this analysis included the following data on 57 adult Pb workers: (1) duration
 28 of employment prior to strike (Days_prestrike); (2) blood Pb concentration prior to start of employment
 29 (BLL_start); (3) blood Pb just prior to a nine-month strike (BLL_prestrike); and (4) blood Pb on return to
 30 work, following strike (BLL_poststrike). The 57 subjects comprised a subset of the 66 subjects in the
 31 dataset described in [Hattis \(1981\)](#). Subjects were excluded from the analysis if pre-strike blood Pb was
 32 $> 75 \mu\text{g/dL}$, post-strike blood Pb was $<$ blood Pb at date of hire, or post-strike blood Pb was $>$ pre-strike
 33 blood Pb. In the absence of information on pre-employment Pb exposures, pre-hire Pb intake was
 34 simulated as a constant ingestion intake ($\mu\text{g/day/kg}$ body weight) that would result in a predicted blood
 35 Pb concentration at age 20 years that was similar to BLL_start ($\pm 1 \mu\text{g/dL}$). Pre-strike occupational
 36 exposure was simulated as a constant ingestion intake ($\mu\text{g/day}$) that would result in a predicted blood Pb
 37 concentration at age = (20 years + duration of strike) that was similar to BLL_start ($\pm 1 \mu\text{g/dL}$). During
 38 the strike (assumed to be 270 days in duration), ingestion intake reverted to the pre-hire Pb intake.

39 An example of a simulation for a single subject from the Hattis data is shown in Figure 3-6 for
 40 AALM.CSL. In this simulation, the pre-hire Pb intake and pre-strike exposure intake were calibrated to

1 predict blood Pb concentrations similar to the observations made at the time of hire and at the start of the
 2 strike. In this case, the predicted post-strike blood Pb concentration (18.5 µg/dL) was within 10% of the
 3 observed (17.0 /dL). A pseudo first-order elimination rate (d^{-1}) and $t_{1/2}$ were estimated from the observed
 4 blood Pb concentrations at the beginning and end of the strike as follows (Equations 3-2 and 3-3):

$$5 \quad k = \ln \left(\frac{BLL_{pre-strike}}{BLL_{post-strike}} \right) / 270 \quad \text{Eq. (3-2)}$$

$$6 \quad t_{1/2} = \frac{\ln(2)}{k} \quad \text{Eq. (3-3)}$$

7
 8
 9 The $t_{1/2}$ calculated from the blood Pb concentrations predicted from the model and observations were 371
 10 days and 320 days, respectively. The calculated values for $t_{1/2}$ do not reflect the actual elimination kinetics
 11 of Pb from blood in this subject, or predicted from the AALM, because both would be expected to be
 12 multi-phasic over the 270-day interval. However, it serves as a convenient metric for comparing model
 13 performance when applied to the entire set of 57 subjects.

14 Both ICRPv005.FOR and AALM.CSL were successfully calibrated to the blood Pb
 15 concentrations measured at time of hire and just prior to the strike ($r^2 = 1.0$). Predicted and observed
 16 post-strike blood Pb concentrations were also correlated, but showed substantially more variability that
 17 could not be accounted for by the models, as expected for model predictions ($r^2 = 0.47$; Figure 3-7).

18 Figure 3-8 shows the distribution of calculated $t_{1/2}$ values for the Hattis subjects. Summary
 19 statistics for the evaluation are presented in Table 3-4. The median $t_{1/2}$ predicted from the observations
 20 was 633 days (GSD 2.4). The median from AALM.CSL was 483 days (GSD 1.6) and the median from
 21 ICRPv005.FOR was 274 days (GSD 1.6). The average difference between the individual observed and
 22 predicted $t_{1/2}$ values was -5% for AALM.CSL and -37% for ICRPv005.FOR. AALM.FOR predicted $t_{1/2}$
 23 (median 465 days, GSD 1.6; percent difference -8%) that were similar to AALM.CSL prediction.

24 **3.3.2. Pb Elimination Kinetics in Workers with Dose Reconstruction ([Nilsson et al., 1991](#))**

25 [Nilsson et al. \(1991\)](#) reported longitudinal data on blood and finger bone Pb concentrations in 14 Pb
 26 workers for period ranging from 8–18 years following cessation of their occupational exposures. The
 27 median blood Pb concentration at the end of exposure was approximately 45 µg/dL. The decline in bone
 28 Pb concentration was described by a first-order model with a single rate constant. Estimates of
 29 elimination half-times for each individual were reported. The group median was 16 years (95% CI: 12,
 30 23). The decline in blood Pb was described by a tri-exponential model with the following parameters.

31

Parameter	Unit	C1 (95% CI)	C2 (95% CI)	C3 (95% CI)
$t_{1/2}$	year	34 day (29, 41)	1.2 year (0.85, 1.8)	13 year (10, 18)
C	µg/dL	10.2	12.6	22.8

32

1 AALM simulations were run for a constant Pb intake from birth to age 60 years, to achieve a terminal
2 blood Pb concentration of approximately 45 $\mu\text{g/dL}$ (2000 $\mu\text{g/day}$), followed by 20 years without
3 exposure. A first-order exponential rate was estimated for the decline in cortical bone Pb concentrations
4 predicted for 20 years following cessation of exposure. Figure 3-9 compares rates of elimination of Pb
5 from bone and blood with the corresponding empirical models derived for the Pb workers ([Nilsson et al.,
6 1991](#)). Elimination rates of Pb from bone predicted from the optimized models are within the 95% CI of
7 the empirical model and yield standardized residuals that range within the -2, 2, criteria ($r^2 = 0.99$).
8 Elimination half-times predicted for bone Pb (16 years) were identical to estimates from [Nilsson et al.
9 \(1991\)](#). Although elimination rates from blood predicted by the optimized models are approximately at
10 the confidence limits of the empirical model, the initial model divergence is due largely to the slower
11 elimination kinetics observed during the first 5 years following cessation of exposure; after which the
12 models converge on the empirical model ($r^2 = 0.96$). Half-times predicted for the period 5 to 20 years
13 after exposure were 1.25 years, similar to values predicted for C2 (1.2 year) from [Nilsson et al. \(1991\)](#).

14 **3.3.3. Blood Pb Accrual and Elimination Kinetics in Adults with Known Pb Doses** 15 **([Rabinowitz et al., 1976](#))**

16 [Rabinowitz et al. \(1976\)](#) conducted a pharmacokinetics study in which four adults ingested daily doses of
17 [207Pb] nitrate for periods up to 124 days. Concentrations of 207Pb in blood, urine, and feces were then
18 monitored during and following cessation of exposure, and data on daily intakes and blood concentrations
19 for each subject were reported. Absorption fractions for Pb were estimated for each individual based on
20 mass balance in feces.

21 Figure 3-10 compares observed and predicted blood 207Pb concentrations from AALM.FOR and
22 AALM.CSL. Gastrointestinal absorption fractions were set in both models to the estimates for each
23 individual reported in [Rabinowitz et al. \(1976\)](#). No other changes were made to parameter values. Both
24 models predicted the rise and decline in blood Pb concentrations in temporal patterns that agreed with
25 observations. Values for r^2 for AALM predictions are 0.99, 0.98, 0.92, and 0.97 for Subjects A, B, D, and
26 E, respectively.

27 **3.3.4. Post-mortem Soft Tissue-to-Bone Pb Ratio ([Barry, 1975](#))**

28 Four studies provide data for measurements of post-mortem soft tissue and bone Pb concentrations
29 ([Gerhardsson et al., 1995](#); [Barry, 1981, 1975](#); [Gross et al., 1975](#)). [Gerhardsson et al. \(1995\)](#) reported only
30 soft tissue Pb concentrations; whereas, the other three studies reported soft tissue and bone Pb
31 concentrations that can be used to estimate the ratios. [Barry \(1981, 1975\)](#) reported data for children and
32 adults in age brackets, so the data from [Barry \(1975\)](#) was used as the primary source to optimize
33 parameters for kidney/bone and liver/bone Pb ratios as a function of age. [Barry \(1975\)](#) reported data on
34 tibia Pb concentrations that are simulated as cortical bone concentrations in the AALM models. Since
35 [Barry \(1975\)](#) reported group mean tissue concentrations (not ratios in autopsy cases), the mean tissue-to-
36 bone ratios were approximated from the group means. Figure 3-11 compares predicted and observed
37 kidney/bone and liver/bone Pb ratios in adults. Values for r^2 for kidney/bone predictions (of average of
38 male and female ratios) were 0.95. Values for r^2 for liver/bone predictions were 0.96 and 0.93 for AALM,
39 respectively.

3.3.5. Plasma-to-Bone Pb Ratio in Workers ([Hernandez-Avila et al., 1998](#); [Cake et al., 1996](#))

Two studies provide data to evaluate the relationship between plasma or serum blood Pb and bone Pb concentrations ([Hernandez-Avila et al., 1998](#); [Cake et al., 1996](#)). [Cake et al. \(1996\)](#) measured paired serum, tibia, and calcaneus Pb concentrations in 49 adult male Pb workers, and reported corresponding linear regression parameters. [Hernandez-Avila et al. \(1998\)](#) measured paired plasma, tibia and patella Pb concentrations in 26 adults (20 female) who had no known occupational exposures to Pb. These data can be used to derive corresponding linear regression parameters for the log-transformed plasma Pb. Individual subject data were digitized from Figure 1 of [Hernandez-Avila et al. \(1998\)](#), and linear regression parameters derived for the untransformed plasma Pb concentrations, in order to compare these with the linear regression parameters from [Cake et al. \(1996\)](#).

Bone Pb/plasma Pb slopes at age 50 years were predicted from the AALM for a series of simulations in which Pb intake was varied from 1 to 1000 µg/day. Table 3-5 and Figure 3-12 compare predicted and observed slopes based on data from [Cake et al. \(1996\)](#) and [Hernandez-Avila et al. \(1998\)](#). The bone/plasma ratios predicted from the AALM were within the 95% CI of the [Cake et al. \(1996\)](#) estimates and were also within the 95% CI of the [Hernandez-Avila et al. \(1998\)](#) for tibia.

3.3.6. Plasma Pb – Blood Pb Relationship (Meta-data)

Six studies provided data on individual human subjects that can be used to evaluate the relationship between plasma Pb and blood Pb concentrations. Measurements of plasma Pb were made using either inductively coupled plasma mass spectrometry ([Smith et al., 2002](#); [Bergdahl et al., 1999](#); [Bergdahl et al., 1998](#); [Hernandez-Avila et al., 1998](#); [Bergdahl et al., 1997](#); [Schutz et al., 1996](#)) or stable isotope dilution with thermal ionization mass spectrometry ([Manton et al., 2001](#)). In all of these studies, methods were employed to control for sample contamination, which is of particular importance in measurements of the low Pb levels found in plasma. Taken together, the observations from these reports varied over a wide range of blood Pb (approximately 0.34–94.8 µg/dL) and plasma Pb (approximately 0.0014–1.92 µg/dL) levels. These studies provided 406 individual measurements of plasma Pb and blood Pb, in adult workers as well as individuals with no known history of occupational exposure to Pb ([SRC, 2003](#)). Only one study provides similar data in children ([Bergdahl et al., 1999](#)). The observations in children do not appear to differ substantially from those for adults.

A best fit (least-squares) model for combined data from the above six studies was identified, and is presented in Equation 3-4:

$$\text{Blood Pb} = 87.0 \cdot \text{Plasma Pb}^{0.5} - 3.89 \quad (r^2=0.90) \quad \text{Eq. (3-4)}$$

Figures 3-13 compares the observed and predicted plasma-whole blood Pb relationship in adults. Standardized residuals for the optimized models are within acceptable limits (-2, 2). The r^2 values for predictions are 0.99 and 0.98.

3.3.7. Blood Pb Elimination Kinetics in Infants with Known Doses ([Sherlock and Quinn, 1986](#); [Ryu et al., 1983](#))

Only two studies provide data on the relationships between Pb dose and blood Pb concentration in infants ([Sherlock and Quinn, 1986](#); [Ryu et al., 1983](#)). In the [Ryu et al. \(1983\)](#) study, blood Pb concentrations were monitored in 25 formula-fed infants. From birth to age 111 days, infants were fed formula

1 (packaged in cartons) that had a Pb concentration of approximately 20 µg/L. From age 112 to 195 days, a
2 subset of the infants (n = 7) were switched to formula (packaged in cans) that had a Pb concentration of
3 approximately 57 µg/L. Formula intakes were measured, and provided estimates of Pb intakes in each
4 subject. [Ryu et al. \(1983\)](#) reported a table of individual Pb intakes, and presented a figure illustrating
5 group mean blood Pb concentrations at various ages (these data were digitized for use in this analysis).
6 Standard errors (or deviations) of mean blood Pb concentrations were not reported; however, as discussed
7 below, based on [Sherlock and Quinn \(1986\)](#), standard errors may have been approximately 10% of the
8 means. The parameter for maternal blood Pb concentration was set at 10 µg/dL, the reported maternal
9 mean for the study. Lead absorption was not quantified in [Ryu et al. \(1983\)](#); therefore, the
10 gastrointestinal absorption fraction during infancy was set to 40%, based on estimates from mass balance
11 studies ([Ziegler et al., 1978](#)). No other changes were made to parameter values. Figure 3-14 compares
12 predicted and observed blood Pb concentrations for the two exposure regimens (carton formula or carton
13 followed by canned formula). Simulations are shown for the mean intake (12–20 µg/day) and ± 1 SD
14 (10–18 µg/day, 15–22 µg/day). AALM.CSL and AALM.FOR simulations encompass most of the
15 observations within ±1 SD of the mean intakes. If standard errors of mean blood Pb concentrations were
16 10% of the mean, standardized residuals for AALM predictions ranged from -3.7 to 0.15 for carton
17 exposures (mean -1.2). The AALM captures the increase in blood Pb concentration associated with the
18 switch the higher Pb intakes for canned formula and the overall temporal trends in the observations; r² for
19 predictions were 0.85.

20 [Sherlock and Quinn \(1986\)](#) measured blood Pb concentration in 131 infants at age 13 weeks and
21 estimated dietary intake of Pb for each infant based on Pb measurements made in duplicate diet samples
22 collected daily during week 13. [Sherlock and Quinn \(1986\)](#) provided a plot of blood Pb means and
23 standard errors for group mean dietary Pb intakes (these data were digitized for use in this analysis). The
24 parameter for maternal blood Pb concentration was set at 18 µg/dL, the reported maternal geometric
25 mean. The gastrointestinal absorption fraction was set at 40% for infants; the same value used in
26 simulations of [Ryu et al. \(1983\)](#). Figure 3-15 compares predicted and observed blood Pb concentrations
27 for the range of Pb intakes in the study. AALM.CSL and AALM.FOR models reproduce the general
28 shape of the observed curvilinear dose-blood Pb relationship; the apparent plateau observed at the higher
29 end of the dose range, however, it is achieved at higher doses in the models (>800 µg/day). Although the
30 model results for the plateau contributed to high residuals at the highest Pb intake (>200 µg/day),
31 standardized residuals for lower Pb doses ranged from -4.8 to 1.5 (mean -2.3). The overall dynamics of
32 increasing blood Pb with increasing Pb dose was predicted with r² = 0.95. One possible explanation for
33 the higher plateaus in the dose-blood Pb relationship predicted from both models is that the models may
34 estimate higher saturation levels of Pb in RBCs than actually occurred in the infants in the [Sherlock and](#)
35 [Quinn \(1986\)](#) study. Parameter values for RBC uptake are based on data collected on adults, and have not
36 been optimized for infants due to an absence of good supporting data (see Section 3.3.6).

37 **3.3.8. Blood Pb Elimination Kinetics in Infants with Dose Reconstruction (ATSDR)**

38 Agency for Toxic Substances and Disease Registry (ATSDR) made available for this analysis
39 longitudinal blood Pb data in children following intervention in response to measurement of an elevated
40 blood Pb concentration. The data included dates of birth and dates and results of repeated Pb
41 measurements in 12 females and 12 males. Interventions included interruption of the exposure which
42 allows an evaluation of elimination kinetics of blood Pb. However, other interventions may have also
43 been conducted but were not documented in the data made available for this analysis. Intervention is

1 likely to have included chelation therapy in children whose blood Pb concentration exceeded 45 µg/dL.
2 Chelation would be expected to have affected rates of decline in blood Pb concentration during the first 1-
3 3 weeks following the diagnosis of elevated blood Pb. The longitudinal blood Pb data available for
4 longer periods would reflect post-chelation kinetics and are suitable for evaluating model predictions of
5 blood Pb elimination kinetics.

6 Since actual exposures to Pb were unknown for each child, the exposures leading up to the first blood Pb
7 measurements were reconstructed as a constant baseline Pb intake (µg/day) that resulted in a blood Pb
8 concentration of 5 µg/dL at age 6 months. Selection of 5 µg/dL as the target for the baseline simulation is
9 supported by the observations that that average terminal blood Pb concentration was 5.5 µg/dL (± 2.4 SD,
10 $n = 24$). Some children had blood Pb concentrations reported prior to an episode of elevated blood Pb
11 concentrations; the mean was 5.3 µg/dL (± 2.4 SD, $n = 4$). Another uncertainty is the reconstruction of the
12 level and duration of the elevated exposure that occurred prior to the detection of the elevated blood Pb.
13 Since there was no information about the exposure level or duration, these were parameters were
14 calibrated to the blood Pb observations to achieve optimal residuals and r^2 for the predictions. Examples
15 of successful exposure constructions are shown in Figures 3-16 to 3-18. Although, there is considerable
16 uncertainty about the reconstructed exposures, in each case, the AALM simulated the blood Pb
17 elimination kinetics from observations well beyond the expected period of chelation. Figure 3-18 shows
18 one of the few cases in which a baseline blood Pb measurement was available prior to the elevated
19 exposure. The timing of this baseline measurement considerably decreases the uncertainty about the
20 duration of the elevated exposure. Since the baseline measurement was made at age 450 days and first
21 elevated blood Pb was measured at age 810 days, the duration was likely to have been no more than 360
22 days. The optimized duration (age day 600 – 800) and exposure level (13,000 ppm Pb in dust) provided a
23 good fit to the observed elimination kinetics (r^2 0.81). The simulations shown in Figures 3-16 to 3-18 are
24 examples of one approach to reconstructing the Pb exposures that occurred prior to the blood Pb
25 observations.

26 **3.3.9. Comparison to IEUBK Model for Pb in Children**

27 Figure 3-19 compares predictions of the AALM and the IEUBK model for a continuous dust Pb intake of
28 10 µg/day. In both models, the relative bioavailability (RBA) for Pb in dust was assumed to be 60%.
29 This corresponds to an absolute bioavailability of approximately 20% at age 2 years in the AALM and
30 30% in the IEUBK model. At age 2 years the IEUBK model predicts a blood Pb concentration of 1.18
31 µg/dL; the AALM predicts 1.25 µg/dL.

32 **3.3.10. Comparison to Adult Lead Methodology**

33 Figure 3-20 and Table 3-6 compare predictions of adult blood Pb concentrations from the Adult Lead
34 Methodology and AALM, for an exposure to 1000 ppm. In both models, the RBA for Pb in dust was
35 assumed to be 60%. This corresponds to an absolute bioavailability of approximately 4.8% in the AALM
36 and 12% in the Adult Lead Methodology. The Adult Lead Methodology predicts a blood Pb
37 concentration of 2.9 µg/dL; the AALM predicts 3.1 µg/dL at age 30 years (mid-point for age range in the
38 Adult Lead Methodology, 17-45 years).

1 3.4. DATA NEEDS FOR FURTHER REFINEMENT OF THE AALM

2 The AALM.FOR model discussed in this report demonstrates the considerable advancements that have
3 been made since a development of ICRPv005.FOR in terms of its capability and evaluation predictions of
4 Pb body burdens, including blood Pb concentrations in children and blood and bone Pb concentrations in
5 adults. Blood Pb concentrations in adults predicted from the AALM are very similar to predictions from
6 the EPA Adult Lead Methodology (ALM) for the same soil Pb concentrations. Predictions for infants are
7 similar between the AALM and the IEUBK. Work done to date has been responsive to comments
8 received on both models from peer reviews conducted in 2005 and 2014 (see Section 3.5).

9 Recommendations for data to reduce uncertainty in the predictions obtained from AALM.FOR and
10 AALM.CSL, and improve the consistency among all model predictions include the following:

- 11 • *Further verify AALM predictions.* Additional observations in humans should be identified that
12 can serve to evaluate the performance of the optimized AALM (and that were not used in the
13 optimization). Ideally, these would be blood and/or bone Pb measurements in people for whom
14 Pb intakes are known with reasonable certainty. Ethical concerns typically preclude Pb dosing
15 experiments; therefore, Pb doses must be estimated with accurate tools such as duplicate diet
16 surveys or dietary recalls and information on Pb levels in diet and other relevant exposure media.
17 Types of data that would be valuable for model validation include: (1) blood soft tissue or bone
18 Pb levels in children or adults for whom Pb dosage is known or can be reliably estimated from
19 exposure data; (2) changes in blood, soft tissue or bone Pb levels in children or adults following
20 and abrupt change (increase or decrease) in Pb exposure; (3) steady state (or quasi-steady state)
21 blood/soft tissue blood/bone Pb ratios in children or adults; (4) urinary Pb clearance from blood
22 or plasma in children or adults; and (5) plasma/whole blood concentration ratios in children.
- 23 • *Evaluate and document the empirical basis for exposure model parameters.* Most of the
24 exposure parameter values currently in the AALM serve as placeholders and should, in the future,
25 be replaced with default values for specific receptor populations for which an empirical basis can
26 be provided.
- 27 • *Further refine the gastrointestinal tract model.* AALM.FOR allows the user to input values for
28 RBA of Pb in exposure media. This is important for risk assessment applications because the
29 absorption fraction Pb is known to vary with the environmental medium in which it is contained
30 (e.g. Pb in soil can have a lower absorption fraction than Pb dissolved in water). However, in the
31 current version of AALM.FOR, the RBA adjustment is applied to the media-specific Pb intake
32 rather than to the absorption fraction (*FI*) in the small intestine (see Section 2.2.3). In this
33 configuration, Pb that is not absorbed when RBA is <1 does not appear in feces. This will result
34 in an underestimation of fecal Pb excretion and a negative mass balance (excretion < intake). A
35 model that adjusts the absorption fraction by RBA would provide a more accurate representation
36 of medium-specific absorption and excretion of Pb. This would be similar to the modeling
37 approach to RBA that is contained in AALM.CSL.
- 38 • *Further refine the respiratory tract (RT) model.* The current version of AALM.FOR uses a 4-
39 compartment RT model from the [Leggett \(1993\)](#) model in which Pb intake to the RT represents
40 the deposited dose (μg Pb deposited in the RT per day), which must be calculated outside of
41 AALM.FOR for a given set of assumptions regarding the air Pb concentration ($\mu\text{g}/\text{m}^3$), inhaled

1 particle size and minute (day) and volume day volume (m³/day). A model that would use inputs
2 of air Pb concentration, particle size and Pb species would be more useful for applications to
3 simulating air Pb exposures. This could be similar to the simplified version of the [ICRP \(1994\)](#)
4 model that was implemented in the beta test version of AALM.CSL (v. 4.2, July 2015).

- 5 • *Refinement of the bone mineral model.* The AALM includes calculations for converting
6 concentrations of Pb in bone wet weight to concentration per g bone mineral by dividing the wet
7 weight concentration by the ash fraction of bone. This conversion is important for comparing
8 model predictions of bone Pb concentrations with bone X-ray fluorescence (XRF) data, which is
9 typically reported in units of Pb per g bone mineral. In AALM.CSL, bone ash fractions were
10 assumed to be 0.55 and 0.50 for cortical and trabecular bone, respectively ([ICRP, 1981](#)). In
11 ICRPv005.FOR, the bone ash fractions were assumed to be 0.55 for cortical bone and 0.18 for
12 trabecular bone. AALM.CSL values have been adopted for AALM.FOR and the different values
13 for trabecular bone have not been reconciled. Further research that could provide a stronger
14 empirical basis for these values would improve confidence in simulations of XRF observations.

15 **3.5. CONCLUSIONS AND IMPLICATIONS FOR MODELING LEAD BODY BURDENS**

16 The current version of AALM.FOR represents a substantial update to ICRPv005.FOR used in the
17 Approach for Estimating Exposures and Incremental Health Effects due to Lead During Renovation,
18 Repair and Painting Activities in Public and Commercial Buildings ([U.S. EPA, 2014b](#)) and appendices
19 ([U.S. EPA, 2014a](#)). The updates include new parameters for simulating physiological growth and
20 gastrointestinal absorption, as well as updated parameters that govern rates of exchange of Pb between
21 plasma, RBCs, bone, kidney and liver (Table 3-2). AALM.FOR predicts blood, bone and soft tissue Pb
22 levels that are identical AALM.CSL and provides an alternative Fortran platform to acslX, which is no
23 longer commercially supported, for implementing the AALM.

24 **3.5.1. Evaluation of AALM.FOR Performance**

25 AALM.FOR was evaluated with a larger set of observations in children and adults, including some data
26 that had not been used in previous evaluations of ICRPv005.FOR. Data on Pb dose-blood Pb
27 relationships is limited to a three studies; one of adults in which five male subjects were administered
28 known doses of a stable Pb isotope for periods of 2 to 6 months ([Rabinowitz et al., 1976](#)) and two studies
29 of infants in which Pb ingestion doses were estimated from dietary (formula) Pb measurements and
30 exposures were for approximately 3 months ([Ryu et al., 1983, n = 25](#)); ([Sherlock and Quinn, 1986, n =](#)
31 [131](#)). No data were available on dose-blood Pb concentration relationships in older children or
32 adolescents for whom Pb ingestion doses were known with certainty. Several studies have reconstructed
33 Pb intakes in children from exposure models supported by measurements of environmental exposure
34 concentrations ([Dixon et al., 2009](#); [TerraGraphics Environmental Engineering, 2004](#); [Malcoe et al., 2002](#);
35 [Hogan et al., 1998](#); [Lanphear et al., 1998](#); [Bornschein et al., 1985](#)). However, these studies were not
36 considered in the current evaluations of AALM.FOR and may be useful for future efforts to validate a
37 version of the AALM that combines the biokinetics model (AALM.FOR) with a multimedia exposure
38 model.

39 Although limited in size, these evaluations suggest that AALM.FOR can provide an accurate prediction of
40 dose-blood Pb relationships when actual doses are known or can be calculated with certainty. In general,
41 AALM.FOR predicted the observed blood Pb concentrations and dynamics in infants and adults in

1 response to changing Pb dosing (see Figures 3-10, 3-14). AALM.FOR also predicted quasi-steady state
2 blood Pb concentrations in infants across a range of ingestion doses of Pb (Figures 3-15). The model
3 predicted a higher plateau for the dose-blood Pb relationship than was observed in infants (Figure 3-15),
4 however, this difference would be of quantitative significance only at intakes resulting in blood Pb
5 concentrations >30 µg/dL. These evaluations show that the model reliably predicts both quasi-steady
6 state blood Pb concentrations as well the rates of change Pb that occur with a change in exposure.

7 AALM.FOR also predicted the observed relationships between plasma and whole blood Pb
8 concentrations in adults (Figure 3-13). Transfer out of RBCs in AALM.FOR is age-dependent and faster
9 in children than in adults. The validity of the age-dependence was not rigorously explored in this
10 analysis. What little data there are on plasma-blood Pb relationships in children does not suggest an
11 appreciable difference in the relationship for children and adults ([Bergdahl et al., 1999](#)). Since the age-
12 dependence could not be rigorously evaluated it is retained in AALM.FOR. AALM.FOR also predicted
13 the observed relationships between plasma and bone Pb concentrations in adults (Figure 3-12) and
14 between kidney, liver and bone Pb concentrations in children and adults based on post-mortem data
15 (Figure 3-11). This suggests that the model accurately predicts the ratios of the exchange kinetics (rates
16 into tissue and out to plasma) that give rise to the age-dependent distribution of Pb between bone and soft
17 tissue.

18 AALM.FOR predicted the observed changes in blood Pb concentrations in children and adults for
19 reconstructed exposures estimated based on observed blood Pb measurements (Figures 3-8, 3-9, 3-16 to
20 3-18). These evaluations indicate that the model accurately predicts observed elimination kinetics of Pb
21 from blood in children and adults, and bone in adults. AALM.FOR predicts more rapid elimination of Pb
22 from bone in children compared to adults (Figure 3-3). This is consistent with more active bone growth
23 and turnover of bone mineral during childhood which should contribute to more volatile bone Pb stores
24 ([O'Flaherty, 1995](#); [Leggett, 1993](#)). However, the kinetics of bone Pb in children predicted by the model
25 have not been quantitatively verified as no data were available on kinetics of elimination of Pb from bone
26 in children.

27 Collectively, the above observations provide added confidence for applications of AALM.FOR for
28 predicting Pb body burdens associated with long-term steady state exposures or short-term intermittent
29 exposures, such as those associated with public and commercial building renovations.

30 **3.5.2. Response to Peer Review of ICRPv005.FOR**

31 The updates made to ICRPv005.FOR and further evaluations of ICRPv005.FOR and AALM.FOR address
32 several comments made by peer reviewers of the *Approach for Estimating Exposures and Incremental*
33 *Health Effects due to Lead During Renovation, Repair and Painting Activities in Public and Commercial*
34 *Buildings* ([Versar, 2015](#); [U.S. EPA, 2014b](#)). These are summarized below.

35 *Rationale for selecting the Leggett model over the O'Flaherty model.* Peer reviewers suggested that
36 performance of the Leggett and O'Flaherty models be evaluated and that a stronger rationale be provided
37 for selecting the Leggett model for applications to public and commercial renovation assessments. This
38 report does not specifically address performance of the O'Flaherty model; however, the model was
39 extensively evaluated Chapter 4. The latter report described the development and evaluation of
40 AALM.CSL which includes modules that implement biokinetics models based on either the Leggett
41 model (AALM-LG.CSL) or O'Flaherty model (AALM-OF.CSL). A conclusion of the latter report was

1 that AALM-LG.CSL provided superior agreement to the [Rabinowitz et al. \(1976\)](#) observations compared
2 to AALM-OF.CSL. This conclusion supports selection of the Leggett model as the basis for AALM.FOR
3 and for applications of AALM.FOR, rather than the O'Flaherty model, to assessments of public and
4 commercial building renovations. Additional considerations that support use of AALM.FOR were: (1)
5 the need for Monte Carlo applications of the model which require sufficient computational speed afforded
6 by the Fortran code; and (2) limited future availability of an acslX program to run AALM.CSL, because
7 acslX is no longer being commercially supported.

8 *Accounting for sex differences in biokinetics.* The peer reviewers suggested that the model should
9 simulate sex differences in Pb biokinetics. The analyses described in this report could not evaluate sex
10 differences in biokinetics because there are no data on dose-body burden relationships in humans that
11 would allow such evaluations. ICRPv005.FOR was updated in creating AALM.FOR to include
12 algorithms that control growth of the body, volumes of plasma and blood and masses of bone and soft
13 tissues AALM.FOR includes parameters to simulate male or female growth. AALM.FOR was shown to
14 predict elimination kinetics of Pb from blood in male and female children when exposures were
15 reconstructed (Figure 3-16 to 3-17), and soft tissue-bone Pb relationships in males and females (Figure 3-
16 11).

17 *Evaluation of relationship between plasma-whole blood Pb concentrations.* The peer reviewers
18 suggested that the model should be evaluated for accurately predicting the plasma-blood Pb concentration
19 ratio. A meta-dataset of observations of plasma-blood Pb concentrations in children and adults was
20 assembled for evaluation of model performance. In all of these studies, methods were employed to
21 control for sample contamination, which is of particular importance in measurements of the low Pb levels
22 found in plasma. The dataset used in the evaluation included paired observations of plasma and whole
23 blood Pb concentration for 409 adults ([Smith et al., 2002](#); [Bergdahl et al., 1999](#); [Bergdahl et al., 1998](#);
24 [Hernandez-Avila et al., 1998](#); [Bergdahl et al., 1997](#); [Schutz et al., 1996](#)). The relationship between
25 plasma and whole blood Pb concentrations predicted from AALM.FOR agreed with observations (Figure
26 3-13). Only one study provides similar data in children ([Bergdahl et al., 1999](#)). Based on these data, the
27 plasma-blood relationships in children and adults do not appear to differ substantially.

28 *Accounting for relative bioavailability (RBA) of ingested Pb.* The peer reviewers suggested that RBA of
29 Pb in dust/soil needs to be included as part of the ingestion calculations. This has been included in
30 AALM.FOR. However, by making RBA an adjustment on the ingested dose, rather than the
31 gastrointestinal absorption fraction, the RBA adjustment will result in an underestimation of fecal Pb
32 excretion and a negative mass balance (excretion < intake) if RBA is <1 (see Sections 2.2.3). An error in
33 the Pb intake-excretion mass balance will not affect the simulation internal kinetics of Pb or body burdens
34 (e.g., blood or bone concentrations), although, it may be noteworthy for some research applications.
35 Further refinement of the model at some point in the future to make the RBA an adjustment to the
36 absorption fraction in the small intestine is discussed in Section 3.4.

37 *Revaluation of model predictions of blood Pb kinetics in the [Rabinowitz et al. \(1976\)](#) study.* The peer
38 reviewers suggested that the model should be revaluated with the [Rabinowitz et al. \(1976\)](#) data to ensure
39 that changes made to the model in creating ICRPv005.FOR did not degrade performance of the model to
40 accurately simulate these observations. AALM.FOR predicted blood Pb concentrations and the temporal
41 pattern of the rise and decline in blood Pb concentrations observed in the [Rabinowitz et al. \(1976\)](#)
42 subjects (Figure 3-10).

1 *Evaluation of model performance for Hattis data.* The peer reviewers suggested that the model be
2 evaluated for predicting blood Pb concentrations in a cohort of workers described in [Hattis \(1981\)](#). These
3 data included blood Pb concentrations in workers measured at the date of hire and prior to and following a
4 nine-month strike. Although pre-hire exposures were unknown, it was possible to calibrate the post-hire
5 and pre-strike exposures to achieve agreement with blood Pb concentrations at the time of hire and just
6 prior to the strike, and then predict without further calibration the post-strike blood Pb. After calibration
7 to the blood Pb concentrations measured at time of hire and just prior to the strike ($r^2 = 1.0$), AALM.FOR
8 predicted rates of decline in blood Pb concentration (pseudo first-order $t_{1/2}$) for individual subjects and for
9 the group median that agreed with the observations (Table 3-4).

10 *Evaluation of model performance for the Nie et al. data.* The peer reviewers suggested that the model be
11 evaluated for predicting blood and bone Pb concentrations in a cohort of workers described in [Nie et al.](#)
12 [\(2005\)](#) including use of some unpublished Nie et al. data. These data were used in an analyses of an
13 implementation of the Leggett model developed by California EPA ([CalEPA, 2013](#)). There were no data
14 on actual exposures experienced by the workers in this cohort. As described in Section 3.3, the Nie et al.
15 data were reviewed and evaluated. Although attempts were made to reconstruct exposures so that blood
16 and bone Pb concentrations could be predicted and compared to observations, ultimately, it was
17 concluded that the data were not suitable for model evaluations because of the uncertainty in the
18 exposures that preceded the blood and bone Pb measurements and that occurred during the measurement
19 period.

20 *Evaluation of model performance for intermittent exposures.* Renovations of public and commercial
21 building renovations can result in elevated Pb exposures that may persist for several days to several
22 months. Therefore, assessment methods applied to renovation-related exposure scenarios must be able to
23 predict blood and bone Pb levels that might occur as a result of short-term or intermittent exposures to
24 children or adults. Several evaluations described in this report suggest that AALM.FOR can be expected
25 to reliably predict blood Pb kinetics associated with short-term or intermittent exposures. (1)
26 AALM.FOR predicted the rate of accrual and elimination of Pb from blood in adult subjects who were
27 exposed to Pb over periods of 2-6 months (Figure 3-10). (2) The model predicted the increase in blood
28 Pb that was observed in infants who were abruptly switched to a higher Pb level diet following
29 approximately 100 days of ingesting a lower Pb level diet (Figure 3-14). (3) The model predicted the rate
30 of decline in blood Pb that was observed following interventions to decrease elevated exposures that
31 occurred over periods of 200 – 400 days (Figures 3-16 to 3-18). (4) The model predicted the decrease in
32 blood Pb concentrations that occurred in Pb workers following a nine-month strike (Table 3-4).

33 **3.5.3. Summary**

34 Collectively, the updates made to ICRPv005.FOR to create AALM.FOR and evaluations of AALM.FOR
35 provide increased confidence in applying a biokinetics modeling approach to support estimations of Pb
36 body burdens following a variety of potential Pb exposure scenarios. AALM.FOR offers an improved
37 modeling tool for predicting exposure-body burden relationships for intermittent as well as chronic Pb
38 exposures.

1 **TABLE 3-1. CHANGES MADE TO ICRPV004.FOR TO CREATE ICRPV005.FOR**

ICRPv004.FOR^a	ICRPv005.FOR	Output/Functionality Affected
Adult kidney mass	Age-dependent kidney mass based on ICRP (2002)	Age-dependent kidney Pb concentrations
Adult bone mass	Age-dependent bone mass based on ICRP (2002)	Age-dependent bone Pb concentrations
Constant hematocrit	Age-dependent hematocrit based on ICRP (2002)	Age-dependent RBC and plasma volumes
Constant trabecular bone fraction (20%)	Age-dependent trabecular bone fraction from Table M-1 of U.S. EPA (2014a)	Age-dependent cortical and trabecular bone Pb concentrations
RBC Pb saturation threshold (25 µg/dL blood) and maximum (350 µg/dL RBC)	RBC Pb saturation threshold (0 µg/dL blood) and maximum (270 µg/dL RBC)	Pb uptake– blood Pb relationship
Transfer rate from (d ⁻¹) plasma to RBC birth–10 years: <ul style="list-style-type: none"> • birth: 0.462 • 0.27 y: 0.462 • 1 y: 0.462 • 5 y: 0.277 • 10 y: 0.139 	Transfer rate from (d ⁻¹) plasma to RBC birth–10 years: <ul style="list-style-type: none"> • birth: 0.562 • 0.27 y: 0.562 • 1 y: 0.562 • 5 y: 0.277 • 10 y: 0.277 	Plasma– RBC Pb relationship in children
Deposition fraction from RBC to diffusible plasma (0.24)	Deposition fraction from RBC to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.20 • 0.27 y: 0.20 • 1 y: 0.20 • 5 y: 0.21 • 10 y: 0.22 • ≥15 y: 0.22 	Plasma– RBC Pb relationship in children
Transfer rate (d ⁻¹) from non-exchangeable cortical bone to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.00822 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00154 • 10 y: 0.00089 • 15 y: 0.000512 • ≥25 y: 0.000082 	Transfer rate (d ⁻¹) from non-exchangeable cortical bone to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.0102 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00154 • 10 y: 0.00089 • 15 y: 0.000512 • 18 y: 0.000370 • 24 y: 0.000082 • ≥30 y: 0.000041 	Bone to plasma Pb kinetics, in late adolescence (age 15–19 years) and adults (≥30 years)

ICRPv004.FOR^a	ICRPv005.FOR	Output/Functionality Affected
<p>Transfer rate (d⁻¹) from non-exchangeable trabecular bone to diffusible plasma:</p> <ul style="list-style-type: none"> • birth: 0.00822 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00181 • 10 y: 0.00132 • 15 y: 0.000956 • ≥25 y: 0.000493 	<p>Transfer rate (d⁻¹) from non-exchangeable trabecular bone to diffusible plasma:</p> <ul style="list-style-type: none"> • birth: 0.0102 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00181 • 10 y: 0.00132 • 15 y: 0.000956 • 18 y: 0.000781 • 24 y: 0.000493 • 30 y: 0.000247 • 40 y: 0.000247 • 45 y: 0.000274 • 55 y: 0.000301 • 65 y: 0.000329 • 75 y: 0.000356 	<p>Bone-to-plasma Pb transfer kinetics (age 15–18 years), adults (≥25 years)</p>

Based on ([U.S. EPA, 2014a, b](#)).

^aICRPv004.FOR is an implementation of the [Leggett \(1993\)](#) model.

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1 TABLE 3-2. DIFFERENCES IN ICRPV005.FOR AND AALM.CLS BIOKINETICS

ICRPv005.FOR	AALM.FOR	Output/Functionality Affected
Age-dependent blood and plasma volumes based on ICRP (2002)	Age-dependent blood and plasma volumes based on O'Flaherty (1995, 1993)	Age-dependent blood Pb concentration
Age-dependent bone mass based on ICRP (2002)	Age-dependent bone mass based on O'Flaherty (1995, 1993)	Age-dependent cortical and trabecular bone Pb concentration
Age-dependent trabecular bone fraction based from Table M-1 of U.S. EPA (2014a)	Age-dependent cortical and trabecular bone masses based on O'Flaherty (1995, 1993)	Age-dependent cortical and trabecular bone Pb concentration
Age-dependent kidney mass based on ICRP (2002)	Age-dependent kidney mass based on O'Flaherty (1995, 1993)	Age-dependent kidney Pb concentration
Adult liver mass	Age-dependent liver mass based on O'Flaherty (1995, 1993)	Age-dependent liver Pb concentration
Age-dependent absorption fraction (<i>FI</i>): <ul style="list-style-type: none"> • birth: 0.45 • 0.27 y: 0.45 • 1 y: 0.30 • 5 y: 0.30 • 10 y: 0.30 • 15 y: 0.30 • ≥25 y: 0.15 	Age-dependent absorption fraction (<i>FI</i>): <ul style="list-style-type: none"> • birth: 0.39 • 0.27 y: 0.39 • 1 y: 0.38 • 5 y: 0.17 • ≥10 y: 0.12 	Absorption fraction for ingested Pb
Absorption fraction for ingested Pb not adjusted for RBA	Media-specific ingestion intakes adjusted for RBA	Intake-fecal mass balance
RBC Pb saturation threshold: 0 µg/dL blood) Maximum: 270 µg/dL RBC	RBC Pb saturation threshold: 20 µg/dL blood) Maximum: 350 µg/dL RBC)	Pb uptake–blood Pb relationship
Transfer rate (d^{-1}) from non-exchangeable cortical bone to diffusible plasma (RCORT): <ul style="list-style-type: none"> • birth: 0.0102 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00154 • 10 y: 0.00089 • 15 y: 0.00512 • ≥25 y: 0.0000822 	Transfer rate (d^{-1}) from non-exchangeable cortical bone to diffusible plasma (RCORT): <ul style="list-style-type: none"> • birth: 0.0204 • 0.27 y: 0.01644 • 1 y: 0.00576 • 5 y: 0.00308 • 10 y: 0.00178 • 15 y: 0.00124 • ≥25 y: 0.0001644 	Shorter retention of Pb in cortical bone
Transfer rate (d^{-1}) from non-exchangeable trabecular bone to diffusible plasma (RTRAB): <ul style="list-style-type: none"> • birth: 0.0102 	Transfer rate (d^{-1}) from non-exchangeable trabecular bone to diffusible plasma (RTRAB): <ul style="list-style-type: none"> • birth: 0.0204 	Shorter retention of Pb on trabecular bone

ICRPv005.FOR	AALM.FOR	Output/Functionality Affected
<ul style="list-style-type: none"> • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00181 • 10 y: 0.00132 • 15 y: 0.000956 • ≥25 y: 0.000493 	<ul style="list-style-type: none"> • 0.27 y: 0.01644 • 1 y: 0.00576 • 5 y: 0.00362 • 10 y: 0.00264 • 15 y: 0.001912 • ≥25 y: 0.000986 	
Fraction of total transfer from the exchangeable bone directed to non-exchangeable bone (FLONG): 0.2	Fraction of total transfer from the exchangeable bone directed to non-exchangeable bone (FLONG): 0.6	Longer retention of Pb in cortical and trabecular bone
Transfer rate (d ⁻¹) from liver compartment 2 to diffusible plasma (RLVR2): <ul style="list-style-type: none"> • birth: 0.00693 • 0.27 y: 0.00693 • 1 y: 0.00693 • 5 y: 0.00693 • 10 y: 0.00190 • 15 y: 0.00190 • ≥25 y: 0.00190 	Transfer rate (d ⁻¹) from liver compartment 2 to diffusible plasma (RLVR2): <ul style="list-style-type: none"> • birth: 0.000693 • 0.27 y: 0.000693 • 1 y: 0.000693 • 5 y: 0.001386 • 10 y: 0.000570 • 15 y: 0.000570 • 25 y: 0.000570 • 30 y: 0.001425 • 40 y: 0.003040 • 60 y: 0.003420 • 90 y: 0.00380 	Longer retention of Pb in liver
Transfer rate (d ⁻¹) from kidney compartment 2 to diffusible plasma (RKDN2): <ul style="list-style-type: none"> • birth: 0.00693 • 0.27 y: 0.00693 • 1 y: 0.00693 • 5 y: 0.00693 • 10 y: 0.00190 • 15 y: 0.00190 • ≥25 y: 0.00190 	Transfer rate (d ⁻¹) from kidney compartment 2 to diffusible plasma (RKDN2): <ul style="list-style-type: none"> • birth: 0.000693 • 0.27 y: 0.000693 • 1 y: 0.000693 • 5 y: 0.000693 • 10 y: 0.000190 • 15 y: 0.000190 • 25 y: 0.000190 • 30 y: 0.000950 • ≥40 y: 0.00190 	Longer retention of Pb in kidney
Deposition fraction from diffusible plasma to kidney compartment 2 (TKDN2): 0.0002	Transfer rate (d ⁻¹) from kidney compartment 2 to diffusible plasma (TKDN2): 0.0004	Faster transfer from diffusible plasma to kidney at all ages
Deposition fraction from diffusible plasma to kidney compartment 1 (TKDN1): 0.02	Deposition fraction from diffusible plasma to kidney compartment 1 (TKDN1): 0.025	Faster transfer from diffusible plasma to kidney at all ages

ICRPv005.FOR	AALM.FOR	Output/Functionality Affected
Deposition fraction from diffusible plasma to urine (TOURIN): 0.015	Deposition fraction from diffusible plasma to urine (TOURIN): 0	All urinary excretion occurs from kidney

1

1 **TABLE 3-3. DIFFERENCES BETWEEN AALM.FOR AND AALM.CSL**

AALM.FOR	AALM.CSL	Output/Functionality Affected
Numerical integration time steps controlled by user input	Numerical integration time steps controlled by user Gear (1971) algorithm	Numerical integration error
Media-specific ingestion intakes adjusted for RBA	GI tract absorption fraction adjusted for media-specific RBA	Fecal Pb mass balance
4-compartment RT model that requires user inputs for deposition rate ($\mu\text{g}/\text{day}$)	12-compartment model that accepts user inputs for air concentration, particle size and absorption class	Simulations of Pb deposition and absorption of inhaled Pb

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1 **TABLE 3-4. BLOOD LEAD PREDICTIONS FROM THE AALM FOR 57 SUBJECTS IN THE**
 2 **HATTIS DATASET**

		Hattis		ICRPv005		AALM.CSL		AALM.FOR	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
BLL at hire	µg/dL	20	7	20	7	20	7	20	7
BLL at strike	µg/dL	48	11	49	13	48	11	48	11
BLL after strike	µg/dL	33	9	23	7	31	7	31	7
BLL half-time	days	1027	1433	312	184	553	370	523	314
BLL half-time delta				-0.37	0.59	-0.05	0.54	-0.08	0.52

		Hattis		ICRPv005		AALM.CSL		AALM.FOR	
		GM	GSD	GM	GSD	GM	GSD	GM	GSD
BLL half-time	days	633	2.4	274	1.6	483	1.6	465	1.6

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		Hattis		ICRPv005.FOR		AALM.CSL		AALM.FOR	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
		n							
BLL at hire (µg/dL)		20	7	20	7	20	7	20	7
BLL at strike (µg/dL)		48	11	49	13	48	11	48	11
BLL after strike (µg/dL)		33	9	23	7	31	7	31	7
BLL half-time (d)		1027	1433	312	184	553	370	523	314
BLL half-time delta (d)				-0.37	0.59	-0.05	0.54	-0.08	0.52

		Hattis		ICRPv005.FOR		AALM.CSL		AALM.FOR	
		GM	GSD	GM	GSD	GM	GSD	GM	GSD
BLL half-time (d)		633	2.4	274	1.6	483	1.6	465	1.6

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1 **TABLE 3-5. COMPARISON OF PREDICTED AND OBSERVED PLASMA PB/BONE PB**
 2 **SLOPES**

Model	Study	Bone	Predicted Slope	Observed Slope	SE	95%CL	Residual
AALM	CA96	Cortical	0.037	0.052	0.013	0.027, 0.077	-1.16
AALM	CA96	Trabecular	0.040	0.041	0.007	0.027, 0.054	-0.16
AALM	HE98	Cortical	0.037	0.036	0.011	0.014, 0.058	0.12
AALM	HE98	Trabecular	0.040	0.025	0.004	0.017, 0.033	3.67

CA96, [Cake et al. \(1996\)](#); HE98, [Hernandez-Avila et al. \(1998\)](#)

3

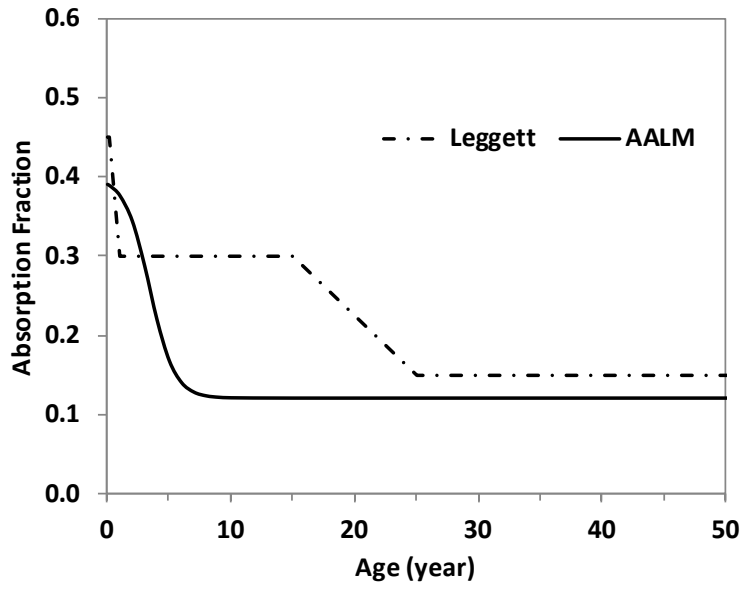
4 **TABLE 3-6. COMPARISON OF ALM AND AALM PREDICTIONS OF BLOOD PB**
 5 **CONCENTRATIONS IN ADULTS**

Parameter	Description	Units	ALM	AALM
PbS	Soil lead concentration	µg/g or ppm	1000	1000
BKSF	Biokinetic Slope Factor	µg/dL per µg/day	0.4	NA
PbB ₀	Baseline Blood Pb	µg/dL	1.5	1.5
IR _s	Soil Ingestion Rate	g/day	0.050	0.05
AF _{s, D}	Absorption Fraction	--	0.12	0.072
EF _{s, D}	Exposure Frequency	days/yr	219	219
AT _{s, D}	Averaging Time	days/yr	365	365
PbB _{adult}	Blood Pb Concentration	µg/dL	2.9	2.9

ALM, Adult Lead Methodology. See Figure 3-20 for AALM input parameter values.

6

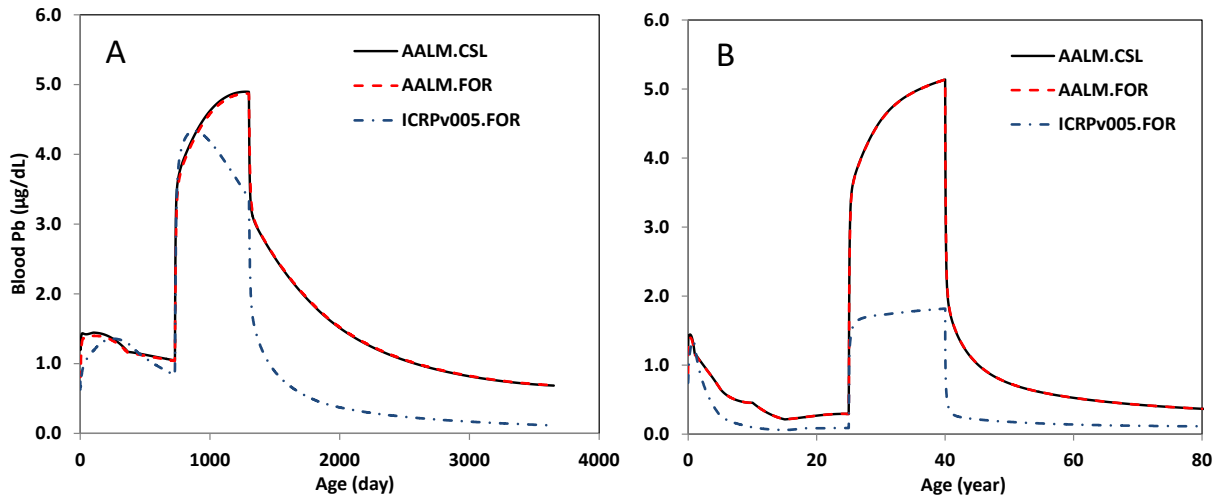
1 **FIGURE 3-1. GASTROINTESTINAL ABSORPTION OF PB IN THE (LEGGETT, 1993)**
2 **MODEL AND AALM, OPTIMIZED TO (RYU ET AL., 1983).**



3

4

1 **FIGURE 3-2. COMPARISON OF ACCRUAL AND ELIMINATION KINETICS OF BLOOD PB**
2 **IN CHILDREN (A) AND ADULTS (B) PREDICTED FROM AALM.CSL, AALM.FOR AND**
3 **ICRPV005.FOR.**

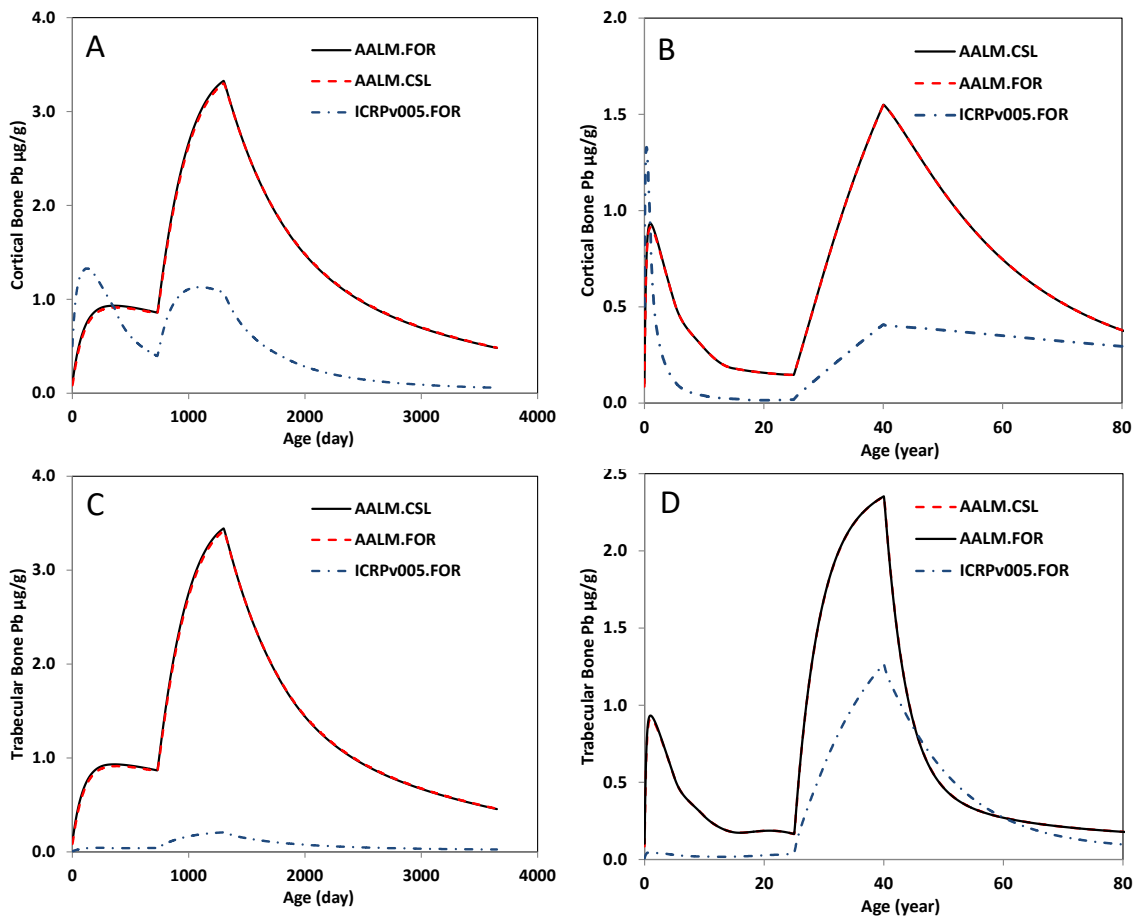


4

5 The simulated Pb exposure was a constant baseline intake (5 µg/day) beginning at birth. In the child
6 simulation, a period of elevated intake of (40 µg/day) began on day 720 and ended on day 1300. In the
7 adult simulation, a period of elevated intake of (105 µg/day) began at age 25 years and ended at age 40
8 years.

9

1 **FIGURE 3-3. COMPARISON OF ACCRUAL AND ELIMINATION KINETICS OF CORTICAL**
 2 **BONE (A, B) AND TRABECULAR BONE (C, D) PB IN CHILDREN (A, C) AND ADULTS (B, D)**
 3 **PREDICTED FROM AALM.CSL, AALM.FOR AND ICRPV005.FOR.**

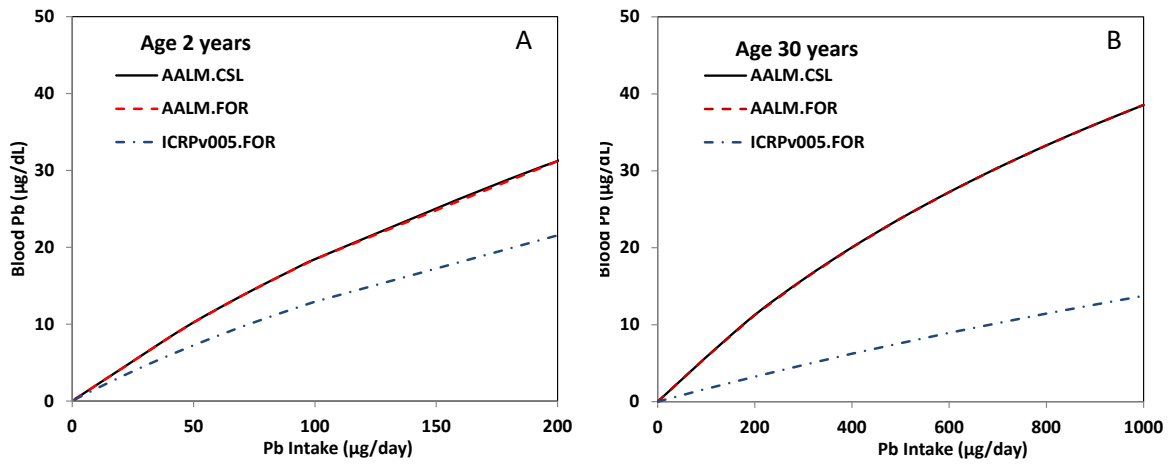


4

5 The simulated Pb exposure was a constant baseline intake (5 µg/day) beginning at birth. In the child
 6 simulation, a period of elevated intake of (40 µg/day) began on day 720 and ended on day 1300. In the
 7 adult simulation, a period of elevated intake of (105 µg/day) began at age 25 years and ended at age 40
 8 years.

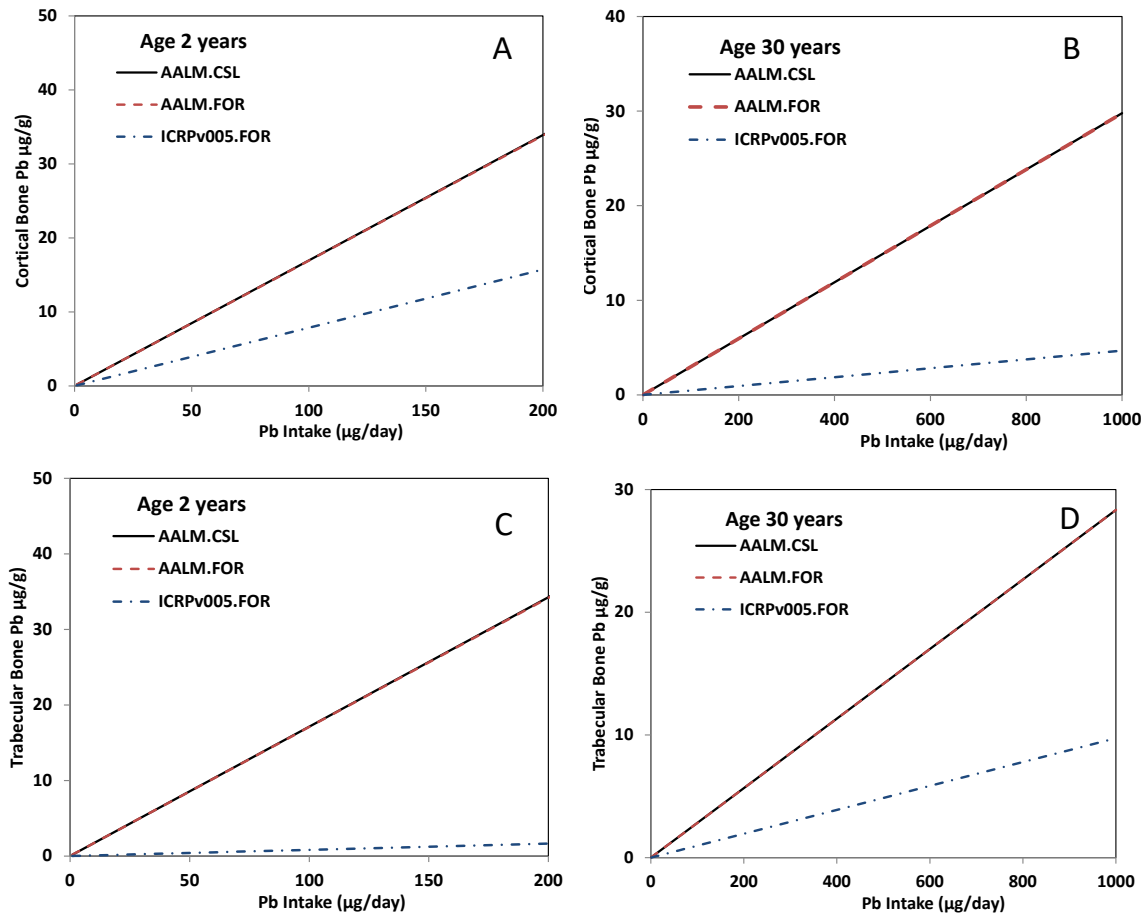
9

1 **FIGURE 3-4. COMPARISON OF RELATIONSHIPS BETWEEN PB INTAKE (G/DAY) AND**
2 **BLOOD PB IN CHILDREN (A) AND ADULTS (B) PREDICTED FROM AALM.CSL,**
3 **AALM.FOR AND ICRPV005.FOR.**



4

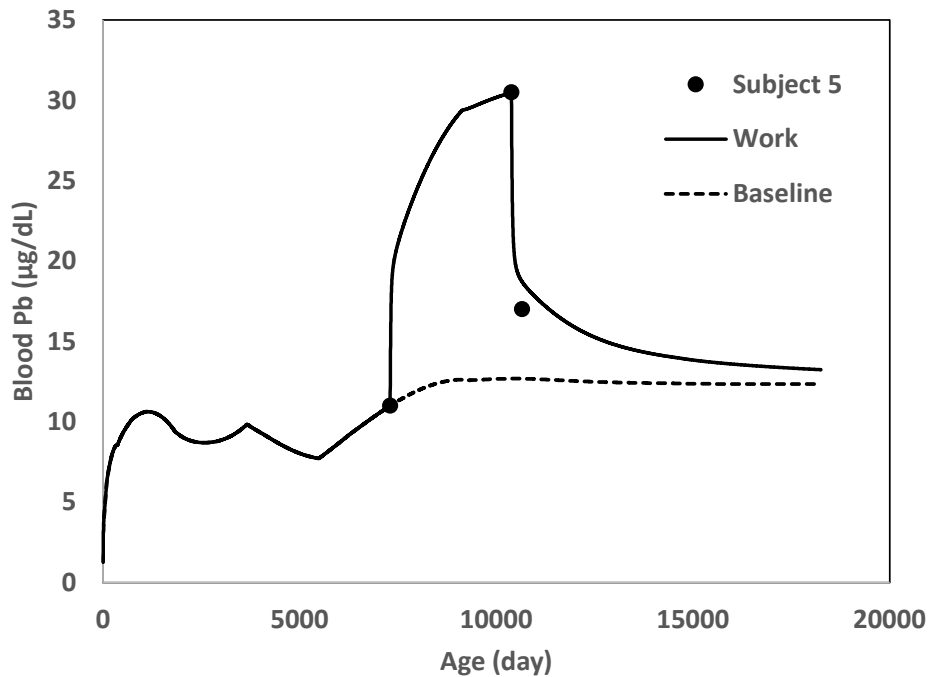
1 **FIGURE 3-5. COMPARISON OF RELATIONSHIPS BETWEEN PB INTAKE (G/DAY) AND**
2 **CORTICAL (A, B) AND TRABECULAR (C, D) BONE PB IN CHILDREN (A, C) AND ADULTS**
3 **(B, D) PREDICTED FROM AALM.CSL, AALM.FOR AND ICRPV005.FOR.**



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5

1 **FIGURE 3-6. AALM.CLS SIMULATION OF OBSERVATIONS FOR HATTIS COHORT**
 2 **SUBJECT 5.**



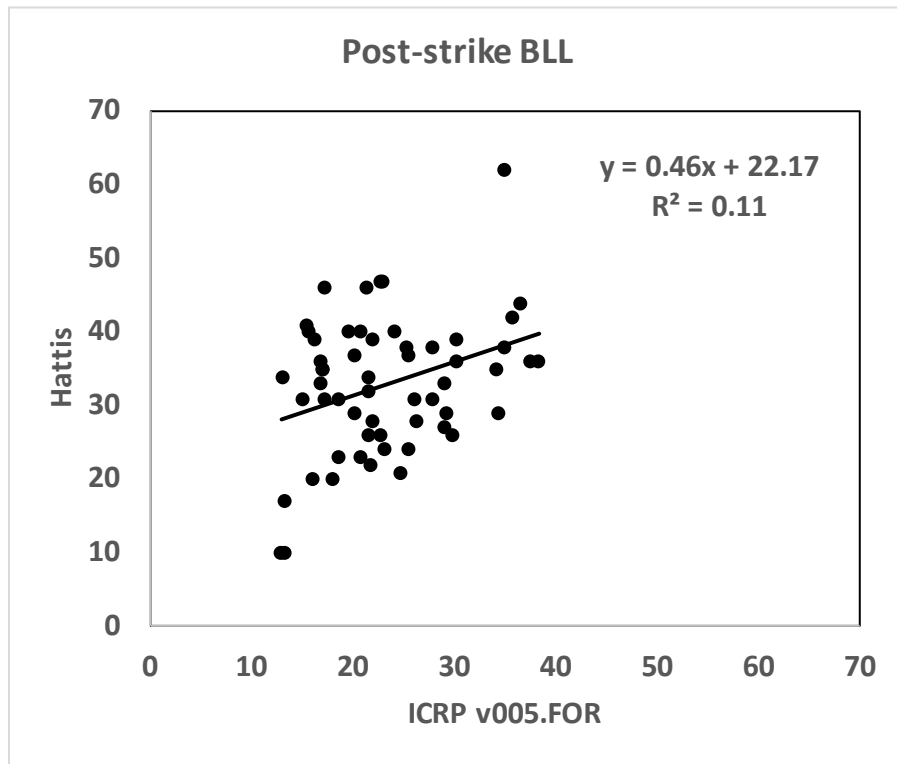
3

Age		AALM BLL (µg/dL)	Observed BLL (µg/dL)	Ratio (Pred./Obs.)
7300	days	10.6	11.0	0.96
10384	days	30.6	30.5	1.00
10654	days	18.5	17.0	1.09
k	day ⁻¹	0.00187	0.00216	0.86
t _{1/2}	day	372	320	1.16

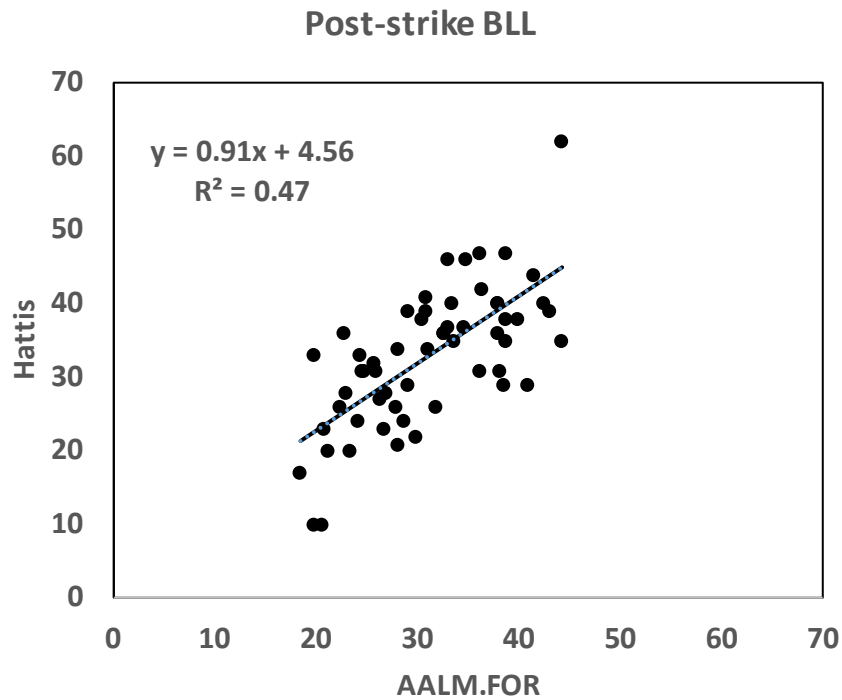
4

5 The subject (unknown age and sex) experience an occupational exposure that was interrupted by 9-month
 6 strike. Pre-strike exposures were reconstructed as a constant Pb ingestion (µg/kg/day) that resulted in a
 7 pre-hire blood Pb that was within 1 µg/dL of the reported pre-hire blood Pb (11 µg/dL) for the subject.
 8 Pre-strike exposures were reconstructed as a constant Pb ingestion (µg/day), for the reported pre-strike
 9 employment durations (3084 days), that resulted in a pre-strike blood Pb that was within 1 µg/dL of the
 10 reported pre-strike blood Pb (30.5 µg/dL) for the subject. During the 9-month strike (assumed to be 270
 11 days), exposure reverted to the per/kg baseline level. The elimination half-time from blood was
 12 calculated from pre-strike and post-strike blood Pb concentrations, assuming a first-order elimination.
 13 The elimination half-time predicted from the observed blood Pb data is 320 days. The half-time predicted
 14 from the AALM.CLS is 372 days.

1 **FIGURE 3-7. COMPARISON OF ICRPV005.FOR (TOP) AND AALM.FOR (BOTTOM)**
2 **PREDICTIONS AND OBSERVED BLOOD PB CONCENTRATIONS AFTER THE STRIKE**
3 **FOR 57 SUBJECTS IN THE HATTIS COHORT.**

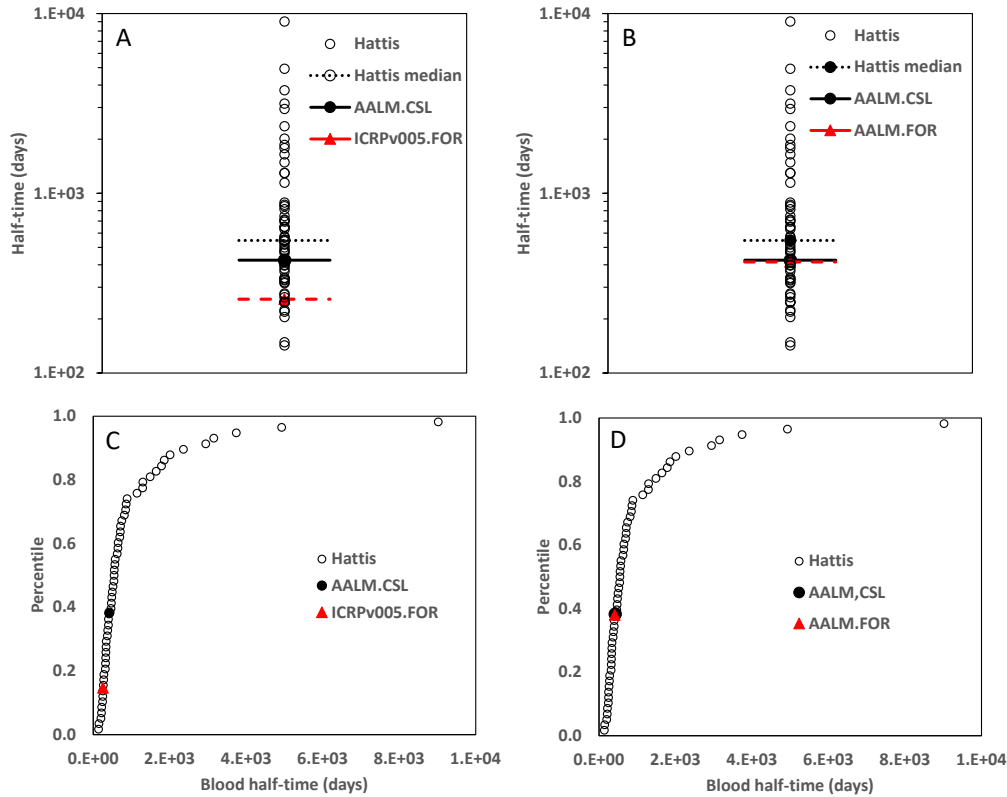


4



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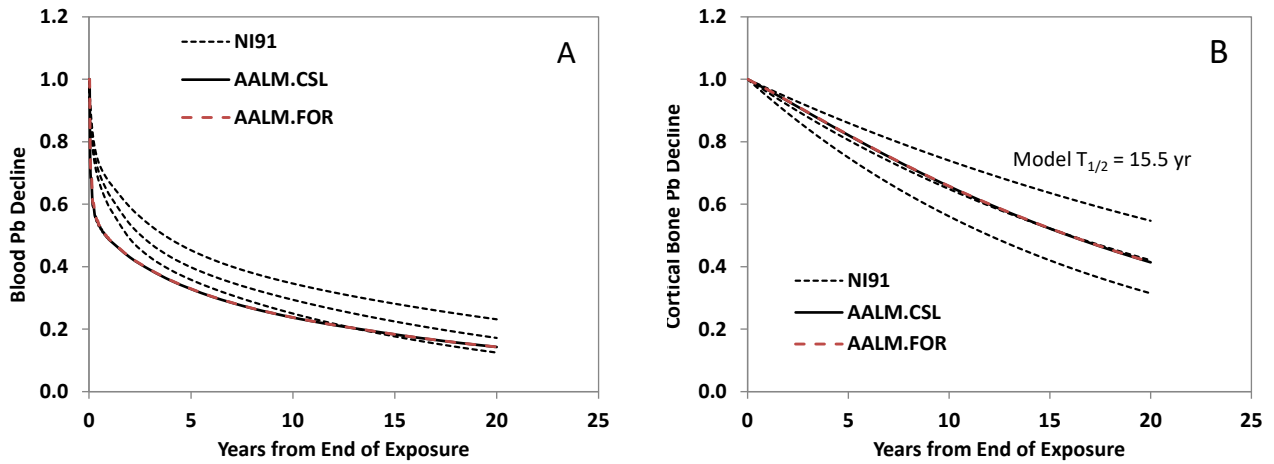
1 **FIGURE 3-8. AALM.CSL, AALM.FOR AND ICRPV005.FOR SIMULATIONS OF BLOOD PB**
 2 **ELIMINATION HALF-TIME FOR 57 SUBJECTS IN THE HATTIS COHORT.**



3
 4 Panel A compares the half-times predicted for the observations with medians predicted from the
 5 AALM.CSL and ICRPV005.FOR. Panel C displays the same data as percentiles of the half-times
 6 predicted from the observations for AALM.CSL and ICRPV005.FOR. Panels B and D display the
 7 corresponding plots comparing AALM.CSL and AALM.FOR. Half-times were calculated as follows:
 8 $\text{half-time} = \ln(2) / [\ln(\text{pre-strike}/\text{post-strike})/270]$.

9

1 **FIGURE 3-9. AALM.CSL AND AALM.FOR SIMULATIONS OF ELIMINATION KINETICS OF**
2 **PB FROM BLOOD (A) AND BONE (B).**

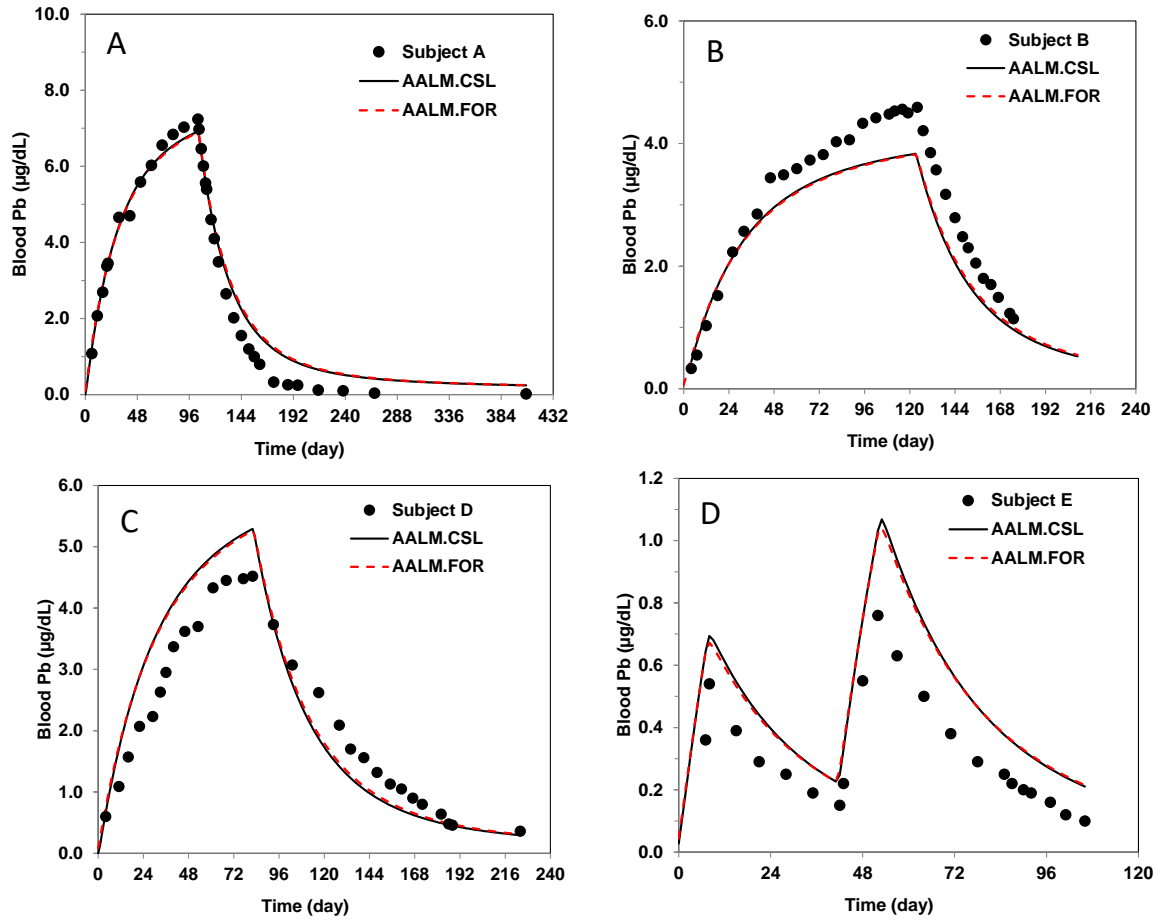


3

4 Dotted lines show the elimination from based on the median and upper and lower 95% confidence limits
5 of the tri-exponential model retired Pb workers (n = 14, median age 60 years at time of retirement)
6 reported in [Nilsson et al. \(1991\)](#).

7

1 **FIGURE 3-10. AALM.CSL AND AALM.FOR SIMULATIONS OF BLOOD PB**
 2 **CONCENTRATIONS IN INDIVIDUALS WHO RECEIVED INGESTION DOSES OF [²⁰²PB]-**
 3 **NITRATE ([RABINOWITZ ET AL., 1976](#)).**

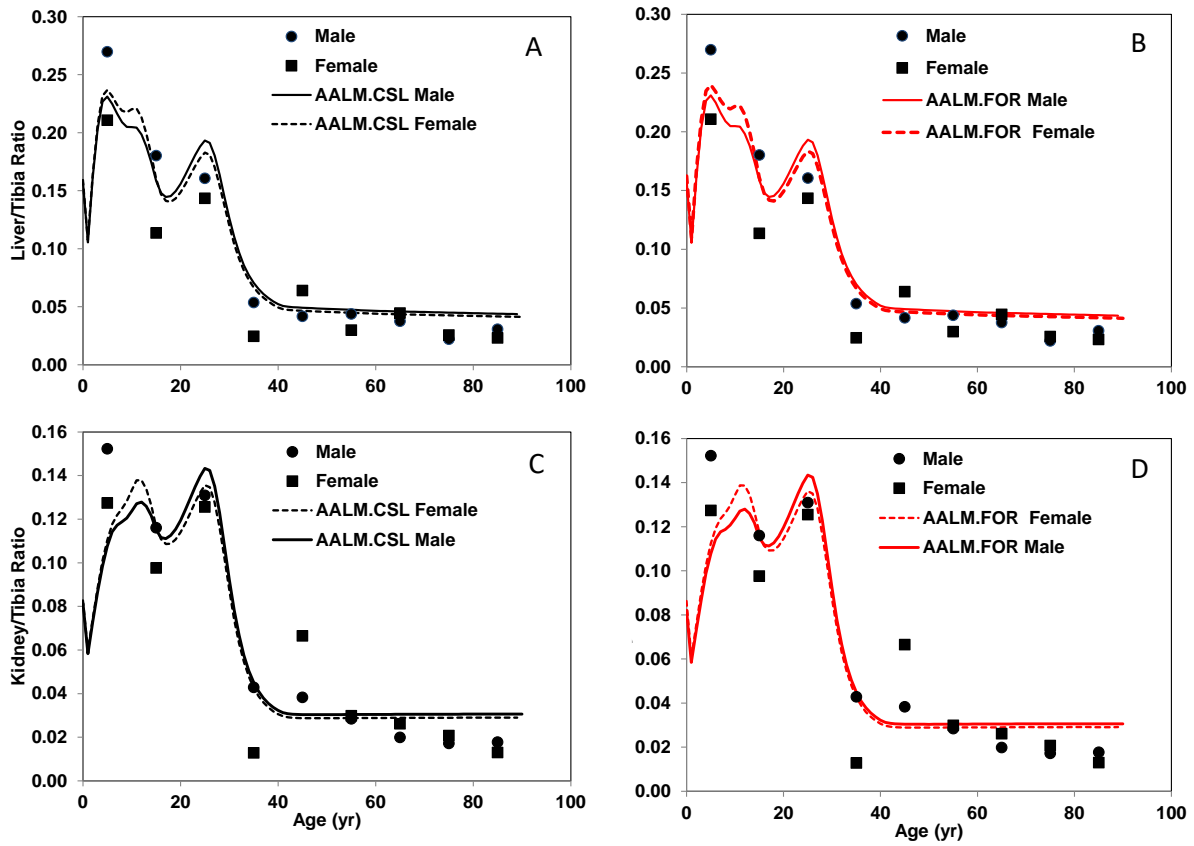


4

5 Subject A received 204 µg/day for 104 days, Subject B received 185 µg/day for 124 days, Subject D
 6 received 105 µg/day for 83 days, and Subject E received 99 µg/day for on days 1–8 and days 42–51.
 7 Estimated absorption fractions were 8.5% for Subject A, 6.5% for Subject B, 10.9% for Subject D and
 8 9.1% for Subject E.

9

1 **FIGURE 3-11. AALM AND LFM SIMULATIONS OF POST-MORTEM SOFT TISSUE/TIBIA**
2 **PB RATIOS.**

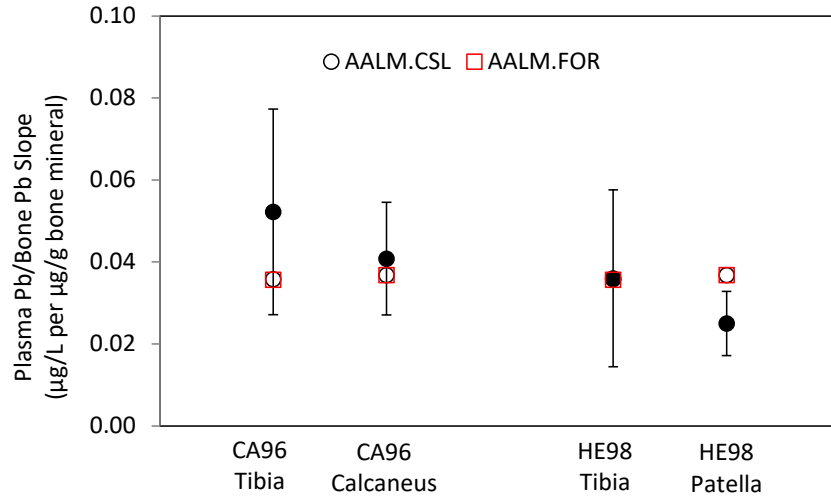


3

4 Shown are means for 9 (liver, A and B) and 8 (kidney, C and D) individual predicted from the
5 AALM.CSL (A, C) or AALM.FOR (B, D), based on [Barry \(1975\)](#).

6

1 **FIGURE 3-12. AALM.CSL AND AALM.FOR SIMULATIONS OF PLASMA PB/BONE PB**
2 **RATIO IN ADULTS.**

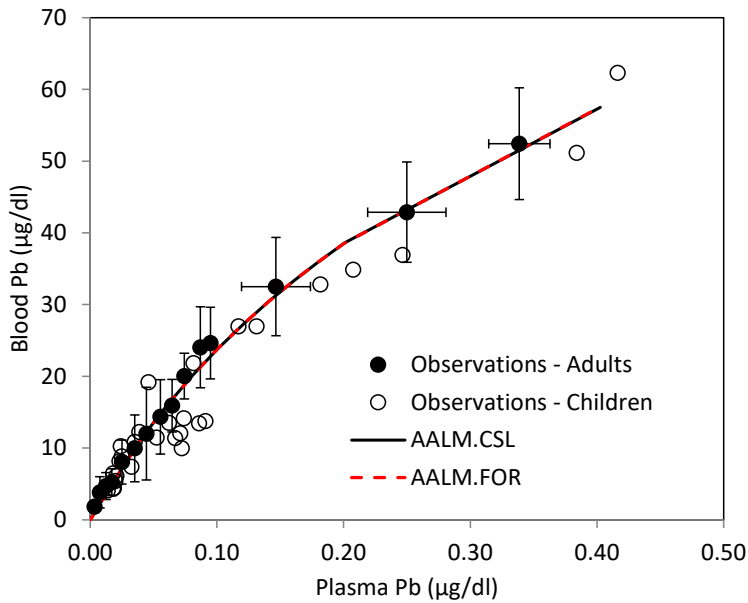


3

4 Observations are means and 95% CIs, based on CA96, [Coke et al. \(1996\)](#); HE98, [Hernandez-Avila et al.](#)
5 [\(1998\)](#).

6

1 **FIGURE 3-13. SIMULATION OF WHOLE BLOOD AND PLASMA PB IN ADULTS.**

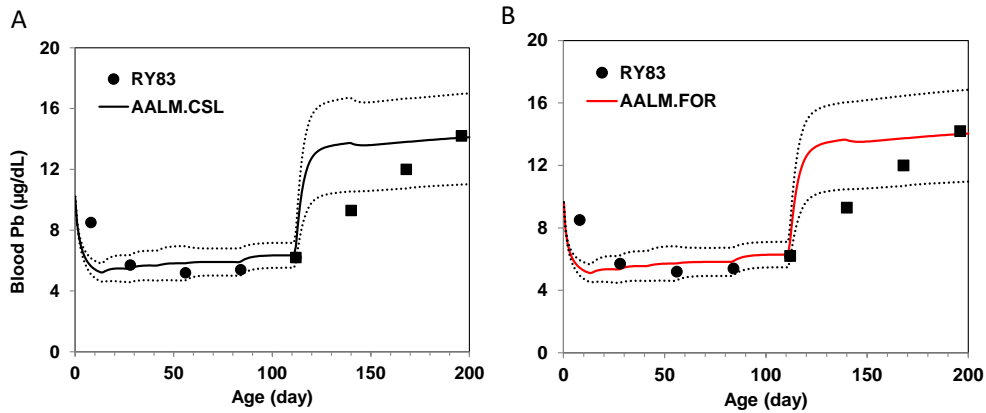


2

3 Combined data for adult individuals (N = 406) from all studies were quantized into ranges of plasma Pb;
 4 shown are mean and standard deviations for ranges ([Smith et al., 2002](#); [Bergdahl et al., 1999](#); [Bergdahl et](#)
 5 [al., 1998](#); [Hernandez-Avila et al., 1998](#); [Bergdahl et al., 1997](#); [Schutz et al., 1996](#)). The r^2 for predictions
 6 and observations was 0.99. Data for children (n = 29) are overlaid on the adult data ([Bergdahl et al.,](#)
 7 [1999](#)).

8

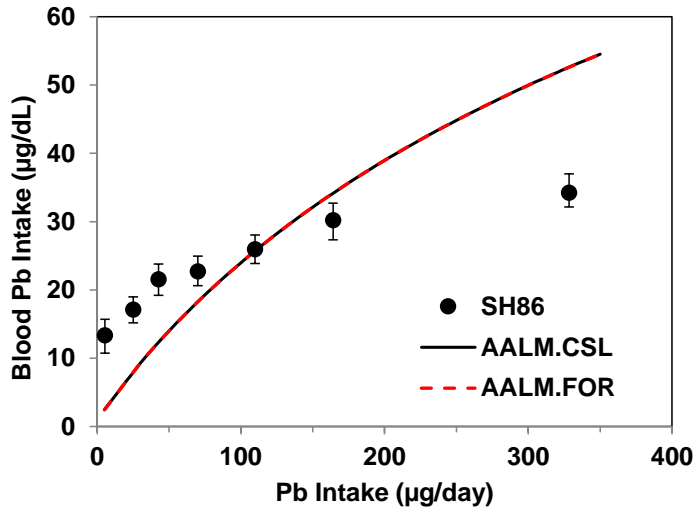
1 **FIGURE 3-14. AALM.CSL (A) AND AALM.FOR (B) SIMULATIONS OF FORMULA-FED**
2 **INFANTS FROM (RYU ET AL., 1983).**



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Data (RY83) are from infants fed formula from cartons (12–20 µg/day) from age 8–196 days (closed circles, n=25) and then a subset (closed squares, n = 7) that were switched to formula from cans at age 112 days (60–63 µg/day). Solid lines show simulations of the mean Pb intakes; dotted lines show simulations of ±1 SD of mean intakes.

1 **FIGURE 3-15. AALM.CSL AND AALM.FOR SIMULATIONS OF FORMULA-FED INFANTS.**

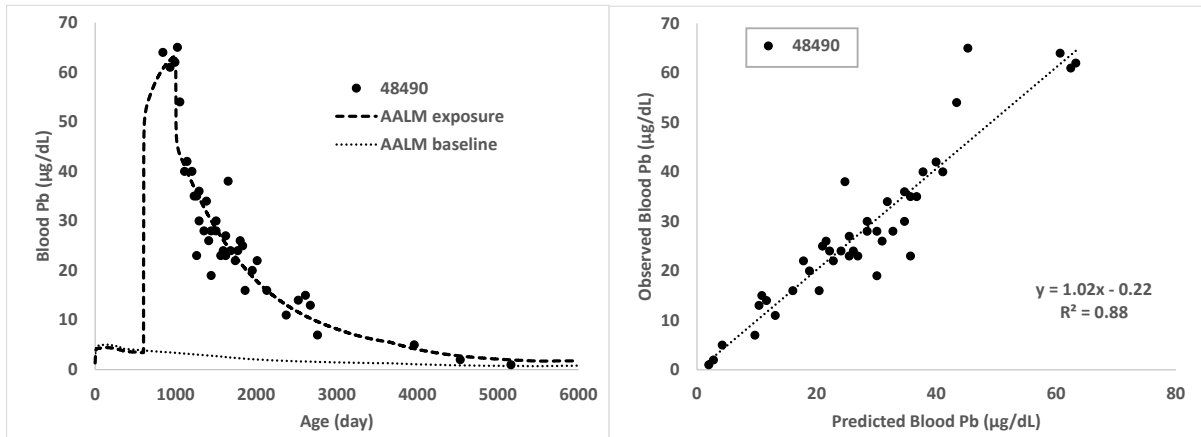


2

3 Data are for 131 infants, age 91 days from [Sherlock and Quinn \(1986\)](#).

4

1 **FIGURE 3-16. AALM SIMULATION OF SUBJECT 48490 (FEMALE).**

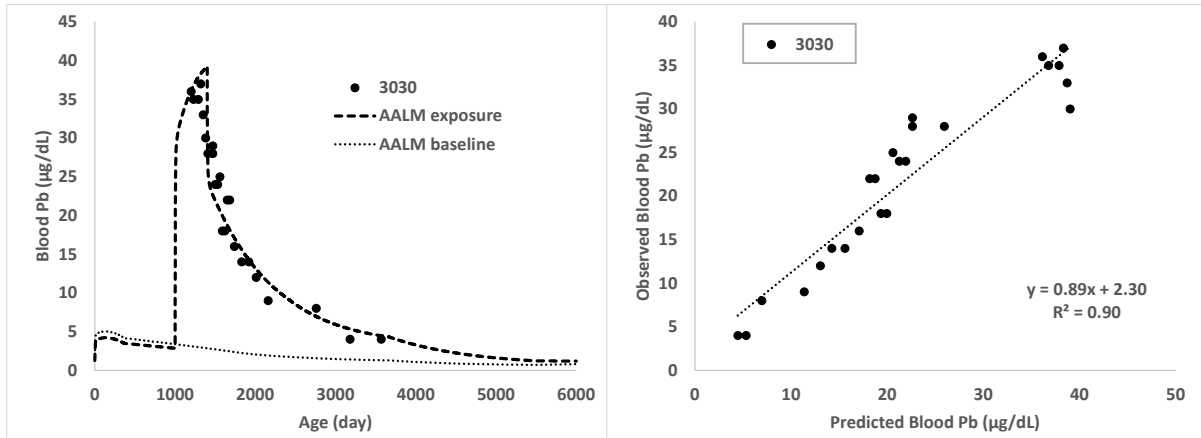


2

3 Baseline (15 µg/day) was set to achieve a 6-month BLL of approximately 5 µg/dL, consistent with data
4 for other subjects. Exposure to 22,000 ppm dust Pb (RBA = 0.6) began on age day 600 and continued to
5 age day 1000. Data provided by ATSDR.

6

1 **FIGURE 3-17. AALM SIMULATION OF SUBJECT 3030 (MALE).**

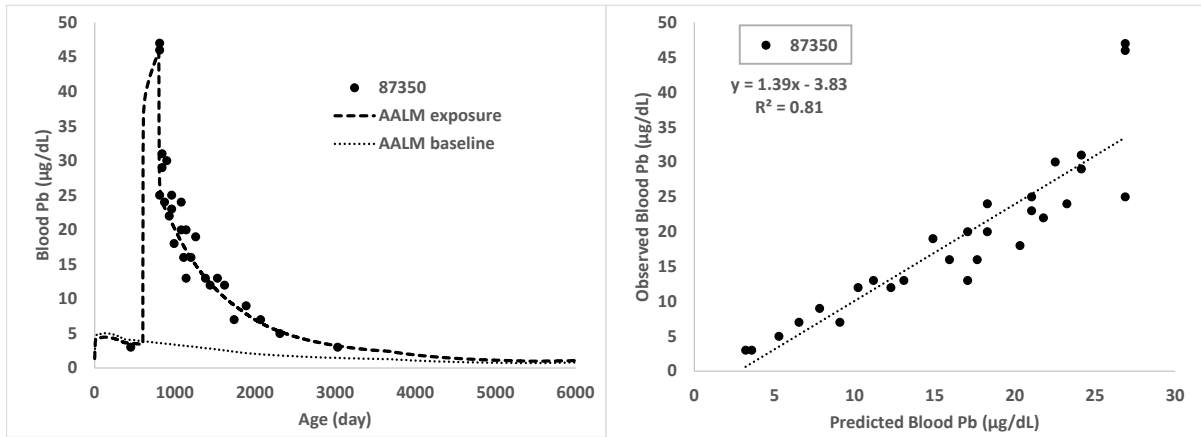


2

3 Baseline (15 µg/day) was set to achieve a 6-month BLL of approximately 5 µg/dL, consistent with data
4 for other subjects. Exposure to 11,000 ppm dust Pb (RBA = 0.6) began on age day 1000 and continued to
5 age day 1400. Data provided by ATSDR.

6

1 **FIGURE 3-18. AALM SIMULATION OF SUBJECT 87350 (FEMALE).**

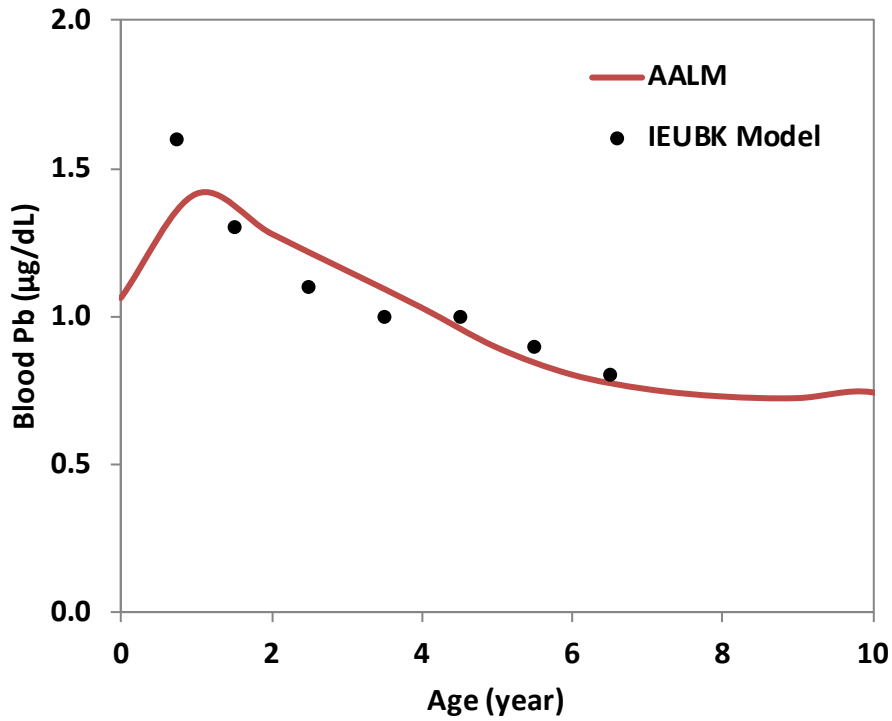


2

3 Baseline (15 µg/day) was set to achieve a 6-month BLL of approximately 5 µg/dL, consistent with data
4 for other subjects. Exposure to 13,000 ppm dust Pb (RBA = 0.6) began on age day 600 and continued to
5 age day 800. Data provided by ATSDR.

6

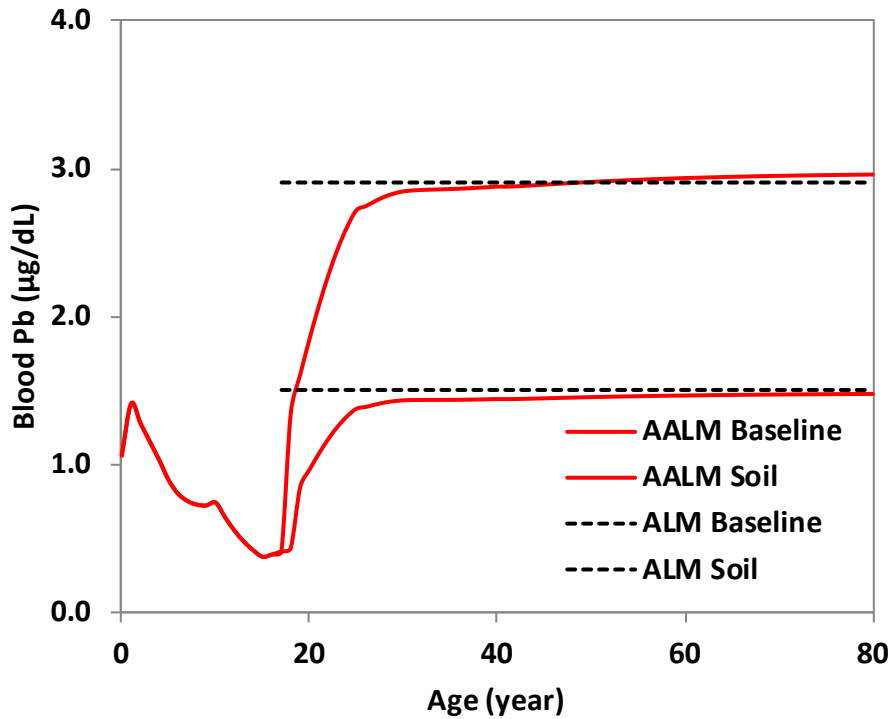
1 **FIGURE 3-19. COMPARISON OF BLOOD PB PREDICTIONS OF AALM AND IEUBK**
2 **MODEL.**



3
4
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7

Maternal blood Pb was assumed to be 1 µg/dL. Exposure was to Pb in soil (RBA = 0.6) at a constant intake (10 µg/day). Absorption parameters were: AF1 C1=0.40 (AF1=0.39 at birth), AF1 C2=0.28 (AF1=0.12 at age ≥10 years). The average AF1 for age 0-7 years was 0.26.

1 **FIGURE 3-20. COMPARISON OF BLOOD Pb PREDICTIONS OF AALM AND ALM.**



2

3 AALM input parameters:

4 OTHER Baseline Pb=6 µg/day

5 OTHER Pulse Pb=12 µg/day

6 OTHER Pulse start= 6205 day (17 years)

7 OTHER RBA = 1

8 SOIL baseline Pn = 0 µg/day

9 SOIL Pulse Pb=600 µg/g (1000*219/365)

10 SOIL IRs = 0.05 at age ≥15 years

11 SOIL RBA = 0.6

12 AF1 C1=0.40 (AF1=0.39 at birth), AF1 C2=0.28 (AF1=0.12 at age ≥10 years)

13

14

1 **CHAPTER 4. EVALUATION AND DEVELOPMENT OF AALM.CLS**

2 **4.1. INTRODUCTION**

3 This chapter summarizes developments in the AALM that were initiated in early 2013 by EPA's Office of
4 Research and Development (ORD)/National Center for Environmental Assessment (NCEA). Six major
5 objectives have been realized in this most recent effort, and are described in this report including: (1)
6 recoding of the AALM biokinetics models from Visual C to the more robust kinetic model development
7 software, Advance Continuous Simulation Language, ACSL[®] (acslX); (2) addition of a user friendly,
8 flexible, and transparent exposure model interface implemented in Microsoft Excel[®](Excel); (3)
9 capability to run either the Leggett (AALM-LG) or O'Flaherty (AALM-OF) biokinetics models from the
10 same exposure model interface, and with the same exposure and absorption conditions; (4) a more
11 realistic RT model representation in both the Leggett and O'Flaherty biokinetics models compared with
12 earlier versions; (5) accessible and transparent output for easy comparison of the predictions from the
13 Leggett and O'Flaherty biokinetics models; and (6) an evaluation and optimization of the Leggett and
14 O'Flaherty biokinetics models against a common set of observations that lead to the version of the
15 AALM in acslX (AALM.CLS v.4.2, July 2015).

16 Section 4.2 provides a brief overview the functional structure of AALM.CLS. Section 4.3 compares the
17 structures of the two biokinetics models contained in the AALM.CLS (AALM-LG, AALM-OF). Section
18 4.4 describes the outcomes of model runs that compare predictions of blood and tissue Pb levels obtained
19 from the AALM-LG and AALM-OF. Section 4.5 presents the results of sensitivity analyses coefficients
20 (SSCs) conducted from the AALM.CLS biokinetics models. Section 4.6 presents the conclusions from
21 the model comparison. Section 4.7 presents results of an empirical evaluation and optimization of the
22 AALM-LG and AALM-OF. Section 4.8 provides conclusions and discusses implications of performance
23 of the optimized models for model applications. Section 4.9 discusses differences between the
24 AALM.CLS model output and the IEUBK model for similar exposures, identifies AALM model
25 parameter changes that resolve the differences, and provides a rationale for changes in the parameter
26 values. Section 4.10 outlines the next steps to be taken, and the data needed to further develop and
27 evaluate the AALM.CLS.

28 **4.2. OVERVIEW OF AALM.CLS STRUCTURE**

29 The AALM predicts blood and tissue Pb masses (μg) and concentrations ($\mu\text{g/g}$) resulting from exposures
30 to Pb in air, drinking water, surface dust, food, or miscellaneous Pb ingestion pathways. The AALM
31 exposure module allows the user to simulate multi-pathway exposures that are constant or that vary in
32 time increments as small as one day; and that occur at any age from birth to 90 years. The user can select
33 to run a Pb biokinetics simulation based on either the Leggett (AALM-LG) or O'Flaherty (AALM-OF)
34 biokinetics models. The ICRP Human Respiratory Tract Model ([HRTM; ICRP, 1994](#)) deposition and
35 absorption parameters are used in both the AALM-LG and AALM-OF. The user can select
36 gastrointestinal absorption fractions for any age values as well as values for relative bioavailability (RBA)
37 of Pb from all ingestion pathways.

38 The AALM software architecture consists of three components: (1) a macro-enabled Excel workbook
39 (INPUT&OUTPUT.xlsm) that implements the exposure model and provides user access to all exposure
40 and biokinetics parameters in the AALM; (2) an acslX program that implements a Leggett-based

1 biokinetics model (AALM-LG.csl); and (3) an acsIX program that implements an O'Flaherty-based
2 biokinetics model (AALM-OF.csl).

3 The data flow for AALM simulations is shown in Figure 4-1. The AALM simulation is implemented in
4 acsIX with AALM_LG.csl (or AALM_OF.csl). Input parameter values are selected by the user in a
5 macro-enabled INPUT&OUTPUT Excel file (.xslm). Macros in the INPUT&OUTPUT Excel file pass the
6 input parameter values to a comma-delimited (CSV) text file (INPUT.DAT). Data in INPUT.DAT are
7 imported into the AALM acsIX program with acsIX m-file scripts. Output variables from the simulation
8 are passed from acsIX to a CSV file (OUTPUT.DAT) and are read into the INPUT&OUTPUT Excel file
9 with Excel macros.

10 AALM inputs and outputs are controlled and recorded in the *INPUT&OUTPUT.xslm* workbook. This
11 workbook has several functions: (1) allows setting of input parameter values for AALM simulations; (2)
12 macros in this workbook are used to pass data to and from acsIX; (3) allows plotting of AALM output
13 data; and (4) provides a complete record of input values and results of each AALM simulation.

14 Worksheets in *INPUT&OUTPUT.xslm* allow the user to set exposure scenarios for Pb in air (*Air*), surface
15 dust, (*Dust*), drinking water (*Water*), food (*Food*) and/or other ingestion intakes (*Other*). Exposures can
16 be discrete (i.e., a series of exposures at selected ages), and/or pulsed in a repeating frequency (e.g., 2
17 days/week for 3 months/year, for a selected age range). The AALM uses inputs from all exposure media
18 when it creates biokinetics simulations. This allows construction of complex multi-pathway exposure
19 scenarios having varying temporal patterns. Worksheets in *INPUT&OUTPUT.xslm* also allow the user to
20 set values for parameters that control Pb absorption and relative bioavailability in each medium (*RBA*),
21 and biokinetics (*Lung*, *Systemic*, *Sex*). All settings are recorded in the *INPUT&OUTPUT.xslm* workbook
22 and can be recalled to re-run the simulation.

23 The two biokinetics models in the AALM have been modified from the originally reported [Leggett \(1993\)](#)
24 and [O'Flaherty \(1995, 1993\)](#) models. The important modifications include: (1) removal of all exposure
25 components (moved to the Excel implementation); (2) implementation of a simplified version of the
26 ICRP HRTM ([ICRP, 1994](#)) in both biokinetics models; (3) implementation of the O'Flaherty model
27 growth algorithms in both biokinetics models to enable output of Pb concentrations in tissues in both
28 models, and to unify blood and tissue volumes; and (4) implementation of relative bioavailability factors
29 for ingested Pb from each exposure medium.

30 **4.3. COMPARISON OF STRUCTURES OF AALM-LG AND AALM-OF BIODYNAMICS** 31 **MODELS**

32 The AALM has two systemic biokinetics modules, one that is based on the [Leggett \(1993\)](#) model
33 (AALM-LG) and the other based on the [O'Flaherty \(1995, 1993\)](#) model (AALM-OF). Figures 4-2 and 4-3
34 show the structures of both models. Table 4-1 summarizes some of the major differences between the two
35 modules. The most important difference is the way each model simulates Pb kinetics in bone. Both
36 models represent kinetics of Pb in bone that are influenced by changes in the rates of bone turnover (bone
37 formation and resorption). In general, the major features of bone Pb kinetics in both models are as
38 follows: (1) relatively rapid transfers of Pb between plasma and bone forming surfaces; (2) increased
39 bone Pb uptake during periods of bone growth; (3) incorporation of Pb into bone matrix and release of Pb
40 from bone matrix during bone resorption; (4) maturation of bone associated with lower rates of bone
41 turnover and related decreased mobility of Pb in bone matrix; and (5) more rapid turnover of trabecular

1 bone Pb, relative to mature cortical bone. However, these processes are parameterized very differently in
2 the two models.

3 AALM-LG simulates bone as a multi (6)-compartment system (see Figure 4-4) consisting of 3 cortical
4 and 3 trabecular compartments that are distinguished by different Pb transfer rates: (1) relatively rapid
5 exchange of Pb between diffusible plasma and surfaces of cortical and trabecular bone; (2) slower
6 exchange of Pb at bone surfaces with an exchangeable Pb pool in bone volume; and (3) slow transfer of a
7 portion of Pb in bone volume to a non-exchangeable pool that is released from bone to diffusible plasma
8 only when bone is resorbed. Bone growth and maturation are simulated by age-dependent adjustments in
9 rate coefficients for Pb transfers from plasma-to-bone surfaces, and from bone matrix to plasma. This
10 approach simulates outcomes of the bone formation and resorption with bone Pb kinetics parameters,
11 rather than simulating the underlying physiology of bone formation and resorption directly with
12 parameters that govern formation and resorption.

13 AALM-OF simulates bone formation, resorption, and maturation of bone explicitly, and links these
14 processes to uptake and release of Pb from bone (see Figure 4-5). In AALM-OF, bone turnover in cortical
15 and trabecular bone is simulated with parameters that govern age-dependent bone formation and
16 resorption of bone. Two phases of bone turnover are simulated. In juvenile bone, formation and resorption
17 rates in cortical and trabecular bone are relatively high (high bone turnover) and formation dominates,
18 resulting in bone growth, which ceases at age 25 years. In mature bone, formation and resorption rates are
19 slower and bone formation rate equals resorption rate, resulting in remodeling, but no net growth of bone.
20 Transfers of Pb into and out of trabecular bone are governed by age-dependent rates of bone formation
21 and resorption, respectively. Cortical bone is assumed to consist of two regions: (1) metabolically active
22 cortical bone in which Pb transfers are governed solely by rates of bone formation and resorption; and
23 (2) mature cortical bone in which Pb undergoes exchange with bone calcium. The later process is
24 simulated as bidirectional radial diffusion of Pb in between eight concentric shells of cortical bone.

25 The approach to modeling bone in AALM-OF (i.e., bone Pb kinetics as a function of bone physiological
26 parameters) offers two major advantages: (1) inclusion of parameters that control bone physiology (e.g.,
27 growth, volume, maturation) supports simulation of changes to bone mineral metabolism that might affect
28 bone production, growth, or maturation (e.g., disease, nutrition, menopause, weightlessness), and
29 predictions of the effects that these changes might have on bone Pb kinetics. An analogous simulation in
30 the AALM-LG requires direct knowledge (or assumptions) of the effects of these changes on bone Pb
31 transfer coefficients; and (2) advances in the knowledge of bone physiology (e.g., metabolism, growth,
32 resorption, disease) and of bone kinetics for other elements (e.g., calcium, strontium) can be incorporated
33 into the model to improve the parameterization and parameter values of the model, and its capability to
34 simulate and predict bone growth, volume, and maturation. In contrast, specialized studies for all the
35 different age related scenarios would be needed to improve values for the less physiologically
36 representation of bone Pb kinetics in the AALM-LG model based on compartment transfer rates that
37 change with age.

38 **4.4. COMPARISON OF AALM-LG AND AALM-OF PREDICTIONS OF BLOOD AND** 39 **TISSUE PB**

40 Differences in the structures of the Leggett and O'Flaherty biokinetics models would be expected to result
41 in different predictions of blood and tissue Pb levels for similar Pb exposure assumptions ([Maddaloni et](#)
42 [al., 2005](#)). The revised AALM provides a convenient platform for comparing the models, because it

1 allows both to be run using the same exposure and absorption settings. Two types of comparisons were
2 made of AALM-LG and AALM-OF: (1) age profiles for blood and tissue Pb levels following an exposure
3 to a constant Pb intake ($\mu\text{g}/\text{day}$) were simulated and compared; and (2) dose-response relationships
4 between ingested dose and Pb levels were compared by simulating a series of increasing Pb intakes. In
5 either type of simulation, parameters that control Pb absorption and growth were set to the same values
6 (defaults for AALM-OF), so that differences in blood and tissue Pb levels could be attributed entirely to
7 differences in the simulation of systemic (post-absorption) biokinetics.

8 **4.4.1. Comparison of Model Predictions for Constant Pb Intake**

9 Figures 4-6 thru 4-9 show results of the simulations for a constant ingestion of $5 \mu\text{g Pb}/\text{day}$ beginning at
10 birth and extending to age 30 years. This exposure results in predicted blood Pb concentrations less than 5
11 $\mu\text{g}/\text{dL}$, which is well below the concentration at which saturation of uptake into RBCs significantly
12 affects blood Pb levels. Figure 4-6 shows the age profiles for selected output variables ($\mu\text{g Pb}$ in blood,
13 bone, soft tissue and total body). Figure 4-7 shows the differences expressed relative to the AALM-LG
14 (arbitrarily selected as the reference for presentation of the results). A negative value in Figure 4-7
15 indicates that the prediction from AALM-OF is less than that from AALM-LG. For example, -0.65 in
16 Figure 4-7 indicates that the AALM-OF blood Pb prediction is less than the AALM-LG prediction, and
17 the magnitude of the difference is 65% relative to the AALM-LG value. Figure 4-8 compares predicted
18 cumulative urinary and fecal Pb excretion. Figure 4-9 compares elimination rates following cessation of
19 exposure.

20 Several differences between the models are evident from these comparisons.

- 21 • AALM-OF predicts lower blood Pb levels prior to age 10 years (64–65%), after which, the
22 models begin to converge on similar blood Pb levels, with adult predictions from the AALM-OF
23 exceeding AALM-LG by approximately 20%.
- 24 • AALM-OF predicts lower bone Pb levels in children prior to age 10 years (63–68%), after which,
25 the models begin to converge on similar bone Pb levels, with adult predictions from the AALM-
26 OF exceeding AALM-LG by approximately 18%.
- 27 • AALM-OF predicts lower soft tissue Pb levels (all tissues combined, excluding bone) at all ages
28 (59–92%).
- 29 • Both models predict similar accumulation of Pb over the lifetime, reflected in similar total body
30 burdens (agreement is within 10%).
- 31 • With cessation of exposure, both models predict rapid declines of Pb in blood ($t_{1/2} = 30\text{--}50$ days)
32 and soft tissue, with a slower decline in bone Pb ($t_{1/2} 10\text{--}20$ years).
- 33 • Both models predict multiple rates of decline in blood Pb. In adults, the half-time for the first
34 50 days following cessation of exposure is approximately 36 days in AALM-LG and 46 days in
35 AALM-OF. The half-time for the period 5–20 years following cessation of exposure is 12.7 years
36 in AALM-LG, and 10.9 years in AALM-OF. The slow phase results from transfer of bone Pb to
37 blood.

- 1 • Both models predict a more rapid decline in bone Pb in children compared to adults following
2 cessation of exposure. The two models predicted similar half-times for bone Pb elimination in
3 children ($t_{1/2} = 3.00$ [AALM-LG], 2.24 years [AALM-OF]).
- 4 • Although both models predict slower elimination of Pb from bone in adults, AALM-OF predicts
5 a more rapid decline ($t_{1/2} = 12.6$ year) than AALM-LG ($t_{1/2} = 19.7$ year).
- 6 • AALM-OF predicts a higher rate of urinary excretion of Pb compared to AALM-LG. Fecal
7 excretion is identical in both models because it is dominated by unabsorbed Pb and
8 gastrointestinal absorption parameters were set to the same values in both models for the
9 comparison simulations.

10 Amounts of Pb in tissues are converted to Pb concentrations in both models by dividing Pb masses by
11 age-dependent values for tissue weights. The latter are predicted in both models from the body growth
12 and tissue growth models developed by [O'Flaherty \(1995\)](#). The blood and bone Pb concentrations
13 predicted for an exposure to 5 µg Pb/day are shown in Figure 4-10. Differences in the model predictions
14 of tissue Pb masses are reflected in the tissue Pb concentrations. The magnitudes of the differences
15 between models (i.e., ratio AALM-LG/AALM-OF) are the same for Pb masses and concentrations,
16 because both models use the same tissue growth algorithms, which predict the same tissue volumes and
17 weights.

18 **4.4.2. Comparison of Predicted Dose-Response for Blood and Tissue Pb**

19 Although both AALM-LG and AALM-OF are mathematically linear models (i.e., all state variables are
20 defined with linear differential equations), they predict curvilinear dose-response relationships for blood
21 Pb resulting from a saturable capacity of red blood cells (RBC) to take up Pb. Dose-response relationships
22 predicted from AALM-LG and AALM-OF are shown in Figures 4-11 and 4-12, for children (age 5 years)
23 and adults (age 30 years), respectively. Although curvature of the dose-response relationship for blood
24 derives from saturation of uptake of Pb in RBCs, the two models use different computational approaches
25 to model the saturable uptake. AALM-LG simulates binding of Pb in red blood cells with rate coefficients
26 for transfer of Pb from plasma to RBCs (child and adult, $t_{1/2} = 0.0014$ days), and from RBCs to plasma
27 (child $t_{1/2} = 2.5$ days, adult $t_{1/2} = 5$ days). This results in a rapid uptake, slower release, and accumulation
28 of RBC Pb. The plasma-blood concentration ratio is governed, in part, by the ratio of these transfer
29 coefficients (plasma to RBC/RBC to plasma). The higher ratio in children (i.e., exit rate is faster) results
30 in higher plasma-RBC concentration ratios in children. Above a non-linear, threshold Pb concentration in
31 red blood cells (60 µg/L), the rate constant for transfer into RBCs declines with increasing intracellular
32 concentration, approaching zero (no uptake) at a saturating concentration of 350 µg/dL RBC (see
33 Equation 4-1).

$$34 \quad TOORBC = TORBC \cdot \left[1 - \left(\frac{RBCCONC - RBCNL}{SATRAT - RBCNL}\right)\right]^{1.5} \quad \text{Eq. (4-1)}$$

35 where $TOORBC$ is the deposition fraction from diffusible plasma to red blood cells; $TORBC$ the age-
36 scaled deposition fraction from diffusible plasma to red blood cells below non-linear threshold;
37 $RBCCONC$ the red blood cell Pb concentration (µg/dL RBC volume); $RBCNL$ the non-linear uptake
38 kinetics threshold concentration (µg Pb/dL RBC volume); and $SATRAT$ the maximum capacity of the red
39 blood cell compartment (µg Pb/dL RBC volume).

1 AALM-OF simulates a binding equilibrium (rather than kinetics) in which Pb in plasma achieves
 2 instantaneous equilibrium with unbound Pb in RBCs, which is in equilibrium with bound Pb. Binding
 3 parameters include a maximum capacity (270 µg Pb/dL RBC) and half-saturation concentration (0.75
 4 µg/dL RBC), with the relationship represented as follows (see Equation 4-2):

$$5 \quad CB = (1 - HCT) \cdot CP + HCT \cdot CP \cdot \left\{ G + \frac{BIND}{KBIND + CP} \right\} \quad \text{Eq. (4-2)}$$

6 where *CB* is the blood Pb concentration (µg/dL), *CP* the plasma Pb concentration (µg/dL); *HCT* is the
 7 hematocrit; *G* the ratio of unbound RBC Pb to plasma Pb; *BIND* the maximum capacity of RBC binding
 8 (µg/dL); and *KBIND* the half-saturation coefficient (µg/dL). One advantage of this approach is that the
 9 parameters *BIND* and *KBIND* have a direct empirical basis, as they have been estimated from data on Pb
 10 concentrations in plasma and RBCs (e.g., [Bergdahl et al., 1998](#); [O'Flaherty, 1993](#)). However, a
 11 disadvantage is that it represents plasma-RBC kinetics as essentially being instantaneous; whereas,
 12 observations made following injection of radiolead suggest that kinetics may be slower and more complex
 13 [see [Leggett \(1993\)](#) for discussion of these observations].

14 The different parameterizations of RBC saturation are evident in the relationships between plasma and
 15 blood Pb predicted from the two models. In both models, the plasma-blood concentration ratio increases
 16 with increasing blood Pb concentration, as the RBC approaches saturation. In AALM-OF, the plasma-
 17 blood Pb ratio below saturation remains nearly constant with age (0.007); whereas, in AALM-LG, the
 18 plasma:blood ratios are higher in children compared to adults. AALM-LG predicts a plasma-blood ratio
 19 that declines from 0.01 at age 1 year to 0.003 at ages beyond 10 years (below saturation).

20 Both models predict linear dose-response relationships for bone Pb, and for all other tissue Pb. The
 21 predicted dose-response relationships for bone are more similar in adults, whereas, AALM-LG predicts a
 22 steeper dose-response relationship for bone in children. The steeper dose-response relationship for bone
 23 Pb in children occurs in AALM-LG even though the elimination rates from bone are similar in both
 24 models. This suggests that the differences between model results for bone Pb is related to the rates of
 25 deposition of Pb in bone, rather than to differences in rates of bone Pb elimination.

26 **4.5. SENSITIVITY ANALYSIS OF AALM-LG AND AALM-OF**

27 Relative to the AALM-LG, AALM-OF predicts lower amounts and concentrations of Pb in blood in
 28 children, higher amounts and concentrations of Pb in blood in adults, and lower amounts and
 29 concentrations of Pb in soft tissues in at all ages. Numerous individual parameters or combinations of
 30 parameters could contribute to these differences. AALM-LG has 39 parameters and AALM-OF has
 31 35 parameters that collectively determine the biokinetics of absorbed Pb in each model to varying
 32 degrees. These parameters and their nominal values are presented in Tables 4-2 (AALM-LG) and 4-3
 33 (AALM-OF). A univariate sensitivity analysis was conducted to determine the effect of each parameter
 34 on predictions of Pb in blood, bone, and soft tissues.¹ The sensitivity analysis consisted of running each
 35 model before and after perturbing values for single parameters by a factor of 0.01, in the up and down

¹ This approach to sensitivity analysis does not consider potential interactions between parameters. Sensitivity coefficients measured in univariate analyses may be larger or smaller than SSCs measured in multivariate analyses (i.e., when multiple parameters are varied simultaneously).

1 directions. Parameter sensitivities were assessed by comparing standardized sensitivity coefficients (see
2 Equation 4-3):

$$3 \quad SSC = f'(x) = \frac{ABS[f(x + \Delta x) - f(x - \Delta)]}{2\Delta x} \cdot \frac{x}{f(x)} \quad \text{Eq. (4-3)}$$

4 where SSC is the standardized sensitivity coefficient; $f(x)$ the output variable (e.g., blood Pb) at parameter
5 value x ; and Δ the perturbation of x (e.g., 0.01 x). Values for SSC were determined for blood, bone, and
6 soft tissue Pb at ages selected to represent children (5 years) or adults (30 years).

7 **4.5.1. Sensitivity Analysis of AALM-LG**

8 $SSCs$ were derived for all input parameters to AALM-LG other than those that control Pb absorption or
9 growth. Separate sensitivity analyses were run to determine parameter sensitivity of the total amount of
10 Pb in blood, bone, liver, kidney, or other soft tissues, in children (age 5 years) and adults (age 30 years).
11 $SSCs$ are displayed in order of highest to smallest value for adults in Tables 4-4 thru 4-8. Larger values of
12 SSC indicate larger effects of the parameter on blood Pb. For example, blood Pb is most sensitive to the
13 value of the parameter $TEVF$, the deposition fraction for Pb transfer from diffusible plasma to the
14 extravascular fluid (see Table 4-4). The value 8.38 indicates that a 1% change in $TEVF$ results in an
15 8.38% change in blood Pb. Influential parameters have $SSCs$ that exceed 0.1 (>0.1% change in tissue Pb
16 per 1% change in the input parameter).

17 In the discussion that follows, input parameter values are expressed as their equivalent first-order transfer
18 rates (day^{-1}) shown in Table 4-2 and their corresponding approximate first-order half-times ($t_{1/2}$, day). In
19 AALM-LG, the central distribution compartment is diffusible plasma, which exchanges Pb with other
20 tissue compartments. Input parameters that control transfers of Pb from tissues to diffusible plasma are
21 expressed as first-order rates. Input parameters that control transfers from diffusible plasma to tissues are
22 expressed as deposition fractions. Deposition fractions represent the fractional apportionment of the total
23 outflow of Pb from diffusible plasma (Leggett, 1993). First-order rates are derived in the AALM-LG as
24 the product of deposition fraction and total outflow of Pb from the diffusible plasma compartment
25 ($RPLAS$, see Equation 4-4).

$$26 \quad REFV = TEFV \cdot RPLAS \quad \text{Eq. (4-4)}$$

27 where $REFV$ is the transfer rate from diffusible plasma to the extravascular fluid (day^{-1}); $TEFV$ the
28 deposition fraction for transfer to the extravascular fluid; and $RPLAS$ the total rate of transfer of Pb to all
29 tissues (day^{-1}). The nominal value for $RPLAS$ is 2000 day^{-1} . If the deposition fraction for $TEFV$ is 0.5, the
30 corresponding transfer rate for $TEFV$ is 1000 day^{-1} ($0.5 \times 2000 \text{ day}^{-1}$). Values for transfer rates
31 corresponding to deposition fractions are presented in Table 4-2, so that they can be directly compared to
32 the return transfer rates from tissue to diffusible plasma. The values for the corresponding depositions
33 fractions can be calculated from Equation 4-4.

34 **4.5.1.1. Influential Parameters Common to All Tissues**

35 Several parameters had relatively large influences ($SSC > 0.1$) across all or most of the tissues that were
36 included in the sensitivity analysis and dominate Pb biokinetics in the AALM-LG. These parameters are
37 $TEVF$, $TORBC$, $TOSOFO$, $TOLVRI$, $HITOBL$, and $TBONE$.

1 The parameter *TEVF* controls the rate of transfer of Pb from diffusible (non-bound) plasma to the
 2 extravascular space. The nominal value for the rate is 1000 day⁻¹ (*t*_{1/2} = 1.0 min) or approximately one
 3 half of the total transfer rate out of diffusible plasma to all tissues (2000 day⁻¹). The return rate to
 4 diffusible plasma is 333 day⁻¹ (*t*_{1/2} = 3.0 min). This results in a rapid exchange of Pb in diffusible plasma
 5 with the extravascular fluid, with an equilibrium ratio in which the extravascular fluid contains
 6 approximately 3 times the amount of Pb in diffusible plasma. The extravascular fluid serves as a rapid
 7 exchange reservoir that contributes to plasma Pb. Increasing or decreasing the value of *TEVF* increases or
 8 decreases, respectively, the amount of Pb in plasma and, thereby, blood Pb and the amount of Pb
 9 available for distribution to other tissues. The prominence of *TEVF* in the SSCs for all tissues may also
 10 result from its use in age-scaling of deposition fractions in the model. Deposition fractions for all tissues
 11 other than bone are scaled as function of *TEVF* and *TBONE* (the deposition fraction to bone surfaces) (see
 12 Equation 4-5).

$$13 \quad AGESCL = \frac{1-TEVF-TBONE(t)}{1-TEVF-TBONEL} \quad \text{Eq. (4-5)}$$

14 where *TBONEL* is the terminal value for *TBONE* on the last day of the simulation. The *AGESCL* variable
 15 adjusts the deposition fractions (and total outflow) from diffusible plasma to soft tissues so that their sum
 16 does not exceed total outflow (*TEFV*), while outflow to bone (*TBONE*) varies with age. As a result of its
 17 use to age scale deposition fractions, changes to *TEVF* affects Pb kinetics of RBC, kidney, liver, and other
 18 soft tissues.

19 The parameters *TORBC* and *RRBC* control the transfer rates of Pb into and out of RBCs, respectively.
 20 The nominal values in adults are 480 day⁻¹ (*t*_{1/2} = 2.1 min) and 0.139 day⁻¹ (*t*_{1/2} = 5.0 day). The equilibrium
 21 ratio (*TORBC/RRBC*) is approximately 3450, which results in accumulation of Pb in the RBC, relative to
 22 plasma, and Pb in red blood cells being the dominant contributor to blood Pb. Increasing the transfer rate
 23 into red blood cells (*TORBC*), without a change in the return rate (*RRBC*) increases blood Pb, whereas,
 24 increasing the transfer rate out of red blood cells (*RRBC*), makes more Pb available to the diffusible
 25 plasma compartment for distribution to other tissues, and decreases blood Pb.

26 AALM-LG has three soft tissue compartments, representing fast (*SOF0*), moderate (*SOF1*), and slow
 27 (*SOF2*) kinetic pools of Pb in soft tissues other than blood, kidney, or liver. The parameter *TOSOF0*
 28 controls the rate of transfer from diffusible plasma to the fast compartment. The nominal value in adults is
 29 178 day⁻¹ (*t*_{1/2} = 5.6 min) and the return rate is 2.08 day⁻¹ (*t*_{1/2} = 8.0 hours). Similar to the extravascular
 30 fluid, this soft tissue compartment provides an exchange reservoir to support plasma and blood Pb, as
 31 well as Pb available for distribution to other tissues.

32 The parameters *TOLVRI* and *HITOBL* control the transfer of Pb from diffusible plasma to liver and the
 33 return to plasma, respectively. Nominal values are 80 day⁻¹ (*t*_{1/2} = 12.5 min) for transfer to liver and 0.03
 34 day⁻¹ (*t*_{1/2} = 23.1 day) for return. Similar to the rapid exchange soft tissue compartment, this liver
 35 compartment provides a reservoir to support plasma and blood Pb.

36 The parameter *TBONE* controls the transfer rate from diffusible plasma to surface bone, the only pathway
 37 for entrance of Pb into bone where it can be sequestered into slower kinetic pools of bone volume. The
 38 nominal values are 89 day⁻¹ and 71 day⁻¹ (*t*_{1/2} = 11.2 min, 14.1 min) for trabecular and cortical bone,
 39 respectively. The return value from both types of bone is 0.5 day⁻¹ (14 day). More than 90% of the Pb
 40 body burden resides in bone, as a result, the transfer to bone affects Pb levels in all other tissues. The
 41 terminal value of *TBONE* (*TBONEL*) is also used in the age-scaling of deposition fractions to all tissues

1 other than bone (see Equation 4-5). This is reason why it shows up as an influential parameter across all
2 tissues.

3 **4.5.1.2. Sensitivity Analysis of AALM-LG Blood Pb Predictions**

4 AALM-LG SSCs for blood Pb (*ABLOOD*) are shown in Table 4-4. The most influential parameters on
5 blood Pb (SSCs > 0.1) are *TEFV*, *TORBC*, *TOSOF0*, *RRBC*, *TOLVRI*, *HITOBL*, and *TBONE*. These
6 parameters have SSCs > 0.1 across all tissues (see Section 4.5.1.1).

7 **4.5.1.3. Sensitivity Analysis of AALM-LG Bone Pb Predictions**

8 AALM-LG SSCs for bone Pb (*ABONE*) are shown in Table 4-5. The most influential parameters on bone
9 Pb (SSCs > 0.1) are *TEFV*, *TORBC*, *TBONE*, *TOSOF0*, *FLONG*, *RCS2DF*, *TOLVRI*, *HITOBL*, and
10 *RTS2DF*. The bone model in AALM-LG includes three sub-compartments for cortical and trabecular
11 bone that represent fast (surface bone), moderate (exchangeable), and slow (non-exchangeable) Pb pools
12 (see Figure 4-4). The slow compartment contains most (>90%) of the Pb in bone and, therefore, is the
13 major determinant of the amount of Pb in bone. The parameter *FLONG* controls the rate of transfer of Pb
14 from the moderate to the slow compartment. Lead enters the moderate and slow bone compartments from
15 surface bone, which is in direct exchange with plasma. The parameter *TBONE* controls the rate of transfer
16 of Pb to bone surfaces; nominal values are 89 day⁻¹ and 71 day⁻¹ ($t_{1/2} = 11.2$ min, 14.1 min) for trabecular
17 and cortical bone, respectively. The parameters *RCS2DF* and *RTS2DF* control the rate of return of Pb
18 from bone surface to plasma (0.5 day⁻¹, $t_{1/2} = 1.4$ day).

19 **4.5.1.4. Sensitivity Analysis of AALM-LG Liver Pb Predictions**

20 The most influential parameters on liver Pb (SSCs > 0.1) are *TEFV*, *TORBC*, *TOSOF0*, *TOLVRI*,
21 *HITOH2*, *RLVR2*, *HITOBL*, and *RLVRI* (see Table 4-6). The liver model in AALM-LG includes two
22 sub-compartments representing fast (H1) and slow (H2) pools. Lead in the fast compartment exchanges
23 with plasma and delivers Pb into the slow compartment and to bile. Transfer of Pb into the fast
24 compartments controlled by the parameter *TOLVRI* (80 day⁻¹, $t_{1/2} = 11.2$ min) and return to plasma is
25 controlled by *RLVRI* (0.0312 day⁻¹, $t_{1/2} = 22.2$ day). Transfer of Pb from the fast to the slow compartment
26 is controlled by *HITOH2* (0.00693 day⁻¹, $t_{1/2} = 100$ day) and transfer to bile is controlled by *HITOBL*
27 (0.0312day⁻¹, 22.2 day). Return of Pb to plasma is controlled by *RLVR2* (0.0019 day⁻¹, $t_{1/2} = 365$ day).

28 **4.5.1.5. Sensitivity Analysis of AALM-LG Kidney Pb Predictions**

29 The most influential parameters on kidney Pb (SSCs > 0.1) are *TEFV*, *TORBC*, *TOSOF0*, *RKDN2*,
30 *TOKDNI*, *TOKDN2*, *RKDN2*, *TOLVI*, and *HITOBL* (see Table 4-7). The kidney model in AALM-LG
31 includes two sub-compartments representing urinary route through the kidney (RK1) and a storage
32 compartment that exchanges with plasma (RK2) pools. Transfer of Pb into kidney is controlled by the
33 parameters *TOKDNI* (40 day⁻¹, $t_{1/2} = 25$ min) and *TOKDN2* (0.4 day⁻¹, $t_{1/2} = 1.7$ day). Return of Pb to
34 plasma is controlled by the parameter *RKDN2* (0.0019 day⁻¹, $t_{1/2} = 365$ day).

35 **4.5.1.6. Sensitivity Analysis of AALM-LG Other Soft Tissue Pb Predictions**

36 The most influential parameters on other soft tissue Pb (SSCs > 0.1) are *TEFV*, *TORBC*, *TOSOF0*,
37 *RSOF2*, *TOSOF2*, *TOLVRI*, *HITOBL*, *TOSOF1*, and *RSOF1* (see Table 4-8). AALM-LG has three soft
38 tissue compartments, representing fast (SOF0), moderate (SOF1), and slow (SOF2) kinetic pools of Pb in
39 soft tissues other than blood, kidney, or liver. Transfer into each compartment is controlled by parameters
40 *TOSOF0* (178 day⁻¹, $t_{1/2} = 5.6$ min), *TOSOF1* (10 day⁻¹, 1.7 hours), and *TOSOF2* (2 day⁻¹, $t_{1/2} = 8.3$

1 hours). Return of Pb to plasma is controlled by parameters *RSOF0* (2.08 day^{-1} , $t_{1/2} = 8.0$ hours), *RSOF1*
 2 (0.00416 day^{-1} , $t_{1/2} = 167$ day), and *RSOF2* (0.00038 day^{-1} , 1824 day).

3 **4.5.2. Sensitivity Analysis of AALM-OF**

4 SSCs were derived for all input parameters to AALM-OF other than those that control Pb absorption or
 5 growth. Separate sensitivity analyses were run to determine parameter sensitivity of the total amount of
 6 Pb in blood, bone, liver, kidney, or poorly perfused and well-perfused tissues, in children (age 5 years)
 7 and adults (age 30 years). Input parameter values for AALM-OF are presented in Table 4-3. This is a mix
 8 of parameters for Pb, and parameters that control bone formation and resorption rates that determine
 9 transfer of Pb in and out of deep bone. SSCs for each tissue are displayed in order from highest to
 10 smallest value for adults in Tables 4-9 thru 4-14.

11 **4.5.2.1. Influential Parameters Common to All Tissues**

12 Three parameters had large influences ($\text{SSC} > 0.1$) across all, or most, of the tissues that were included in
 13 the sensitivity analysis, and dominate Pb kinetics in the AALM-OF. These parameters are *C1*, *C2*, and
 14 *C3*. Urinary excretory clearance of Pb from plasma is simulated in AALM-OF as a function of glomerular
 15 filtration rate (GFR). The parameters *C1*, *C2*, and *C3* are unitless parameters in the function that simulates
 16 GFR as a function of age. Changes to these parameters alter the rate of removal of Pb from plasma to
 17 urine and, thereby, the amount of Pb in blood and available for distribution to other tissues.

18 **4.5.2.2. Sensitivity Analysis of AALM-OF Blood Pb Predictions**

19 The most influential parameters on blood Pb ($\text{SSCs} > 0.1$) are *C1*, *C2*, *BIND*, *KBIND*, and *C3* (see Table
 20 4-9). Uptake of Pb into RBCs is simulated in AALM-OF as a binding equilibrium between plasma Pb and
 21 RBC Pb (see Section 2.2). The parameters *BIND* (2.7 mg/L) and *KBIND* (0.0075 mg/L) are the
 22 maximum binding capacity of the RBCs, and the half-saturation concentration of Pb for binding,
 23 respectively. Changing *BIND* or *KBIND* affects the amount of Pb sequestered in RBCs, and the amount
 24 of Pb available to the plasma compartment for distribution to other tissues. Increasing *BIND* increases
 25 RBC binding, and increases blood Pb. Increasing *KBIND* increases the plasma Pb concentration needed
 26 to achieve a given RBC Pb concentration, and decreases blood Pb.

27 **4.5.2.3. Sensitivity Analysis of AALM-OF Bone Pb Predictions**

28 The most influential parameters on bone Pb ($\text{SSCs} > 0.1$) are *C1*, *C2*, *R0*, *RAD8*, *EXPO*, and *C3* (see
 29 Table 4-10). The parameter *R0* controls the clearance of Pb from bone into the vascular sites in bone
 30 (canaliculi) where exchange with plasma occurs. The nominal value is $5\text{E-}7 \text{ cm}^3/\text{day}$. Increasing *R0*
 31 decreases bone Pb. The parameter *RAD8* is the radius of the deepest (eight of 8) diffusion shells in
 32 mature cortical bone. This parameter determines the diffusion volume ($2.14\text{E-}3 \text{ cm}$) and, thereby, the
 33 clearance of Pb from the deepest bone compartment. Increasing *RAD8* decreases bone Pb. The parameter
 34 *EXPO* is a unitless exponent constant in the function that simulates the age-dependency of the bone
 35 volume participating in adult remodeling. During adult remodeling, bone formation and resorption rates
 36 are slower than during child and adolescent growth periods. As a result, exchange of Pb between deep
 37 bone deposits and plasma is slower in mature bone than during growth.

38 **4.5.2.4. Sensitivity Analysis of AALM-OF Liver Pb Predictions**

39 The most influential parameters on liver Pb ($\text{SSCs} > 0.1$) are *C1*, *C2*, *PL*, and *C3* (see Table 4-11).
 40 Exchange of Pb between plasma and liver is simulated in AALM-OF as a flow-limited process

1 determined by the liver/plasma partition coefficient and blood flow to the liver. The parameter PL is the
2 liver/plasma partition coefficient ($PL = 50$). The nominal value is 50. Increasing PL increases liver Pb.

3 **4.5.2.5. Sensitivity Analysis of AALM-OF Kidney Pb Predictions**

4 The most influential parameters on kidney Pb ($SSCs > 0.1$) are $C1$, $C2$, PK , and $C3$ (see Table 4-12).
5 Similar to liver, exchange of Pb between plasma and kidney is simulated in AALM-OF as a flow-limited
6 process determined by the kidney/plasma partition coefficient ($PK = 50$) and blood flow to the kidney.
7 Increasing PK increases kidney Pb.

8 **4.5.2.6. Sensitivity Analysis of AALM-OF Poorly Perfused Tissue Pb Predictions**

9 The most influential parameters on poorly perfused tissue Pb ($SSCs > 0.1$) are $C1$, $C2$, PP , and $C3$ (see
10 Table 4-13). Exchange of Pb between plasma and poorly perfused tissue is simulated in AALM-OF as a
11 flow-limited process determined by the tissue/plasma partition coefficient ($PP = 2.0$) and blood flow to
12 the tissue. Increasing PP increases poorly perfused tissue Pb.

13 **4.5.2.7. Sensitivity Analysis of AALM-OF Well-Perfused Tissue Pb Predictions**

14 The most influential parameters on well-perfused tissue Pb ($SSCs > 0.1$) are $C1$, $C2$, PW , and $C3$ (see
15 Table 4-14). Exchange of Pb between plasma and well-perfused tissue is simulated in AALM-OF as a
16 flow-limited process determined by the tissue/plasma partition coefficient ($PW = 50$) and blood flow to
17 the tissue. Increasing PW increases well-perfused tissue Pb.

18 **4.6. CONCLUSIONS FROM MODEL COMPARISONS AND SENSITIVITY ANALYSES**

19 Table 4-15 lists the dominate parameters causing major differences between predictions from AALM-LG
20 and AALM-OF and corresponding parameter values that had the highest $SSCs$ for each prediction. Data
21 may exist for some of the significant parameters that would allow evaluation and/or optimization of
22 parameter values. AALM-OF parameters $C1$ and $C2$ control GFR, and thereby, urinary clearance of Pb
23 from plasma. Abundant data exist on rates and age (i.e., body size) dependence of glomerular filtration in
24 humans (e.g., [Peters, 2004](#); [Peters et al., 2000](#)). Data on urinary clearance of Pb in humans also exist that
25 may be useful for evaluating model predictions (e.g., [Diamond, 1992](#)).

26 AALM-OF parameters $BIND$ and $KBIND$ and AALM-LG parameters $TORBC$ and $RRBC$ control uptake
27 of Pb into RBCs and, thereby, influence plasma Pb and its distribution to tissues. These parameters can
28 be evaluated against data from studies in which levels of Pb in plasma and whole blood (and/or RBCs)
29 have been measured in humans with methods that ensure sampling of plasma Pb without contamination
30 with Pb from lysed red cells (e.g., [SRC, 2003](#)).

31 Direct empirical evaluation of AALM-OF and AALM-LG parameters that control bone Pb may not be
32 feasible because of lack of data to directly estimate parameter values. However, optimization of
33 influential parameters that control bone Pb levels and relationships between blood and bone Pb may be
34 feasible with data from long-term monitoring studies of blood and bone, where exposure to Pb was
35 abruptly changed (e.g., [retired Pb workers; see U.S. EPA, 2013](#)).

36 Similarly, direct empirical evaluation of AALM-OF tissue-plasma partition coefficients, and AALM-LG
37 transfer rates and deposition fractions that control Pb levels in liver, kidney, and other soft tissues may not
38 be feasible because of lack of data to directly estimate parameter values. However, it may be possible to

1 optimize these parameters against data from cadaver studies in which the distribution of Pb body burden
2 in bone and soft tissue has been measured.

3 **4.7. EVALUATION AND OPTIMIZATION OF THE AALM**

4 Although the sensitivity analyses described in Section 5.0 provide some insight regarding the parameters
5 that contribute to differences in predictions from the two models; a more important objective is to
6 determine what set of parameters provides the most accurate representation of observations of Pb kinetics
7 in humans. Extensive documentation of the development and calibration of the Leggett and O'Flaherty
8 models has been reported ([O'Flaherty, 2000](#); [O'Flaherty et al., 1998](#); [O'Flaherty, 1998, 1995](#); [Leggett,
9 1993](#); [O'Flaherty, 1993](#)). New data have become available since the development of the models ([U.S.
10 EPA, 2013](#)). Important objectives for further development of the AALM are: (1) collect and re-examine
11 all available data for utility in model evaluation, optimization, and validation; (2) conduct a
12 comprehensive evaluation of the models against a common set of data; (3) optimize influential parameters
13 identified in Section 5 that can be informed by the observation data sets; and (4) validate the model
14 against a set of observations not utilized in optimization of the models.

15 Searches for studies of the toxicokinetics of Pb in humans that provide data that might be useful for
16 estimated model parameter values were conducted. Three types of data were of particular interest:
17 (1) blood, tissue, or excreted Pb paired with measured Pb intakes and/or exposures; (2) temporal patterns
18 of blood, tissue, or excreted Pb following an abrupt change in Pb intake or exposure; and (3) paired data
19 for blood and tissues or excreted Pb (e.g., urine/blood or tissue/blood ratios). Based on the available data
20 retrieved and processed from the searches as well as considerations of the results of comparisons of the
21 two models, a stepwise optimization approach was developed, in which specific outputs of the models
22 were evaluated against observations in humans, and key parameters were optimized to achieve agreement
23 with the observations (see Table 4-16).

24 Optimization was achieved using maximum likelihood (MLE) algorithms available in acslX (e.g., Nelder
25 Mead) or if this was not possible, by visual inspection. Optimizations were evaluated by inspection of
26 residuals (Equation 4-6) and the r^2 for the least-squares linear regression of observed and predicted
27 values.

$$28 \quad \text{Residual} = \frac{\text{Predicted} - \text{Observed}}{\text{Standard Deviation of Mean}} \quad \text{Eq. (4-6)}$$

29 The optimization objectives were residuals $\leq \pm 2$ and $r^2 > 0.70$.

30 Most pertinent to the AALM.FOR model are the changes made to the [Leggett \(1993\)](#) model to create the
31 AALM-LG model, based on the evaluations described below. These changes are summarized in Table 4-
32 22.

33 **4.7.1. Unification of Simulation of GI Absorption and Growth**

34 A goal of the optimization was to determine if AALM-LG and AALM-OF would converge on similar
35 predictions for post-absorption kinetics of blood and tissue Pb concentrations. To remove effects of
36 differences in absorption and growth parameters in the two biokinetics modules, the GI absorption and
37 growth parameters from the [O'Flaherty \(1995, 1993\)](#) model were adopted for both AALM sub-models.
38 The resulting AALM GI absorption model is a continuous function (Equation 4-7) that simulates an age-
39 dependent decline in the absorption fraction (AF_{Age}), from the value in infancy to the value in adults.

$$1 \quad AF_{Age} = AF_{C1} - \frac{AF_{C2}}{1+30 \cdot e^{-Age}} \quad \text{Eq. (4-7)}$$

2 The settings ($AF_{C1} = 0.60$, $AF_{C2} = 0.52$) result in $AF = 0.58$ at birth and $AF = 0.08$ in adults (see Figure 4-
3 13, OF default). As discussed in Section 4.7.8, AF_{C1} was set to 0.40 for infants based on [Ryu et al. \(1983\)](#).
4 An AF_{C2} of 0.28 keeps the AF for adults at 0.12 (see Figure 4-13, AALM), which aligns with the Adult
5 Lead Methodology ([U.S. EPA, 2003](#)).

6 Tissue growth in the AALM is simulated as a function of body weight, which is age-dependent (see
7 Figure 4-14). Tissue Pb concentrations are calculated as the Pb mass (μg) divided by the tissue weight (g).
8 Concentrations of Pb in bone wet weight are converted to concentration per gram bone mineral by
9 dividing the wet weight concentration by the ash fraction of bone. This conversion was used to compare
10 model predictions with bone X-ray fluorescence (XRF) data, which is typically reported in units of Pb per
11 g bone mineral. Bone ash fractions were assumed to be 0.55 and 0.50 for cortical and trabecular bone,
12 respectively ([ICRP, 1981](#)).

13 **4.7.2. Optimization of Plasma Pb – Blood Pb Relationship**

14 Six studies provided data on individual human subjects that can be used to evaluate the relationship
15 between plasma Pb and blood Pb concentrations. Measurements of plasma Pb were made using either
16 inductively coupled plasma mass spectrometry ([Smith et al., 2002](#); [Bergdahl et al., 1999](#); [Bergdahl et al.,](#)
17 [1998](#); [Hernandez-Avila et al., 1998](#); [Bergdahl et al., 1997](#); [Schutz et al., 1996](#)) or stable isotope dilution
18 with thermal ionization mass spectrometry ([Manton et al., 2001](#)). In all of these studies, methods were
19 employed to control for sample contamination, which is of particular importance in measurements of the
20 low Pb levels found in plasma. Taken together, the observations from these reports varied over a wide
21 range of blood Pb (approximately 0.34–94.8 $\mu\text{g}/\text{dL}$) and plasma Pb (approximately 0.0014–1.92 $\mu\text{g}/\text{dL}$)
22 levels. These studies provided 406 individual measurements of plasma Pb and blood Pb, in adult workers
23 as well as individuals with no known history of occupational exposure to Pb ([SRC, 2003](#)). Only one study
24 provides similar data in children ([Bergdahl et al., 1999](#)). The observations in children do not appear to
25 differ substantially from those for adults.

26 A best fit (least-squares) model for combined data from the above six studies was identified, and is
27 presented in Equation 4-8:

$$28 \quad \text{Blood Pb} = 87.0 \cdot \text{Plasma Pb}^{0.5} - 3.89 \quad (r^2 = 0.90) \quad \text{Eq. (4-8)}$$

29 AALM-OF parameters KBIND and BIND were optimized (Nelder Mead) against this data set in the
30 AALM-OF function relating plasma Pb and blood Pb (Equation 4-9):

$$31 \quad CB = (1 - HCT) \cdot CP + HCT \cdot CP \cdot \left(\frac{G + BIND}{KBIND + CP} \right) \quad \text{Eq. (4-9)}$$

32 AALM-LG parameter RBCNL was optimized by visual inspection (it was not possible to derive an
33 independent expression for the plasma Pb and blood Pb relationship because relevant parameters control
34 rate constants for transfer of Pb between plasma and RBC compartments).

35 Figures 4-15 compares the observed and predicted whole blood and plasma Pb in adults relationship.
36 Residuals for the optimized models are within acceptable limits (-2, 2). The r^2 values for predictions are
37 0.99 and 0.98.

1 4.7.3. Optimization of Plasma-to-Urine Pb Clearance

2 Four studies provide data to derive estimates of the Pb plasma-to-urine clearance rate (L/day) ([Araki et](#)
3 [al., 1986](#); [Manton and Cook, 1984](#); [Manton and Malloy, 1983](#); [Chamberlain et al., 1978](#)). Clearance
4 estimates from these studies are reported in [Diamond \(1992\)](#). These estimated clearance rates are based
5 on measurements made in a total of 32 (“normal” subjects). The mean of the estimates from the four
6 studies is 18 L/day ± 4 (SD).

7 [Rentschler et al. \(2012\)](#) reported individual subject data on urinary excretion of Pb (µg/g creatinine) and
8 plasma Pb concentration in five cases of Pb poisoning (blood Pb > 80 µg/dL). The cases were followed
9 for periods up to 800 days. If assumptions are made about body weight (not reported) and established
10 associations between creatinine excretion and lead body mass, clearance rates can be estimated from these
11 data. The estimated mean plasma clearance was 43 L/day ± 13 (SD) (range: 32–64 L/day). Lead poisoning
12 may have been a contributing factor to the relatively high clearances based on [Rentschler et al. \(2012\)](#).
13 Therefore, for the purpose of model optimization, 18 L/day was selected as the representative value for
14 plasma-to-urine clearance.

15 In AALM-OF, urinary excretion of Pb is an age-dependent fraction of GFR. Parameters for the GFR
16 function were modified to achieve an adult GFR of approximately 170 L/day/1.73m² (120 mL/min/1.73
17 m² body surface area ([ICRP, 1981](#)), with infant (<1 year) values 30% of the adult value ([Dewoskin and](#)
18 [Thompson, 2008](#)). AALM-OF parameters C2 and C3 were optimized in a function relating age and total
19 Pb excretory clearance (FRX) as shown in Equation 4-10.

$$20 \quad FRX = C1 - C2 / (1 + C3 \cdot e^{-AGE}) \quad \text{Eq. (4-10)}$$

21 AALM-LG parameters TKDN1 and TOURIN were optimized by visual inspection.

22 Figure 4-16 compares predicted and observed urinary clearance in adults. No data are available to
23 evaluate the different age patterns for urinary clearance predicted by AALM-LG and AALM-OF.

24 4.7.4. Optimization of Soft Tissue-to-Bone Pb Ratio

25 Four studies provide data for measurements of post-mortem soft tissue and bone Pb concentrations
26 ([Gerhardsson et al., 1995](#); [Barry, 1981, 1975](#); [Gross et al., 1975](#)). [Gerhardsson et al. \(1995\)](#) reported only
27 soft tissue Pb concentrations; whereas, the other three studies reported soft tissue and bone Pb
28 concentrations that can be used to estimate the ratios. [Barry \(1981, 1975\)](#) reported data for children and
29 adults in age brackets, so the data from [Barry \(1975\)](#) was used as the primary source to optimize
30 parameters for kidney/bone and liver/bone Pb ratios as a function of age.

31 [Barry \(1975\)](#) reported data on tibia Pb concentrations that are simulated as cortical bone concentrations in
32 the AALM models. Since [Barry \(1975\)](#) reported group mean tissue concentrations (not ratios in autopsy
33 cases), the mean tissue-to-bone ratios were approximated from the group means.

34 In AALM-OF, uptake of Pb into kidney, liver, and other well-perfused tissue is assumed to be flow-
35 limited and governed by blood flow and the tissue/plasma partition coefficients, PK, PL, and PW.
36 Attempts to optimize these three parameters failed to accurately simulate the decline in the tissue/bone
37 ratios predicted from the [Barry \(1975\)](#) observations. An improved fit was achieved when the constants
38 PK, PL, and PW were allowed to vary with age according to the function shown in Equation 4-11.

$$39 \quad PK = PKC \cdot (1 + e^{-PKA \cdot AGE}) \quad \text{Eq. (4-11)}$$

1 The parameters PKC and PKA (for kidney), PLC and PLA (for liver), and PWC and PWA (for other
2 well-perfused) were optimized (Nelder Mead) against the tissue/cortical bone ratios derived from the data
3 reported in [Barry \(1975\)](#).

4 AALM-LG parameters TOKDN2 and RKDN2 (for kidney) and RLVR2 (for liver) were optimized by
5 visual inspection. It was not possible to use acsIX parameter estimation functions because RKDN2 and
6 RLVR2 are array variables.

7 Figure 4-17 compares predicted and observed kidney/bone and liver/bone Pb ratios in adults. Standard
8 deviations of observed means were not available for calculating residuals because they were calculated
9 from group mean tissue concentration reported in [Barry \(1975\)](#). Values for r^2 for kidney/bone predictions
10 (of average of male and female ratios) were 0.95 and 0.77 for AALM-LG and AALM-OF, respectively.
11 Values for r^2 for liver/bone predictions were 0.96 and 0.93 for AALM-LG and AALM-OF, respectively.

12 **4.7.5. Optimization of Blood-to-Bone Pb Ratio**

13 Two studies provide data to evaluate the relationship between plasma or serum blood Pb and bone Pb
14 concentrations ([Hernandez-Avila et al., 1998](#); [Cake et al., 1996](#)). [Cake et al. \(1996\)](#) measured paired
15 serum, tibia, and calcaneus Pb concentrations in 49 adult male Pb workers, and reported corresponding
16 linear regression parameters. [Hernandez-Avila et al. \(1998\)](#) measured paired plasma, tibia and patella Pb
17 concentrations in 26 adults (20 female) who had no known occupational exposures to Pb. These data can
18 be used to derive corresponding linear regression parameters for the log-transformed plasma Pb.
19 Individual subject data were digitized from Figure 1 of [Hernandez-Avila et al. \(1998\)](#), and linear
20 regression parameters derived for the untransformed plasma Pb concentrations, in order to compare these
21 with the linear regression parameters from [Cake et al. \(1996\)](#).

22 Bone Pb/Plasma Pb slopes at age 50 years were predicted from AALM-LG and AALM-OF from a series
23 of simulations in which Pb intake was varied from 1 to 1000 $\mu\text{g}/\text{day}$. Table 4-17 and Figure 4-18 compare
24 predicted and observed slopes based on data from [Cake et al. \(1996\)](#) and [Hernandez-Avila et al. \(1998\)](#).
25 Given the relatively low residuals for cortical bone, which were within the range -2 to 2, no further
26 optimization for either model was needed for the respective parameters.

27 **4.7.6. Optimization of Bone Pb Elimination Kinetics**

28 [Nilsson et al. \(1991\)](#) reported longitudinal data on blood and finger bone Pb concentrations in 14 Pb
29 workers for period ranging from 8–18 years following cessation of their occupational exposures. The
30 median blood Pb concentration at the end of exposure was approximately 45 $\mu\text{g}/\text{dL}$. The decline in bone
31 Pb concentration was described by a first-order model with a single rate constant. Estimates of
32 elimination half-times for each individual were reported. The group median was 16 years (95% CI: 12,
33 23). The decline in blood Pb was described by a tri-exponential model with the following parameters.

Parameter	Unit	C1 (95% CI)	C2 (95% CI)	C3 (95% CI)
$t_{1/2}$	year	34 day (29, 41)	1.2 year (0.85, 1.8)	13 year (10, 18)
C	$\mu\text{g}/\text{dL}$	10.2	12.6	22.8

34

1 AALM-OF simulations were run for a constant Pb intake from birth to age 60 years, to achieve a terminal
2 blood Pb concentration of approximately 45 $\mu\text{g/dL}$ (1000 $\mu\text{g/day}$), followed by 20 years without
3 exposure. A first-order exponential rate was estimated for the decline in cortical bone Pb concentrations
4 predicted for 20 years following cessation of exposure. The AALM-OF parameter R0 (coefficient for Pb
5 diffusion out of bone mineral into canalicules) was optimized (visual inspection) to achieve an
6 elimination half-time from cortical cone of 16 years, the median value based on the [Nilsson et al. \(1991\)](#)
7 results.

8 AALM-LG simulations were run for a constant Pb intake from birth to age 60 years, to achieve a terminal
9 blood Pb concentration of approximately 45 $\mu\text{g/dL}$ (2000 $\mu\text{g/day}$), followed by 20 years without
10 exposure. A first-order exponential rate was estimated for the decline in cortical bone Pb concentrations
11 predicted for 20 years following cessation of exposure. The AALM-LG parameters FLONG (fraction of
12 total transfer from the exchangeable bone directed to non-exchangeable bone) and RCORT (transfer rate
13 from non-exchangeable cortical bone to diffusible plasma) were optimized (visual inspection) to achieve
14 an elimination half-time from cortical bone of 16 years, the median value based on the [Nilsson et al.](#)
15 [\(1991\)](#) results. FLONG and RCORT are age-dependent arrays and were varied in the optimization by
16 applying a constant (proportional) adjustment to all elements in the age array. The same adjustment factor
17 was therefore applied to child and adult values, even though the optimization was made against data only
18 for adults. The same adjustment factor was also applied to RTRAB (transfer rate from non-exchangeable
19 cortical bone to diffusible plasma).

20 Figure 4-19 compares rates of elimination of Pb from bone and blood with the corresponding empirical
21 models derived for Pb workers ([Nilsson et al., 1991](#)). Elimination rates of Pb from bone predicted from
22 the optimized models are within the 95% CI of the empirical model and yield residuals that range within
23 the -2, 2, criteria ($r^2 = 0.99$). Elimination half-times predicted for bone Pb (16 years) were identical to
24 estimates from [Nilsson et al. \(1991\)](#). Although elimination rates from blood predicted by the optimized
25 models are approximately at the confidence limits of the empirical model, the initial model divergence is
26 due largely to the slower (AALM-LG) or faster (AALM-OF) elimination kinetics during the first 5 years
27 following cessation of exposure; after which the models converge on the empirical model ($r^2 = 0.96$
28 AALM-LG; $r^2 = 0.99$ AALM-OF). Half-times predicted for the period 5 to 20 years after exposure were
29 1.25 years from AALM-LG and 1.06 years from AALM-OF, similar to values predicted for C2 (1.2 year)
30 from [Nilsson et al. \(1991\)](#).

31 **4.7.7. Evaluation of Blood Pb Elimination Kinetics in Adults**

32 [Rabinowitz et al. \(1976\)](#) conducted a pharmacokinetics study in which four adults ingested daily doses of
33 [^{207}Pb] nitrate for periods up to 124 days. Concentrations of ^{207}Pb in blood, urine, and feces were then
34 monitored during and following cessation of exposure, and data on daily intakes and blood concentrations
35 for each subject were reported. Absorption fractions for Pb were estimated for each individual based on
36 mass balance in feces.

37 Figure 4-20 compares observed and predicted blood ^{207}Pb concentrations for the optimized AALM-LG
38 and AALM-OF. Gastrointestinal absorption fractions were set in both models to the estimates for each
39 individual reported in [Rabinowitz et al. \(1976\)](#). No other changes were made to parameter values.
40 Although both models AALM-LG predict a rise and decline in blood Pb concentrations, AALM-LG
41 predictions are closer to the observations. Values for r^2 for AALM-LG predictions are 0.99, 0.98, 0.92,
42 and 0.97 for Subjects A, B, D, and E, respectively. Values for r^2 for AALM-OF predictions range from

1 0.08 (Subject E) to 0.24 (Subjects A, B, and D). AALM-OF predicts slower accrual and decline of blood
2 Pb, and lower peak blood Pb concentrations.

3 **4.7.8. Evaluation of Blood Pb Elimination Kinetics in Infants**

4 Only two studies provide data on the relationships between Pb dose and blood Pb concentration in infants
5 ([Sherlock and Quinn, 1986](#); [Ryu et al., 1983](#)). In the [Ryu et al. \(1983\)](#) study, blood Pb concentrations
6 were monitored in 25 formula-fed infants. From birth to age 111 days, infants were fed formula
7 (packaged in cartons) that had a Pb concentration of approximately 20 µg/L. From age 112 to 195 days, a
8 subset of the infants (n = 7) were switched to formula (packaged in cans) that had a Pb concentration of
9 approximately 57 µg/L. Formula intakes were measured, and provided estimates of Pb intakes in each
10 subject. [Ryu et al. \(1983\)](#) reported a table of individual Pb intakes, and presented a figure illustrating
11 group mean blood Pb concentrations at various ages (these data were digitized for use in this analysis).
12 Standard errors (or deviations) of mean blood Pb concentrations were not reported; however, as discussed
13 below, based on [Sherlock and Quinn \(1986\)](#), standard errors may have been approximately 10% of the
14 means. The parameter for maternal blood Pb concentration was set at 10 µg/dL, the reported maternal
15 mean for the study. Lead absorption was not quantified in [Ryu et al. \(1983\)](#); therefore, the gastrointestinal
16 absorption fraction during infancy was set to 40%, based on estimates from mass balance studies ([Ziegler
17 et al., 1978](#)). No other changes were made to parameter values. Figure 4-21 compares predicted and
18 observed blood Pb concentrations for the two exposure regimens (carton formula or carton followed by
19 canned formula). Simulations are shown for the mean intake (12–20 µg/day) and ± 1 SD (10–18 µg/day,
20 15–22 µg/day). AALM-LG encompasses most of the observations within ±1 SD of the mean intakes.
21 AALM-OF predictions are higher than observations. If standard errors of mean blood Pb concentrations
22 were 10% of the mean, residuals for AALM-LG predictions ranged from -3.7 to 0.15 for carton exposures
23 (mean -1.2). Residuals for AALM-OF predictions ranged from -3.0 to 4.4 (mean 2.0). Both models
24 capture the increase in blood Pb concentration associated with the switch the higher Pb intakes for canned
25 formula and the overall temporal trends in the observations; r^2 for predictions were 0.85 and 0.76 for
26 AALM-LG and AALM-OF, respectively.

27 [Sherlock and Quinn \(1986\)](#) measured blood Pb concentration in 131 infants at age 13 weeks and
28 estimated dietary intake of Pb for each infant based on Pb measurements made in duplicate diet samples
29 collected daily during week 13. [Sherlock and Quinn \(1986\)](#) reported a plot of blood Pb means and
30 standard errors for group mean dietary Pb intakes (these data were digitized for use in this analysis). The
31 parameter for maternal blood Pb concentration was set at 18 µg/dL, the reported maternal geometric
32 mean. The gastrointestinal absorption fraction was set at 40% for infants; the same value used in
33 simulations of [Ryu et al. \(1983\)](#). Figure 4-22 compares predicted and observed blood Pb concentrations
34 for the range of Pb intakes in the study. Both models reproduce the general shape of the observed
35 curvilinear dose-blood Pb relationship; the apparent plateau observed at the higher end of the dose range,
36 however, is achieved at higher doses in the models (>800 µg/day AALM-LG, >600 AALM-OF).
37 Although the model results for the plateau contributed to high residuals at the highest Pb intake (>200
38 µg/day), residuals for lower Pb doses ranged from -4.8 to 1.5 (mean -2.3) for AALM-LG and -4.3 to 2.2
39 (mean - 1.0) for AALM-OF. The overall dynamics of increasing blood Pb with increasing Pb dose was
40 predicted with $r^2 = 0.95$ for AALM-LG and 0.98 for AALM-OF. One possible explanation for the higher
41 plateaus in the dose-blood Pb relationship predicted from both models is that the models may estimate
42 higher saturation levels of Pb in RBCs than actually occurred in the infants in the [Sherlock and Quinn](#)

1 [\(1986\)](#) study. Parameter values for RBC uptake are based on data collected on adults, and have not been
2 optimized for infants due to an absence of good supporting data (see Section 4.7.2).

3 **4.8. CONCLUSIONS AND IMPLICATIONS OF PERFORMANCE OF OPTIMIZED** 4 **MODELS**

5 The initial configuration of the AALM biokinetics model was an acslX implementation of the [Leggett](#)
6 [\(1993\)](#) and [O'Flaherty \(1995, 1993\)](#) models. The AALM.CLS (v. 4.2, July 2015) introduced several
7 changes to both models, including new parameters (see Table 4-18), and has optimized parameter values
8 against the same data sets. Some of the data used in the optimization were not available at the time the
9 original models were developed. Optimization against a common set of data resulted in convergence of
10 model predictions for blood, bone, and soft tissue (see Figures 4-23 and 4-24). The optimized AALM-LG
11 and AALM-OF predict similar blood, bone, and soft tissue Pb concentration (see Table 4-19). Evaluation
12 of model predictions of blood Pb relationships at known ingestion doses of Pb was limited to data in a
13 few adult subjects ([Rabinowitz et al., 1976](#)), and only two studies in infants (where Pb ingestion doses
14 were estimated from dietary [formula] Pb measurements) ([Sherlock and Quinn, 1986](#); [Ryu et al., 1983](#)).
15 No data were available on blood Pb concentrations in children or adolescents, for whom Pb ingestion
16 doses were known with certainty. Several studies have reconstructed Pb intakes in children from exposure
17 models supported by measurements of environmental exposure concentrations ([Dixon et al., 2009](#);
18 [TerraGraphics Environmental Engineering, 2004](#); [Malcoe et al., 2002](#); [Hogan et al., 1998](#); [Lanphear et al.,](#)
19 [1998](#); [Lanphear and Roghmann, 1997](#); [Bornschein et al., 1985](#)). However, these studies were not
20 considered for evaluation of the AALM biokinetics models since they would introduce exposure
21 uncertainty into the evaluation.

22 Although limited in scope, these evaluations provide several insights into model performance. In general,
23 the AALM, in both AALM-LG and AALM-OF configurations, predicted-observed blood Pb dynamics in
24 infants and adults, in response to changing Pb dosing (see Figures 4-20 thru 4-22). In infants, observed
25 blood Pb concentrations were on average within ± 2 SE of the observed mean (mean residual range -2, 2).
26 AALM-LG and AALM-OF predict similar quasi-steady state blood Pb concentrations in infants
27 (Figures 4-21 and 4-22). Both models predict a higher plateau for the dose-blood Pb relationship than was
28 observed in infants, however, this difference would be of quantitative significance only at intakes
29 resulting in blood Pb concentrations >30 $\mu\text{g/dL}$.

30 AALM-OF predicts slower than observed blood Pb kinetics in adults compared to AALM-LG. This
31 resulted in larger differences between predicted and observed blood Pb concentrations in controlled,
32 short-term, exposure studies. More rapid blood Pb kinetics predicted by AALM-LG provided a closer
33 agreement to observations (see Figure 4-20). Although short-term exposure studies revealed important
34 differences in blood Pb kinetics predicted by AALM-LG and AALM-OF, both models predict well the
35 long-term elimination rates of Pb from bone following decades of exposure, and its effect on long-term
36 elimination of Pb from blood, that have been observed in worker populations following cessation of
37 exposure (see Figure 4-19).

38 Optimization exercises also revealed differences in model structure that are relevant to model
39 applications. Attempts to optimize AALM soft tissue/bone lead ratios solely by adjusting tissue/plasma
40 partition coefficients were unsuccessful. Improved performance was achieved by introducing age-
41 dependence and larger values for partition coefficients. [O'Flaherty \(1995, 1993\)](#) assigned values of 50 to
42 the kidney/plasma and liver/plasma partition coefficients. The optimized values are substantially higher;

1 approximately 1350 for plasma/kidney, and 1600 for plasma/liver, in infants that progressively decrease
2 with age to adult values of approximately 700 and 800 respectively. It is possible, and likely, that these
3 large adjustments were necessary because the assumption of flow-limited transfer of Pb into and out of
4 soft tissue Pb does not accurately reflect the complexities of age-dependent transport and retention of Pb
5 in soft tissues. In support of this hypothesis, optimization of the bidirectional transfer coefficients that
6 govern uptake and retention of Pb in kidney and liver successfully predicted observations made in infants,
7 children and adults (see Figure 4-17).

8 AALM-LG and AALM-OF were also successfully optimized to predict observed relationships between
9 plasma and whole blood Pb concentrations in adults even though the two models use very different
10 mathematical approaches to simulating uptake and retention of Pb in RBCs. AALM-OF simulates binding
11 of Pb with RBCs as a saturable instantaneous equilibrium. AALM-LG simulates bidirectional transfer
12 between plasma and RBCs, with saturable transfer into RBCs. Transfer out of RBCs in AALM-LG is
13 age-dependent and faster in children than in adults. The validity of the age-dependence was not rigorously
14 explored in this analysis. What little data there are on plasma-RBC relationships in children does not
15 suggest an appreciable difference in the relationship for children and adults ([Bergdahl et al., 1999](#)). Since
16 the age-dependence assumption could not be rigorously evaluated it is retained in AALM-LG.

17 The most substantial differences in the structures of AALM-LG and AALM-OF are in the simulation of
18 bone Pb kinetics. In AALM-LG, bone Pb kinetics are represented as age-dependent rate coefficients for
19 transfer of Pb into and out of bone. In AALM-OF, bone Pb kinetics are simulated as outcomes of a
20 physiological model of bone formation and resorption. The physiological approach to bone metabolism
21 implemented in AALM-OF allows the model to be used to explore relationships between bone
22 metabolism and Pb kinetics. This is potentially useful for simulating Pb kinetics in various bone
23 metabolism contexts associated with life stages [e.g., pregnancy and menopause, [O'Flaherty \(2000\)](#)];
24 diseases (e.g., bone wasting diseases); and environments (e.g., weightlessness)].

25 Although, at this time, the AALM remains a research model, it possesses several attributes (discussed in
26 the following bullets) that make it attractive in human health risk assessment when estimating Pb internal
27 dosimetry following real or hypothetical environmental exposures.

- 28 • Currently, human health risk assessment of Pb is conducted using two separate regulatory
29 models, the IEUBK model for Lead in Children and Adult Lead Methodology. The IEUBK
30 model has a terminal age of 7 years. The Adult Lead Methodology is limited to adults. The
31 AALM provides a single physiological/compartamental model capable of predicting blood Pb
32 concentrations at all ages from birth through adulthood. The AALM would replace or supplement
33 the results of the two separate models, and would provide additional assessment capability for
34 older children and adolescent subpopulations.
- 35 • The current regulatory model, the Adult Lead Methodology is a slope factor model in which
36 biokinetics are represented as a single variable relating the linear slope of the change in blood Pb
37 concentration per unit change of absorbed Pb ($\mu\text{g}/\text{day}$). The AALM offers a more mechanistic
38 approach to simulating Pb kinetics that can incorporate information on age, growth, life stage,
39 and other physiological variables that may affect Pb kinetics.
- 40 • The AALM can simulate exposures in time steps as small as a single day. This allows predictions
41 of blood Pb concentrations associated with acute or highly intermittent exposures. The IEUBK
42 model and Adult Lead Methodology simulate quasi-steady state blood Pb concentration

1 associated with exposures that have durations of >3 months. Shorter-term dynamics of blood Pb
2 concentrations expected to occur with exposures that vary over days or weeks cannot be
3 simulated with the IEUBK model or the ALM.

- 4 • The AALM can predict concentrations of Pb in bone. This offers the potential for using estimates
5 of bone Pb as an internal dosimeter in assessing health risk from exposure to environmental Pb.
6 Bone Pb may be more suitable than blood Pb when predicting risk for certain effects of Pb such
7 as hypertension ([U.S. EPA, 2013](#)).
- 8 • The RT model in the AALM provides a more realistic simulation of inhaled aerosols of Pb that
9 incorporates information on air Pb concentrations, air Pb particle size, solubility, receptor activity
10 levels (which determine inhalation volumes), and age. This capability of the AALM is a major
11 improvement over the RT representation in the IEUBK model, which consists only of parameters
12 for inhalation volumes, and a single parameter for the absorption fraction of inhaled Pb (from the
13 lung and GI tract). The Adult Lead Methodology does not represent the RT.

14 **4.9. CALIBRATING THE AALM TO THE IEUBK MODEL**

15 Figure 4-25 compares predictions of the AALM and the IEUBK model for a continuous dust Pb intake of
16 10 µg/day. In both models, the relative bioavailability (RBA) for Pb in dust was assumed to be 60%. This
17 corresponds to an absolute bioavailability of approximately 20% at age 2 years in the AALM and 30% in
18 the IEUBK model. At age 2-3 years the IEUBK model predicts a blood Pb concentration of 1.1 µg/dL;
19 AALM-LG and AALM-OF predict 2.1 and 2.8 µg/dL, respectively.

20 Table 4-20 compares predictions of adult blood Pb concentrations from the Adult Lead Methodology and
21 AALM.CLS, for an exposure to 1000 ppm. In both models, the RBA for Pb in dust was assumed to be
22 60%. This corresponds to an absolute bioavailability of approximately 4.8% in the AALM and 12% in the
23 Adult Lead Methodology. The Adult Lead Methodology predicts a blood Pb concentration of 2.9 µg/dL;
24 AALM-LG and AALM-OF predict 3.1 and 4.6 µg/dL at age 30 years (mid-point for age range in the
25 Adult Lead Methodology, 17-45 years), respectively.

26 The optimized AALM discussed in Section 4.7 thus predicts blood Pb concentrations in children that are
27 approximately 2-fold higher than the currently established regulatory IEUBK model based on the same Pb
28 intakes. Data available for optimizing and evaluating performance of the Pb biokinetics models are
29 largely limited to data for Pb kinetics in adults. Only two studies have reported data on intake-blood Pb
30 relationships in infants ([Sherlock and Quinn, 1986](#); [Ryu et al., 1983](#)), and no data of this type are
31 available for children in the age range 1-7 years, the age range simulated in the IEUBK model. Given the
32 large uncertainties in the available data on intake-blood Pb relationships in children, the model
33 differences in absolute terms are relatively small in the context of model capabilities (e.g., approximately
34 1–2 µg/dL in children for a dust Pb ingestion rate of 10 µg/day). These small differences in model
35 estimates, however, could have implications to consider in making risk management decisions at
36 contaminated sites, which are typically based on a “not-to-exceed” blood Pb concentration ([U.S. EPA,
37 1994a](#)).

38 The IEUBK model has a long, established history of use in risk assessment and support for soil clean-up
39 goals at hazardous waste sites. Thus, it was deemed worthwhile to further evaluate the most sensitive
40 AALM parameter values to determine which parameters values could be calibrated against the IEUBK

1 model output for child blood Pb concentrations relative to Pb intake without altering the AALM model
2 performance in simulating the infant and adult data.

3 This additional evaluation identified value changes for a single biokinetic parameter, *RRBC*, that were
4 sufficient to align the AALM-LG results more closely with the IEUBK model results. The *RRBC*
5 parameter controls the rate of return of Pb from RBCs to plasma. Support for adjusting this parameter is
6 based on the following three arguments: (1) sensitivity analyses of the AALM-LG revealed that blood Pb
7 predictions were highly sensitive to parameters controlling plasma-RBC Pb exchange rates (Section 4.5,
8 Table 4-4), (2) the parameter *RRBC* value is derived from an age-dependent array that allows adjustment
9 of the parameter value for children without altering values for infants or adults, precluding degradation of
10 model performance in estimating Pb kinetics for infant and adult subpopulations; and (3) the *RRBC*
11 parameter value for children remains uncertain and has no data support, however the upward adjustment
12 needed for this parameter (i.e., faster outflow from RBCs) is consistent with assumptions that were made
13 in the early development of the Leggett model, namely that removal half-times of Pb from RBCs are
14 expected to be shorter in young children than in adults ([Leggett, 1993](#)). The *RRBC* parameter was
15 adjusted upward until close agreement was achieved between blood Pb predicted by AALM-LG and the
16 IEUBK model for a constant ingestion intake of 10 µg/day Pb in surface dust, and an RBA relative to
17 soluble Pb = 0.60 (compare Figure 4-25 with 4-26).

18 Using the same rationale, red cell parameters in AALM-OF were adjusted to align the AALM-OF blood
19 Pb predictions in children more closely with the IEUBK model results. Unlike the AALM-LG, which
20 represents Pb exchanges between plasma and RBC with first-order rate coefficients, the AALM-OF
21 represents binding of Pb in RBCs as an instantaneous binding equilibrium with plasma Pb controlled by
22 two parameters, a half-saturation parameter (*KBIND*) and maximum binding capacity (*BIND*), both of
23 which are constants and independent of age. Although, either of the two parameters could be adjusted, the
24 half-saturation parameter (*KBIND*) was selected in order to keep the binding capacity unchanged, which
25 is similar to the strategy used in resolving differences with AALM-LG.

26 As illustrated in Figure 4-26, adjustments to the RBC parameters in the AALM-LG and AALM-OF
27 resulted in close agreement with child blood Pb profiles in children predicted by the IEUBK model. At
28 age 2-3 years the IEUBK model predicts a blood Pb concentration of 1.1 µg/dL; AALM-LG and AALM-
29 OF predict 1.3 and 1.5 µg/dL, respectively, for a dust Pb intake of 10 µg/dL. Because the parameter
30 adjustments were age-dependent and were restricted to children, the adjustments had no effect on
31 predictions of Pb kinetics in adults, and the revised AALM models performed similarly to the optimized
32 version in predicting observed Pb kinetics in adults. Similarly, the adjustments made to the AALM RBC
33 parameter values for the children subpopulation had minimal effect on the model predictions of blood Pb
34 levels or kinetics in infants (see Figures 4-27 and 4-28). Blood and tissue Pb concentrations predicted by
35 the revised AALM are presented in Table 4-21.

36 **4.10. DATA NEEDS AND FURTHER EVALUATION OF THE AALM**

37 The improvements in the AALM discussed in this report demonstrate the considerable advancements
38 made in the AALM model capability and exposure interface, as well as the optimized parameters that
39 control important model predictions (e.g., plasma/RBC ratios, soft tissue/bone ratios, plasma-to-urine
40 clearance), and that have been optimized against the available data in infants and adults.

1 Of particular interest to risk assessment applications are predictions of blood and bone Pb, as these two
2 biomarkers have been used extensively to establish dose-response relationships for health effects of Pb in
3 humans ([U.S. EPA, 2013](#)). The two models predict long-term accrual of Pb in blood and bone Pb levels in
4 adults (ages >16 years), that differ by less than 20%. This agreement is remarkable, given the very
5 different approaches used to simulate bone Pb, which is the major depot for Pb in the body. This
6 magnitude of difference is less than observed inter-individual variability in blood and bone Pb
7 measurements in humans ([CDC, 2013](#); [U.S. EPA, 2013](#); [Hu et al., 2007](#)). The two models also predict
8 similar blood Pb concentrations in children. At an earlier age of 2 years, however, blood Pb
9 concentrations predicted from AALM-LG are approximately 25% lower than predictions from AALM-
10 OF, however, data are limited, and additional data are likely to result in improvements in model
11 performance.

12 Blood Pb concentrations in adults predicted from the AALM are very similar to predictions from the
13 Adult Lead Methodology for the same soil Pb concentrations. Predictions for infants are similar between
14 the AALM and the IEUBK. With the adjusted RBC parameter value, the AALM and IEUBK model
15 predict similar blood Pb concentrations in children for the same dust Pb intakes and RBA assumptions.
16 Subject to further external peer review and verification of the AALM results, the agreement between the
17 AALM, the IEUBK model, and the ALM supports the potential future use of the AALM in risk
18 assessment applications to supplement or replace the IEUBK model and the ALM in supporting
19 regulatory decisions. At present, however, the IEUBK model and the ALM remain the established
20 methods that will be used for regulatory decisions.

21 Recommendations for data to reduce uncertainty in the AALM model results, and improve the
22 consistency among all model predictions include the following:

- 23 • *Resolve differences between the AALM-LG and AALM-OF predictions of blood Pb kinetics.*
24 AALM-OF predicts slower accrual and elimination of Pb from blood compared to AALM-LG,
25 while AALM-LG more closely reproduced blood Pb kinetics observed in the short-term Pb dosing
26 studies of [Rabinowitz et al. \(1976\)](#). Additional data on blood Pb kinetics may serve to improve
27 the optimization of both models, and resolve these differences. This will be important for
28 application of either model to simulating blood Pb dynamics associated with short-term or highly
29 variable exposures.
- 30 • *Evaluate and optimize AALM-OF bone metabolism parameters.* A literature search and review of
31 newer data on rates of bone production and resorption may provide a basis for re-optimization of
32 AALM-OF or its extension to include simulations of specific bone metabolism scenarios of
33 interest to toxicology or risk assessment (e.g., pregnancy, osteomalacia).
- 34 • *Further verify AALM-LG and AALM-OF predictions.* Additional observations in humans should
35 be identified that can serve to evaluate the performance of the optimized AALM (and that were
36 not used in the optimization). Ideally, these would be blood and/or bone Pb measurements in
37 people for whom Pb intakes are known with reasonable certainty. Ethical concerns typically
38 preclude Pb dosing experiments; therefore, Pb doses must be estimated with accurate tools such
39 as duplicate diet surveys or dietary recalls and information on Pb levels in diet and other relevant
40 exposure media. Types of data that would be valuable for model validation include: (1) blood soft
41 tissue or bone Pb levels in children or adults for whom Pb dosage is known or can be reliably
42 estimated from exposure data; (2) changes in blood, soft tissue or bone Pb levels in children or

1 adults following and abrupt change (increase or decrease) in Pb exposure; (3) steady state (or
2 quasi-steady state) blood/soft tissue blood/bone Pb ratios in children or adults; (4) urinary Pb
3 clearance from blood or plasma in children or adults; and (5) plasma/whole blood concentration
4 ratios in children.

- 5 • *Evaluate and document the empirical basis for exposure model parameters.* Most of the exposure
6 parameter values in the AALM.CLS serve as placeholders and should, in the future, be replaced
7 with default values for specific receptor populations for which an empirical basis can be
8 provided.
- 9 • *Further refine the RT model.* The AALM.CLS includes values for inhalation rates and deposition
10 fractions for the general public, as defined by [ICRP \(1994\)](#). These values do not adequately
11 represent many receptor populations of interest who have activity levels that differ from general
12 population assumptions (e.g., workers). Additional parameter value matrices should be developed
13 to represent selected receptor populations of interest.

14 Finally, the AALM has been developed with a relatively easy to use and versatile exposure interface,
15 access to model parameters and values, and transparency of model code to support stakeholder use and
16 evaluation internally and external to the Agency. It is recommendation of this report that the AALM be
17 made available to the Agency and the research community as a beta test version to facilitate additional
18 case studies, parameter refinements and external evaluation; and to advance the model towards regulatory
19 use and exposure assessment.

20

1 **TABLE 4-1. SUMMARY OF MAJOR DIFFERENCES BETWEEN STRUCTURES OF AALM-**
 2 **LG AND AALM-OF**

Model Component	AALM-LG	AALM-OF
GI tract	Four compartments representing stomach, small intestine, upper and lower large intestine	No GI tract compartment
Absorption from GI tract	First-order transfer from small intestine to blood	First-order transfer of ingested Pb to liver (portal blood)
Plasma	Two compartments representing diffusible (transferable to other tissues) and bound	One compartment in equilibrium with bound Pb in RBC
RBC	Binding represented with first-order rate transfer rates adjusted for saturating concentration	Binding represented with non-linear binding function (i.e., maximum and half-saturating concentration)
Kidney	Two compartments, first-order transfer rates	One compartment with flow-limited transfer
Liver	Two compartments, first-order transfer rates	One compartment with flow-limited transfer
Other soft tissue	Three compartments, first-order transfer rates	None
Poorly perfused tissue	None	One compartment with flow-limited transfer
Well-perfused tissue	None	One compartment with flow-limit transfer
Brain	One compartment, first-order transfer rates	None
Bone	Six compartments representing surface, exchangeable and non-exchangeable cortical and trabecular bone. Pb transfers governed by age-dependent first-order transfer rates	Transfer to and from metabolically active trabecular and cortical bone governed by age-dependent bone formation and resorption rates, respectively; transfer to and from mature cortical bone governed by radial diffusion
Sweat	First-order transfer from plasma to sweat	None
Miscellaneous excretory routes (e.g., hair)	First-order transfer from other soft tissues to other excretory routes	None

3

4

1 **TABLE 4-2. AALM-LG INPUT PARAMETERS CONTROLLING POST-ABSORPTION PB**
 2 **KINETICS**

No.	Transfer Pathway	Controlling Parameter(s)	Rate at Specified Age (day ⁻¹)					
			0-100 days	1 year	5 years	10 years	15 years	≥25 years
1	Plasma-D to EVF	TEVF	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+03	1.00E+03
2	Plasma-D to RBCs	TORBC	2.97E+02	4.07E+02	4.25E+02	3.67E+02	3.01E+02	4.80E+02
3	Plasma-D to Plasma-B	TOPROT	4.95E-01	6.78E-01	7.09E-01	6.11E-01	5.01E-01	8.00E-01
4	Plasma-D to Urinary bladder	TOURIN	1.86E+01	2.54E+01	2.66E+01	2.29E+01	1.88E+01	3.00E+01
5	Plasma-D to Small intestine	TOFECE	7.43E+00	1.02E+01	1.06E+01	9.17E+00	7.51E+00	1.20E+01
6	Plasma-D to Trab surf	TOBONE (TFRAC)	9.60E+01	5.76E+01	5.68E+01	8.95E+01	1.32E+02	8.90E+01
7	Plasma-D to Cort surf	TBONE (1-TFRAC)	3.84E+02	2.30E+02	1.99E+02	2.69E+02	3.42E+02	7.10E+01
8	Plasma-D to Liver 1	TOLVR1	4.95E+01	6.78E+01	7.09E+01	6.11E+01	5.01E+01	8.00E+01
9	Plasma-D to Urinary path	TOKDN1	2.48E+01	3.39E+01	3.54E+01	3.06E+01	2.51E+01	4.00E+01
10	Plasma-D to Other kidney	TOKDN2	2.48E-01	3.39E-01	3.54E-01	3.06E-01	2.50E-01	4.00E-01
11	Plasma-D to ST0	TOSOF0	1.03E+02	1.42E+02	1.48E+02	1.28E+02	1.05E+02	1.78E+02
12	Plasma-D to ST1	TOSOF1	1.24E+01	1.70E+01	1.77E+01	1.53E+01	1.25E+01	1.00E+01
13	Plasma-D to ST2	TOSOF2	1.24E+00	1.70E+00	1.77E+00	1.53E+00	1.25E+00	2.00E+00
14	Plasma-D to Brain	TOBRAN	5.57E-01	7.63E-01	2.66E-01	2.29E-01	1.88E-01	3.00E-01
15	Plasma-D to Sweat	TOWET	4.33E+00	5.93E+00	6.20E+00	5.35E+00	4.38E+00	7.00E+00
16	RBCs to Plasma-D	RRBC	4.62E-01	4.62E-01	2.77E-01	1.39E-01	1.39E-01	1.39E-01
17	EVF to Plasma-D	RPLAS	3.33E+02	3.33E+02	3.33E+02	3.33E+02	3.33E+02	3.33E+02
18	Plasma-B to Plasma-D	RPROT	1.39E-01	1.39E-01	1.39E-01	1.39E-01	1.39E-01	1.39E-01
19	Cort surf to Plasma-D	RCS2DF	6.50E-01	6.50E-01	6.50E-01	6.50E-01	6.50E-01	5.00E-01
20	Trab surf to Plasma-D	RTS2DF	6.50E-01	6.50E-01	6.50E-01	6.50E-01	6.50E-01	5.00E-01

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No.	Transfer Pathway	Controlling Parameter(s)	Rate at Specified Age (day ⁻¹)					
			0-100 days	1 year	5 years	10 years	15 years	≥25 years
21	Cort surf to Exch vol	RCS2B	3.50E-01	3.50E-01	3.50E-01	3.50E-01	3.50E-01	5.00E-01
22	Trab surf to Exch vol	RTS2B	3.50E-01	3.50E-01	3.50E-01	3.50E-01	3.50E-01	5.00E-01
23	Cort exch vol to Surf	RDIF*(1-FLONG)	1.85E-02	1.85E-02	1.85E-02	1.85E-02	1.85E-02	1.85E-02
24	Trab exch vol to Surf	RDIF*(1-FLONG)	1.85E-02	1.85E-02	1.85E-02	1.85E-02	1.85E-02	1.85E-02
25	Cort exch vol to Nonexch vol	RDIF*FLO NG	4.62E-03	4.62E-03	4.62E-03	4.62E-03	4.62E-03	4.62E-03
26	Trab exch vol to Nonexch vol	RDIF*FLO NG	4.62E-03	4.62E-03	4.62E-03	4.62E-03	4.62E-03	4.62E-03
27	Cort nonexch vol to Plasma-D	RCORT	8.22E-03	2.88E-03	1.54E-03	8.90E-04	5.12E-04	8.22E-05
28	Trab nonexch vol to Plasma-D	RCORT	8.22E-03	2.88E-03	1.81E-03	1.32E-03	9.56E-04	4.93E-04
29	Liver 1 to Plasma-D	RLVR1	3.12E-02	3.12E-02	3.12E-02	3.12E-02	3.12E-02	3.12E-02
30	Liver 1 to Small intestine	HITOSI	3.12E-02	3.12E-02	3.12E-02	3.12E-02	3.12E-02	3.12E-02
31	Liver 1 to Liver 2	HITOH2	6.93E-03	6.93E-03	6.93E-03	6.93E-03	6.93E-03	6.93E-03
32	Liver 2 to Plasma-D	RLVR2	6.93E-03	6.93E-03	6.93E-03	1.90E-03	1.90E-03	1.90E-03
33	Urinary path to Urinary bladder	RBLAD	1.39E-01	1.39E-01	1.39E-01	1.39E-01	1.39E-01	1.39E-01
34	Other kidney to Plasma-D	RKDN2	6.93E-03	6.93E-03	6.93E-03	1.90E-03	1.90E-03	1.90E-03
35	ST0 to Plasma-D	RSOF0	2.08E+00	2.08E+00	2.08E+00	2.08E+00	2.08E+00	2.08E+00
36	ST1 to Plasma-D	RSOF1	4.16E-03	4.16E-03	4.16E-03	4.16E-03	4.16E-03	4.16E-03
37	ST1 to Excreta	S2HAIR	2.77E-03	2.77E-03	2.77E-03	2.77E-03	2.77E-03	2.77E-03
38	ST2 to Plasma-D	RSOF2	3.80E-04	3.80E-04	3.80E-04	3.80E-04	3.80E-04	3.80E-04
39	Brain to Plasma-D	RBRAN	9.50E-04	9.50E-04	9.50E-04	9.50E-04	9.50E-04	9.50E-04

1 **TABLE 4-3. AALM-OF INPUT PARAMETERS CONTROLLING POST-ABSORPTION PB**
 2 **KINETICS**

No.	Parameter	Unit	Value	Parameter Description
1	A1	–	4.0	Constant 1 for bone formation rate algorithm
2	A2	–	0.4	Constant 2 for bone formation rate algorithm
3	A3	–	4.0	Constant 3 for bone formation rate algorithm
4	A5	–	0.6	Constant 5 for bone formation rate algorithm
5	AGE0	year	0	Age at which simulation begins
6	BASE	–	0.1	Base bone formation rate in bone growth algorithm
7	BIND	mg/L	2.7	Maximum capacity of sites in red cells to bind Pb
8	C1	–	1.0	Constant 1 for urinary clearance of Pb as a fraction of GFR
9	C2	–	0.9	Constant 2 for urinary clearance of Pb as a fraction of GFR
10	C3	–	50	Constant 3 for urinary clearance of Pb as a fraction of GFR
11	CON	f	0.65	Fraction of bone blood flow to trabecular bone
12	D0	cm ³ /day	0.0000005	Diffusion constant
13	EXPO	–	0.6	Exponent constant for bone volume participating in adult-type bone remodeling
14	G	NA	1.2	Linear parameter for unbound lead in red cells
15	KBIND	mg/L	0.0075	Half-saturation concentration of Pb for binding by sites in red cells
16	P0	cm ³ /day	0.02	Permeability constant for diffusion from canaliculi to bone
17	PK	f	50	Kidney/plasma partition coefficient
18	PL	f	50	Liver/plasma partition coefficient
19	PP	f	2.0	Poorly perfused/plasma partition coefficient
20	PW	f	50	Well-perfused/plasma partition coefficient
21	QBONEC	f	0.05	Fraction cardiac output going to bone
22	QCC	L/day/kg	340	Cardiac output in the adult
23	QKC	f	0.17	Fraction cardiac output going to kidney
24	QLC	f	0.25	Fraction cardiac output going to liver
25	QWC	f	0.44	Fraction cardiac output going to other well-perfused tissues
26	R0	cm ³ /day	0.0000005	Permeability constant for diffusion from bone to canaliculi
27	RAD1	cm	0.000027	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
28	RAD2	cm	0.000052	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone

No.	Parameter	Unit	Value	Parameter Description
29	RAD3	cm	0.000079	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
30	RAD4	cm	0.000106	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
31	RAD5	cm	0.000133	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
32	RAD6	cm	0.000160	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
33	RAD7	cm	0.000187	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
34	RAD8	cm	0.000214	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
35	S	cm ² /cm	0.000126	Surface area of canaliculi

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1 **TABLE 4-4. AALM-LG STANDARDIZED SENSITIVITY COEFFICIENTS FOR BLOOD PB IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ABLOOD	TEVF	9.16E+00	8.38E+00	Deposition fraction from diffusible plasma to extravascular fluid
ABLOOD	TORBC	5.30E+00	4.93E+00	Deposition fraction from diffusible plasma to RBCs, below non-linear threshold
ABLOOD	TOSOF0	1.50E+00	1.44E+00	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 0
ABLOOD	TBONEL	1.42E+00	1.30E+00	Terminal value of age-scaled deposition fraction from diffusible plasma to surface bone
ABLOOD	RRBC	1.00E+00	9.98E-01	Age-scaled transfer rate from RBC to diffusible plasma
ABLOOD	TOLVR1	4.90E-01	3.85E-01	Deposition fraction from diffusible plasma to liver compartment 2
ABLOOD	H1TOBL	3.25E-01	2.94E-01	Fraction of transfer out of liver compartment 1 to diffusible plasma
ABLOOD	TBONE	1.05E-01	7.16E-02	Age-scaled deposition fraction from diffusible plasma to surface bone
ABLOOD	TFRAC	8.33E-03	7.10E-02	Bone deposition-scaled fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone; 1-TFRAC is the fraction that goes to cortical surface bone
ABLOOD	H1TOH2	7.70E-02	6.58E-02	Fraction of transfer out of liver compartment 1 to liver compartment 2
ABLOOD	TOSOF1	1.16E-01	5.52E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 1
ABLOOD	S2HAIR	7.63E-02	3.63E-02	Deposition fraction from soft tissue compartment 1 to other excreta
ABLOOD	H1TOSI	8.91E-02	2.49E-02	Fraction of transfer out of liver compartment 1 to the small intestine
ABLOOD	TOSOF2	9.31E-03	1.76E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 2
ABLOOD	RCORT	9.00E-02	1.27E-02	Age-scaled transfer rate from non-exchangeable cortical bone to diffusible plasma
ABLOOD	RTS2B	8.11E-03	1.17E-02	Age-scaled transfer rate from surface trabecular bone to exchangeable trabecular bone
ABLOOD	RTS2DF	7.59E-03	1.17E-02	Age-scaled transfer rate from trabecular bone surface to diffusible plasma
ABLOOD	RTRAB	2.12E-02	1.06E-02	Age-scaled transfer rate from non-exchangeable trabecular bone to diffusible plasma
ABLOOD	RDIFF	6.04E-02	1.04E-02	Age-scaled transfer rate from the exchangeable bone, including transfer to surface and non-exchangeable bone

Variable	Parameter	Child	Adult	Parameter Description
ABLOOD	TOFECE	3.23E-02	9.00E-03	Deposition fraction from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by RLVR1)
ABLOOD	TOPROT	1.06E-02	8.24E-03	Deposition fraction from diffusible plasma to protein-bound plasma
ABLOOD	TOKDN2	3.81E-03	3.28E-03	Deposition fraction from diffusible plasma to kidney compartment 2
ABLOOD	TOBRAN	5.10E-03	2.62E-03	Age-scaled deposition fraction from diffusible plasma to brain
ABLOOD	RSOF2	8.49E-03	2.40E-03	Transfer rate from soft tissue compartment 2 to diffusible plasma
ABLOOD	RPROT	3.38E-03	1.66E-03	Transfer rate from bound plasma to diffusible plasma
ABLOOD	RCS2DF	2.21E-02	1.57E-03	Age-scaled transfer rate from cortical bone surface to diffusible plasma
ABLOOD	RCS2B	2.42E-02	1.34E-03	Age-scaled transfer rate from cortical bone surface to exchangeable cortical bone
ABLOOD	FLONG	4.12E-02	1.25E-03	Age-scaled fraction of total transfer from the exchangeable bone directed to non-exchangeable bone
ABLOOD	RSOF1	5.63E-03	4.37E-04	Transfer rate from soft tissue compartment 1 to diffusible plasma
ABLOOD	RPLAS	6.95E-04	2.94E-04	Total transfer rate from diffusible plasma to all compartments
ABLOOD	RLVR2	3.70E-03	2.20E-04	Age-scaled transfer rate from the slow liver compartment 2 to diffusible plasma
ABLOOD	RBRAN	1.66E-03	1.76E-04	Age-scaled transfer rate from brain to diffusible plasma
ABLOOD	RLVR1	3.03E-03	1.00E-04	Transfer rate out of the liver compartment 1, including to small intestine and diffusible plasma
ABLOOD	RSOF0	3.74E-04	1.09E-05	Transfer rate from soft tissue compartment 0 to diffusible plasma
ABLOOD	RKDN2	1.93E-04	1.09E-05	Age-scaled transfer rate from kidney compartment 2 to diffusible plasma
ABLOOD	TOKDN1	1.18E-05	5.81E-06	Deposition fraction from diffusible plasma to kidney compartment 1
ABLOOD	TOURIN	8.88E-06	4.35E-06	Deposition fraction from diffusible plasma to urine
ABLOOD	RSTMC	1.42E-05	3.62E-06	Transfer rate from stomach to small intestine
ABLOOD	SIZEVF	6.52E-06	3.27E-06	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)
ABLOOD	GSCAL	2.30E-05	2.63E-06	Age-scaling factor for GIT transfer
ABLOOD	RULI	4.98E-05	1.07E-06	Transfer rate from upper large intestine to lower large intestine

Variable	Parameter	Child	Adult	Parameter Description
ABLOOD	TOSWET	2.18E-06	1.06E-06	Deposition fraction from diffusible plasma to sweat
ABLOOD	RSIC	5.92E-05	7.18E-07	Transfer rate from small intestine to upper large intestine
ABLOOD	RLLI	5.28E-06	1.16E-07	Transfer rate from lower large intestine to feces
ABLOOD	RKDN1	5.83E-10	1.31E-08	Transfer rate from kidney compartment 1 to urinary pathway
ABLOOD	POWER	0.00E+00	0.00E+00	Exponent for RBC deposition
ABLOOD	RBCNL	0.00E+00	0.00E+00	Threshold concentration in RBC for non-linear deposition from diffusible plasma to RBC
ABLOOD	SATRAT	0.00E+00	0.00E+00	Maximum (saturating) concentration of lead in RBC
ABLOOD	RBLAD	0.00E+00	0.00E+00	Age-scaled transfer rate from urinary bladder to urine

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1 **TABLE 4-5. AALM-LG STANDARDIZED SENSITIVITY COEFFICIENTS FOR BONE PB IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ABONE	TEVF	8.11E+00	8.12E+00	Deposition fraction from diffusible plasma to extravascular fluid
ABONE	TORBC	3.75E+00	3.71E+00	Deposition fraction from diffusible plasma to RBCs, below non-linear threshold
ABONE	TBONE	1.27E+00	1.42E+00	Age-scaled deposition fraction from diffusible plasma to surface bone
ABONE	TOSOF0	1.31E+00	1.32E+00	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 0
ABONE	TBONEL	1.07E+00	1.05E+00	Terminal value of age-scaled deposition fraction from diffusible plasma to surface bone
ABONE	FLONG	3.93E-01	6.80E-01	Age-scaled fraction of total transfer from the exchangeable bone directed to non-exchangeable bone
ABONE	RCS2DF	5.33E-01	6.02E-01	Age-scaled transfer rate from cortical bone surface to diffusible plasma
ABONE	TOLVR1	4.44E-01	3.70E-01	Deposition fraction from diffusible plasma to liver compartment 2
ABONE	H1TOBL	2.81E-01	2.78E-01	Fraction of transfer out of liver compartment 1 to diffusible plasma
ABONE	RTS2DF	1.36E-01	1.48E-01	Age-scaled transfer rate from trabecular bone surface to diffusible plasma
ABONE	TOSOF1	9.53E-02	7.79E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 1
ABONE	H1TOH2	6.29E-02	6.13E-02	Fraction of transfer out of liver compartment 1 to liver compartment 2
ABONE	H1TOSI	9.98E-02	3.06E-02	Fraction of transfer out of liver compartment 1 to the small intestine
ABONE	TOSOF2	5.70E-03	1.94E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 2
ABONE	TOFECE	3.60E-02	1.11E-02	Deposition fraction from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by RLVR1)
ABONE	TOPROT	6.28E-03	6.20E-03	Deposition fraction from diffusible plasma to protein-bound plasma
ABONE	TOBRAN	3.68E-03	3.25E-03	Age-scaled deposition fraction from diffusible plasma to brain
ABONE	TOKDN2	3.13E-03	3.05E-03	Deposition fraction from diffusible plasma to kidney compartment 2
ABONE	RLVR2	8.15E-04	6.26E-04	Age-scaled transfer rate from the slow liver compartment 2 to diffusible plasma

Variable	Parameter	Child	Adult	Parameter Description
ABONE	RKDN2	3.09E-05	3.22E-05	Age-scaled transfer rate from kidney compartment 2 to diffusible plasma
ABONE	GSCAL	4.15E-05	1.35E-05	Age-scaling factor for GIT transfer
ABONE	RULI	8.28E-05	6.79E-06	Transfer rate from upper large intestine to lower large intestine
ABONE	RLLI	8.76E-06	7.29E-07	Transfer rate from lower large intestine to feces
ABONE	RKDN1	9.84E-10	8.50E-08	Transfer rate from kidney compartment 1 to urinary pathway
ABONE	POWER	0.00E+00	0.00E+00	Exponent for RBC deposition
ABONE	RBCNL	0.00E+00	0.00E+00	Threshold concentration in RBC for non-linear deposition from diffusible plasma to RBC
ABONE	SATRAT	0.00E+00	0.00E+00	Maximum (saturating) concentration of lead in RBC
ABONE	RBLAD	0.00E+00	0.00E+00	Age-scaled transfer rate from urinary bladder to urine
ABONE	TOSWET	1.38E-08	9.86E-09	Deposition fraction from diffusible plasma to sweat
ABONE	TOURIN	5.72E-08	4.07E-08	Deposition fraction from diffusible plasma to urine
ABONE	TOKDN1	7.63E-08	1.38E-07	Deposition fraction from diffusible plasma to kidney compartment 1
ABONE	RPROT	5.69E-06	3.42E-06	Transfer rate from bound plasma to diffusible plasma
ABONE	RSIC	1.12E-04	8.33E-06	Transfer rate from small intestine to upper large intestine
ABONE	SIZEVF	4.23E-06	2.34E-05	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)
ABONE	RSTMC	1.52E-05	2.48E-05	Transfer rate from stomach to small intestine
ABONE	RPLAS	3.87E-05	3.19E-05	Total transfer rate from diffusible plasma to all compartments
ABONE	RSOF0	7.55E-05	4.18E-05	Transfer rate from soft tissue compartment 0 to diffusible plasma
ABONE	RRBC	1.06E-03	6.84E-05	Age-scaled transfer rate from RBC to diffusible plasma
ABONE	RLVR1	1.51E-04	4.01E-04	Transfer rate out of the liver compartment 1, including to small intestine and diffusible plasma
ABONE	RBRAN	1.82E-03	1.03E-03	Age-scaled transfer rate from brain to diffusible plasma
ABONE	RSOF2	6.31E-03	1.26E-03	Transfer rate from soft tissue compartment 2 to diffusible plasma
ABONE	RSOF1	1.16E-03	2.10E-03	Transfer rate from soft tissue compartment 1 to diffusible plasma
ABONE	S2HAIR	6.27E-02	5.13E-02	Deposition fraction from soft tissue compartment 1 to other excreta

Variable	Parameter	Child	Adult	Parameter Description
ABONE	RDIFF	2.93E-01	8.41E-02	Age-scaled transfer rate from the exchangeable bone, including transfer to surface and non-exchangeable bone
ABONE	RTS2B	1.38E-01	1.48E-01	Age-scaled transfer rate from surface trabecular bone to exchangeable trabecular bone
ABONE	RTRAB	1.17E-01	1.83E-01	Age-scaled transfer rate from non-exchangeable trabecular bone to diffusible plasma
ABONE	TFRAC	1.03E-02	3.00E-01	Bone deposition-scaled fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone; 1-TFRAC is the fraction that goes to cortical surface bone
ABONE	RCS2B	5.41E-01	6.03E-01	Age-scaled transfer rate from cortical bone surface to exchangeable cortical bone
ABONE	RCORT	4.61E-01	7.07E-01	Age-scaled transfer rate from non-exchangeable cortical bone to diffusible plasma

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1 **TABLE 4-6. AALM-LG STANDARDIZED SENSITIVITY COEFFICIENTS FOR LIVER PB IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ALIVER	TEVF	8.91E+00	8.41E+00	Deposition fraction from diffusible plasma to extravascular fluid
ALIVER	TORBC	4.19E+00	3.94E+00	Deposition fraction from diffusible plasma to RBCs, below non-linear threshold
ALIVER	TOSOF0	1.46E+00	1.45E+00	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 0
ALIVER	TOLVR1	1.48E+00	1.39E+00	Deposition fraction from diffusible plasma to liver compartment 2
ALIVER	TBONEL	1.39E+00	1.31E+00	Terminal value of age-scaled deposition fraction from diffusible plasma to surface bone
ALIVER	H1TOH2	6.09E-01	8.54E-01	Fraction of transfer out of liver compartment 1 to liver compartment 2
ALIVER	RLVR2	5.99E-01	7.92E-01	Age-scaled transfer rate from the slow liver compartment 2 to diffusible plasma
ALIVER	H1TOBL	3.16E-01	2.95E-01	Fraction of transfer out of liver compartment 1 to diffusible plasma
ALIVER	RLVR1	4.83E-01	2.14E-01	Transfer rate out of the liver compartment 1, including to small intestine and diffusible plasma
ALIVER	TBONE	6.32E-02	7.96E-02	Age-scaled deposition fraction from diffusible plasma to surface bone
ALIVER	TFRAC	7.36E-03	7.60E-02	Bone deposition-scaled fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone; 1-TFRAC is the fraction that goes to cortical surface bone
ALIVER	TOSOF1	1.12E-01	5.62E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 1
ALIVER	S2HAIR	7.35E-02	3.69E-02	Deposition fraction from soft tissue compartment 1 to other excreta
ALIVER	H1TOSI	9.28E-02	2.54E-02	Fraction of transfer out of liver compartment 1 to the small intestine
ALIVER	TOSOF2	8.37E-03	1.77E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 2
ALIVER	RCORT	9.61E-02	1.41E-02	Age-scaled transfer rate from non-exchangeable cortical bone to diffusible plasma
ALIVER	RTS2B	3.07E-03	1.36E-02	Age-scaled transfer rate from surface trabecular bone to exchangeable trabecular bone
ALIVER	RTS2DF	2.66E-03	1.35E-02	Age-scaled transfer rate from trabecular bone surface to diffusible plasma
ALIVER	RDIFF	4.72E-02	1.26E-02	Age-scaled transfer rate from the exchangeable bone, including transfer to surface and non-exchangeable bone

Variable	Parameter	Child	Adult	Parameter Description
ALIVER	TOFECE	3.34E-02	9.08E-03	Deposition fraction from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by RLVR1)
ALIVER	RTRAB	2.34E-02	8.01E-03	Age-scaled transfer rate from non-exchangeable trabecular bone to diffusible plasma
ALIVER	TOPROT	7.10E-03	6.65E-03	Deposition fraction from diffusible plasma to protein-bound plasma
ALIVER	TOKDN2	3.67E-03	3.29E-03	Deposition fraction from diffusible plasma to kidney compartment 2
ALIVER	TOBRAN	4.79E-03	2.64E-03	Age-scaled deposition fraction from diffusible plasma to brain
ALIVER	RSOF2	7.94E-03	2.61E-03	Transfer rate from soft tissue compartment 2 to diffusible plasma
ALIVER	RCS2DF	5.38E-03	1.75E-03	Age-scaled transfer rate from cortical bone surface to diffusible plasma
ALIVER	RCS2B	7.19E-03	1.48E-03	Age-scaled transfer rate from cortical bone surface to exchangeable cortical bone
ALIVER	FLONG	4.94E-02	7.59E-04	Age-scaled fraction of total transfer from the exchangeable bone directed to non-exchangeable bone
ALIVER	RSOF1	4.17E-03	5.79E-04	Transfer rate from soft tissue compartment 1 to diffusible plasma
ALIVER	RRBC	2.10E-03	2.48E-04	Age-scaled transfer rate from RBC to diffusible plasma
ALIVER	RBRAN	1.76E-03	1.89E-04	Age-scaled transfer rate from brain to diffusible plasma
ALIVER	RSOF0	3.13E-04	1.22E-05	Transfer rate from soft tissue compartment 0 to diffusible plasma
ALIVER	RPLAS	5.46E-05	5.13E-06	Total transfer rate from diffusible plasma to all compartments
ALIVER	GSCAL	2.56E-05	3.35E-06	Age-scaling factor for GIT transfer
ALIVER	RSTMC	2.51E-05	3.23E-06	Transfer rate from stomach to small intestine
ALIVER	SIZEVF	6.72E-06	2.84E-06	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)
ALIVER	RKDN2	1.45E-04	2.69E-06	Age-scaled transfer rate from kidney compartment 2 to diffusible plasma
ALIVER	RULI	5.24E-05	1.17E-06	Transfer rate from upper large intestine to lower large intestine
ALIVER	RPROT	2.25E-05	9.68E-07	Transfer rate from bound plasma to diffusible plasma
ALIVER	RSIC	5.27E-05	2.33E-07	Transfer rate from small intestine to upper large intestine
ALIVER	RLLI	5.56E-06	1.27E-07	Transfer rate from lower large intestine to feces

Variable	Parameter	Child	Adult	Parameter Description
ALIVER	TOKDN1	3.12E-07	3.12E-08	Deposition fraction from diffusible plasma to kidney compartment 1
ALIVER	RKDN1	6.21E-10	1.44E-08	Transfer rate from kidney compartment 1 to urinary pathway
ALIVER	TOURIN	2.34E-07	1.28E-08	Deposition fraction from diffusible plasma to urine
ALIVER	TOSWET	5.69E-08	3.10E-09	Deposition fraction from diffusible plasma to sweat
ALIVER	POWER	0.00E+00	0.00E+00	Exponent for RBC deposition
ALIVER	RBCNL	0.00E+00	0.00E+00	Threshold concentration in RBC for non-linear deposition from diffusible plasma to RBC
ALIVER	SATRAT	0.00E+00	0.00E+00	Maximum (saturating) concentration of lead in RBC
ALIVER	RBLAD	0.00E+00	0.00E+00	Age-scaled transfer rate from urinary bladder to urine

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1 **TABLE 4-7. AALM-LG STANDARDIZED SENSITIVITY COEFFICIENTS FOR KIDNEY PB IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
AKIDNEY	TEVF	9.08E+00	8.40E+00	Deposition fraction from diffusible plasma to extravascular fluid
AKIDNEY	TORBC	4.27E+00	3.94E+00	Deposition fraction from diffusible plasma to RBCs, below non-linear threshold
AKIDNEY	TOSOF0	1.48E+00	1.44E+00	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 0
AKIDNEY	TBONEL	1.41E+00	1.31E+00	Terminal value of age-scaled deposition fraction from diffusible plasma to surface bone
AKIDNEY	RKDN1	8.20E-01	5.76E-01	Transfer rate from kidney compartment 1 to urinary pathway
AKIDNEY	TOKDN1	8.15E-01	5.76E-01	Deposition fraction from diffusible plasma to kidney compartment 1
AKIDNEY	TOKDN2	1.91E-01	4.30E-01	Deposition fraction from diffusible plasma to kidney compartment 2
AKIDNEY	RKDN2	2.08E-01	4.27E-01	Age-scaled transfer rate from kidney compartment 2 to diffusible plasma
AKIDNEY	TOLVR1	4.88E-01	3.87E-01	Deposition fraction from diffusible plasma to liver compartment 2
AKIDNEY	H1TOBL	3.22E-01	2.95E-01	Fraction of transfer out of liver compartment 1 to diffusible plasma
AKIDNEY	TBONE	9.11E-02	7.58E-02	Age-scaled deposition fraction from diffusible plasma to surface bone
AKIDNEY	TFRAC	8.00E-03	7.36E-02	Bone deposition-scaled fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone; 1-TFRAC is the fraction that goes to cortical surface bone
AKIDNEY	H1TOH2	7.60E-02	6.59E-02	Fraction of transfer out of liver compartment 1 to liver compartment 2
AKIDNEY	TOSOF1	1.15E-01	5.57E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 1
AKIDNEY	S2HAIR	7.53E-02	3.66E-02	Deposition fraction from soft tissue compartment 1 to other excreta
AKIDNEY	H1TOSI	9.02E-02	2.51E-02	Fraction of transfer out of liver compartment 1 to the small intestine
AKIDNEY	TOSOF2	8.99E-03	1.76E-02	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 2
AKIDNEY	RCORT	9.20E-02	1.34E-02	Age-scaled transfer rate from non-exchangeable cortical bone to diffusible plasma
AKIDNEY	RTS2B	6.42E-03	1.27E-02	Age-scaled transfer rate from surface trabecular bone to exchangeable trabecular bone

Variable	Parameter	Child	Adult	Parameter Description
AKIDNEY	RTS2DF	5.94E-03	1.26E-02	Age-scaled transfer rate from trabecular bone surface to diffusible plasma
AKIDNEY	RDIFF	5.60E-02	1.16E-02	Age-scaled transfer rate from the exchangeable bone, including transfer to surface and non-exchangeable bone
AKIDNEY	RTRAB	2.21E-02	9.30E-03	Age-scaled transfer rate from non-exchangeable trabecular bone to diffusible plasma
AKIDNEY	TOFECE	3.27E-02	9.04E-03	Deposition fraction from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by RLVR1)
AKIDNEY	TOPROT	7.16E-03	6.58E-03	Deposition fraction from diffusible plasma to protein-bound plasma
AKIDNEY	TOBRAN	4.99E-03	2.63E-03	Age-scaled deposition fraction from diffusible plasma to brain
AKIDNEY	RSOF2	8.31E-03	2.51E-03	Transfer rate from soft tissue compartment 2 to diffusible plasma
AKIDNEY	RCS2DF	1.65E-02	1.67E-03	Age-scaled transfer rate from cortical bone surface to diffusible plasma
AKIDNEY	RCS2B	1.85E-02	1.41E-03	Age-scaled transfer rate from cortical bone surface to exchangeable cortical bone
AKIDNEY	FLONG	4.39E-02	9.93E-04	Age-scaled fraction of total transfer from the exchangeable bone directed to non-exchangeable bone
AKIDNEY	RSOF1	5.14E-03	5.12E-04	Transfer rate from soft tissue compartment 1 to diffusible plasma
AKIDNEY	RRBC	2.76E-03	2.28E-04	Age-scaled transfer rate from RBC to diffusible plasma
AKIDNEY	RBRAN	1.69E-03	1.83E-04	Age-scaled transfer rate from brain to diffusible plasma
AKIDNEY	RLVR2	3.37E-03	1.32E-04	Age-scaled transfer rate from the slow liver compartment 2 to diffusible plasma
AKIDNEY	RLVR1	2.85E-03	1.07E-04	Transfer rate out of the liver compartment 1, including to small intestine and diffusible plasma
AKIDNEY	RSOF0	3.53E-04	1.16E-05	Transfer rate from soft tissue compartment 0 to diffusible plasma
AKIDNEY	RPLAS	4.93E-05	5.15E-06	Total transfer rate from diffusible plasma to all compartments
AKIDNEY	RSTMC	1.74E-05	3.41E-06	Transfer rate from stomach to small intestine
AKIDNEY	SIZEVF	2.54E-06	3.05E-06	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)
AKIDNEY	GSCAL	2.37E-05	3.01E-06	Age-scaling factor for GIT transfer

Variable	Parameter	Child	Adult	Parameter Description
AKIDNEY	RULI	5.06E-05	1.12E-06	Transfer rate from upper large intestine to lower large intestine
AKIDNEY	RPROT	2.54E-05	9.09E-07	Transfer rate from bound plasma to diffusible plasma
AKIDNEY	RSIC	5.75E-05	2.19E-07	Transfer rate from small intestine to upper large intestine
AKIDNEY	RLLI	5.33E-06	1.21E-07	Transfer rate from lower large intestine to feces
AKIDNEY	TOURIN	2.64E-07	1.21E-08	Deposition fraction from diffusible plasma to urine
AKIDNEY	TOSWET	6.43E-08	2.93E-09	Deposition fraction from diffusible plasma to sweat
AKIDNEY	POWER	0.00E+00	0.00E+00	Exponent for RBC deposition
AKIDNEY	RBCNL	0.00E+00	0.00E+00	Threshold concentration in RBC for non-linear deposition from diffusible plasma to RBC
AKIDNEY	SATRAT	0.00E+00	0.00E+00	Maximum (saturating) concentration of lead in RBC
AKIDNEY	RBLAD	0.00E+00	0.00E+00	Age-scaled transfer rate from urinary bladder to urine

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1 **TABLE 4-8. AALM-LG STANDARDIZED SENSITIVITY COEFFICIENTS FOR OTHER SOFT**
 2 **TISSUE PB IN CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ASOFT	TEVF	6.63E+00	8.12E+00	Deposition fraction from diffusible plasma to extravascular fluid
ASOFT	TORBC	3.14E+00	3.81E+00	Deposition fraction from diffusible plasma to RBCs, below non-linear threshold
ASOFT	TOSOF0	1.10E+00	1.39E+00	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 0
ASOFT	TBONEL	1.06E+00	1.27E+00	Terminal value of age-scaled deposition fraction from diffusible plasma to surface bone
ASOFT	RSOF2	2.36E-01	8.95E-01	Transfer rate from soft tissue compartment 2 to diffusible plasma
ASOFT	TOSOF2	4.68E-01	7.90E-01	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 2
ASOFT	TOLVR1	3.71E-01	3.80E-01	Deposition fraction from diffusible plasma to liver compartment 2
ASOFT	H1TOBL	2.35E-01	2.86E-01	Fraction of transfer out of liver compartment 1 to diffusible plasma
ASOFT	TOSOF1	4.74E-01	2.71E-01	Age-scaled deposition fraction from diffusible plasma to soft tissue compartment 1
ASOFT	RSOF1	4.36E-01	2.04E-01	Transfer rate from soft tissue compartment 1 to diffusible plasma
ASOFT	TFRAC	3.97E-03	6.66E-02	Bone deposition-scaled fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone; 1-TFRAC is the fraction that goes to cortical surface bone
ASOFT	H1TOH2	5.20E-02	6.32E-02	Fraction of transfer out of liver compartment 1 to liver compartment 2
ASOFT	S2HAIR	5.19E-02	4.28E-02	Deposition fraction from soft tissue compartment 1 to other excreta
ASOFT	TBONE	1.17E-01	3.82E-02	Age-scaled deposition fraction from diffusible plasma to surface bone
ASOFT	H1TOSI	8.38E-02	3.11E-02	Fraction of transfer out of liver compartment 1 to the small intestine
ASOFT	RCORT	9.33E-02	2.72E-02	Age-scaled transfer rate from non-exchangeable cortical bone to diffusible plasma
ASOFT	FLONG	6.62E-02	2.38E-02	Age-scaled fraction of total transfer from the exchangeable bone directed to non-exchangeable bone
ASOFT	RDIF	1.38E-02	1.85E-02	Age-scaled transfer rate from the exchangeable bone, including transfer to surface and non-exchangeable bone

Variable	Parameter	Child	Adult	Parameter Description
ASOFT	RSOF0	9.54E-03	1.20E-02	Transfer rate from soft tissue compartment 0 to diffusible plasma
ASOFT	TOFECE	2.99E-02	1.12E-02	Deposition fraction from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by RLVR1)
ASOFT	RCS2DF	5.93E-02	1.07E-02	Age-scaled transfer rate from cortical bone surface to diffusible plasma
ASOFT	RCS2B	5.94E-02	1.02E-02	Age-scaled transfer rate from cortical bone surface to exchangeable cortical bone
ASOFT	TOPROT	5.25E-03	6.37E-03	Deposition fraction from diffusible plasma to protein-bound plasma
ASOFT	RTS2B	1.48E-02	5.37E-03	Age-scaled transfer rate from surface trabecular bone to exchangeable trabecular bone
ASOFT	RTS2DF	1.48E-02	5.23E-03	Age-scaled transfer rate from trabecular bone surface to diffusible plasma
ASOFT	RTRAB	2.34E-02	3.25E-03	Age-scaled transfer rate from non-exchangeable trabecular bone to diffusible plasma
ASOFT	TOKDN2	2.59E-03	3.15E-03	Deposition fraction from diffusible plasma to kidney compartment 2
ASOFT	TOBRAN	3.04E-03	2.83E-03	Age-scaled deposition fraction from diffusible plasma to brain
ASOFT	RLVR2	1.04E-03	6.65E-04	Age-scaled transfer rate from the slow liver compartment 2 to diffusible plasma
ASOFT	RBRAN	1.49E-03	3.24E-04	Age-scaled transfer rate from brain to diffusible plasma
ASOFT	RLVR1	4.97E-04	8.64E-05	Transfer rate out of the liver compartment 1, including to small intestine and diffusible plasma
ASOFT	RRBC	1.51E-03	6.63E-05	Age-scaled transfer rate from RBC to diffusible plasma
ASOFT	RKDN2	4.71E-05	3.31E-05	Age-scaled transfer rate from kidney compartment 2 to diffusible plasma
ASOFT	RSIC	7.97E-05	1.29E-05	Transfer rate from small intestine to upper large intestine
ASOFT	GSCAL	5.87E-05	1.26E-05	Age-scaling factor for GIT transfer
ASOFT	RPLAS	4.96E-06	4.38E-06	Total transfer rate from diffusible plasma to all compartments
ASOFT	RULI	3.04E-05	4.28E-06	Transfer rate from upper large intestine to lower large intestine
ASOFT	RPROT	4.81E-07	1.18E-06	Transfer rate from bound plasma to diffusible plasma
ASOFT	RLLI	3.76E-06	5.16E-07	Transfer rate from lower large intestine to feces

Variable	Parameter	Child	Adult	Parameter Description
ASOFT	SIZEVF	5.87E-07	5.06E-07	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)
ASOFT	RSTMC	5.46E-06	1.73E-07	Transfer rate from stomach to small intestine
ASOFT	TOKDN1	8.53E-09	4.76E-08	Deposition fraction from diffusible plasma to kidney compartment 1
ASOFT	RKDN1	3.29E-11	3.21E-08	Transfer rate from kidney compartment 1 to urinary pathway
ASOFT	TOURIN	6.40E-09	1.19E-08	Deposition fraction from diffusible plasma to urine
ASOFT	TOSWET	1.54E-09	2.88E-09	Deposition fraction from diffusible plasma to sweat
ASOFT	POWER	0.00E+00	0.00E+00	Exponent for RBC deposition
ASOFT	RBCNL	0.00E+00	0.00E+00	Threshold concentration in RBC for non-linear deposition from diffusible plasma to RBC
ASOFT	SATRAT	0.00E+00	0.00E+00	Maximum (saturating) concentration of lead in RBC
ASOFT	RBLAD	0.00E+00	0.00E+00	Age-scaled transfer rate from urinary bladder to urine

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1 **TABLE 4-9. AALM-OF STANDARDIZED SENSITIVITY COEFFICIENTS FOR BLOOD PB IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ABLOOD	C1	2.41E+00	9.34E+00	Constant 1 for urinary clearance of Pb as a fraction of GFR
ABLOOD	C2	1.38E+00	7.54E+00	Constant 2 for urinary clearance of Pb as a fraction of GFR
ABLOOD	BIND	9.92E-01	9.92E-01	Maximum capacity of sites in red cells to bind Pb
ABLOOD	KBIND	9.88E-01	9.89E-01	Half-saturation concentration of Pb for binding by sites in red cells
ABLOOD	P0	5.73E-03	6.19E-02	Permeability constant for diffusion from canaliculi to bone
ABLOOD	R0	4.96E-03	5.58E-02	Permeability constant for diffusion from bone to canaliculi
ABLOOD	RAD8	4.27E-03	3.97E-02	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
ABLOOD	CON	7.51E-04	2.50E-02	Fraction of bone blood flow to trabecular bone
ABLOOD	D0	9.99E-04	1.07E-02	Diffusion constant
ABLOOD	BASE	1.72E-04	9.01E-03	Base bone formation rate in bone growth algorithm
ABLOOD	C3	4.46E-01	7.10E-03	Constant 3 for urinary clearance of Pb as a fraction of GFR
ABLOOD	S	8.26E-04	6.67E-03	Surface area of canaliculi
ABLOOD	RAD1	6.66E-04	5.09E-03	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
ABLOOD	G	1.13E-02	3.48E-03	Linear parameter for unbound lead in red cells
ABLOOD	RAD2	3.67E-04	2.85E-03	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone
ABLOOD	RAD3	2.27E-04	2.16E-03	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
ABLOOD	PL	1.12E-02	2.08E-03	Liver/plasma partition coefficient
ABLOOD	RAD4	1.51E-04	1.88E-03	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
ABLOOD	RAD5	1.04E-04	1.64E-03	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
ABLOOD	RAD6	6.93E-05	1.29E-03	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
ABLOOD	EXPO	7.16E-03	1.12E-03	Exponent constant for bone volume participating in adult-type bone remodeling
ABLOOD	QKC	1.52E-03	1.11E-03	Fraction cardiac output going to kidney
ABLOOD	A1	9.16E-03	1.01E-03	Constant 1 for bone formation rate algorithm
ABLOOD	A3	4.20E-03	9.44E-04	Constant 3 for bone formation rate algorithm

Variable	Parameter	Child	Adult	Parameter Description
ABLOOD	QWC	1.33E-02	9.31E-04	Fraction cardiac output going to other well-perfused tissues
ABLOOD	QLC	1.32E-02	9.16E-04	Fraction cardiac output going to liver
ABLOOD	RAD7	3.62E-05	7.55E-04	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
ABLOOD	A5	0.00E+00	6.65E-04	Constant 5 for bone formation rate algorithm
ABLOOD	PW	2.64E-03	6.07E-04	Well-perfused/plasma partition coefficient
ABLOOD	A2	3.06E-03	1.98E-04	Constant 2 for bone formation rate algorithm
ABLOOD	QBONEC	7.94E-03	1.62E-04	Fraction cardiac output going to bone
ABLOOD	PP	8.01E-05	1.12E-04	Poorly perfused/plasma partition coefficient
ABLOOD	PK	3.60E-05	2.25E-05	Kidney/plasma partition coefficient
ABLOOD	QCC	0.00E+00	0.00E+00	Cardiac output in the adult

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1 **TABLE 4-10. AALM-OF STANDARDIZED SENSITIVITY COEFFICIENTS FOR BONE PB IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ABONE	C1	1.99E+00	8.70E+00	Constant 1 for urinary clearance of Pb as a fraction of GFR
ABONE	C2	9.73E-01	7.12E+00	Constant 2 for urinary clearance of Pb as a fraction of GFR
ABONE	R0	2.79E-02	2.14E-01	Permeability constant for diffusion from bone to canaliculi
ABONE	RAD8	2.63E-02	1.64E-01	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
ABONE	P0	5.73E-03	6.19E-02	Permeability constant for diffusion from canaliculi to bone
ABONE	D0	5.61E-03	4.12E-02	Diffusion constant
ABONE	CON	8.59E-02	3.71E-02	Fraction of bone blood flow to trabecular bone
ABONE	EXPO	2.16E-01	3.07E-02	Exponent constant for bone volume participating in adult-type bone remodeling
ABONE	S	5.50E-03	2.97E-02	Surface area of canaliculi
ABONE	C3	3.78E-01	2.47E-02	Constant 3 for urinary clearance of Pb as a fraction of GFR
ABONE	RAD1	4.42E-03	2.35E-02	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
ABONE	RAD2	2.28E-03	1.29E-02	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone
ABONE	BASE	4.36E-05	1.08E-02	Base bone formation rate in bone growth algorithm
ABONE	RAD3	1.35E-03	9.01E-03	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
ABONE	RAD4	8.09E-04	6.94E-03	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
ABONE	RAD5	4.66E-04	5.34E-03	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
ABONE	RAD6	2.46E-04	3.78E-03	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
ABONE	RAD7	1.06E-04	2.07E-03	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
ABONE	A3	6.95E-03	1.18E-03	Constant 3 for bone formation rate algorithm
ABONE	PL	3.82E-03	1.10E-03	Liver/plasma partition coefficient
ABONE	QKC	4.17E-03	9.41E-04	Fraction cardiac output going to kidney
ABONE	PW	6.23E-03	9.31E-04	Well-perfused/plasma partition coefficient
ABONE	BIND	1.37E-03	8.40E-04	Maximum capacity of sites in red cells to bind Pb
ABONE	KBIND	1.12E-03	8.30E-04	Half-saturation concentration of Pb for binding by sites in red cells

Variable	Parameter	Child	Adult	Parameter Description
ABONE	G	2.96E-03	5.62E-04	Linear parameter for unbound lead in red cells
ABONE	QBONEC	2.66E-03	5.61E-04	Fraction cardiac output going to bone
ABONE	A2	3.42E-03	4.88E-04	Constant 2 for bone formation rate algorithm
ABONE	A5	0.00E+00	2.72E-04	Constant 5 for bone formation rate algorithm
ABONE	QLC	9.11E-03	2.41E-04	Fraction cardiac output going to liver
ABONE	QWC	9.22E-03	2.24E-04	Fraction cardiac output going to other well-perfused tissues
ABONE	PP	1.43E-04	1.36E-04	Poorly perfused/plasma partition coefficient
ABONE	A1	1.50E-02	3.05E-05	Constant 1 for bone formation rate algorithm
ABONE	PK	1.73E-04	1.20E-05	Kidney/plasma partition coefficient
ABONE	QCC	0.00E+00	0.00E+00	Cardiac output in the adult

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1 **TABLE 4-11. AALM-OF STANDARDIZED SENSITIVITY COEFFICIENTS FOR LIVER Pb IN**
 2 **CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
ALIVER	C1	2.39E+00	9.28E+00	Constant 1 for urinary clearance of Pb as a fraction of GFR
ALIVER	C2	1.38E+00	7.56E+00	Constant 2 for urinary clearance of Pb as a fraction of GFR
ALIVER	PL	1.01E+00	9.98E-01	Liver/plasma partition coefficient
ALIVER	P0	5.73E-03	6.19E-02	Permeability constant for diffusion from canaliculi to bone
ALIVER	R0	4.98E-03	5.60E-02	Permeability constant for diffusion from bone to canaliculi
ALIVER	RAD8	4.29E-03	3.98E-02	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
ALIVER	CON	7.53E-04	2.51E-02	Fraction of bone blood flow to trabecular bone
ALIVER	D0	1.00E-03	1.07E-02	Diffusion constant
ALIVER	BASE	1.73E-04	9.04E-03	Base bone formation rate in bone growth algorithm
ALIVER	C3	4.48E-01	7.12E-03	Constant 3 for urinary clearance of Pb as a fraction of GFR
ALIVER	S	8.29E-04	6.69E-03	Surface area of canaliculi
ALIVER	RAD1	6.69E-04	5.11E-03	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
ALIVER	RAD2	3.68E-04	2.85E-03	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone
ALIVER	RAD3	2.28E-04	2.16E-03	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
ALIVER	RAD4	1.51E-04	1.89E-03	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
ALIVER	RAD5	1.05E-04	1.65E-03	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
ALIVER	RAD6	6.96E-05	1.29E-03	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
ALIVER	EXPO	7.19E-03	1.12E-03	Exponent constant for bone volume participating in adult-type bone remodeling
ALIVER	QKC	1.24E-03	1.12E-03	Fraction cardiac output going to kidney
ALIVER	A1	9.35E-03	1.01E-03	Constant 1 for bone formation rate algorithm
ALIVER	QLC	1.34E-02	9.67E-04	Fraction cardiac output going to liver
ALIVER	A3	4.21E-03	9.38E-04	Constant 3 for bone formation rate algorithm
ALIVER	QWC	1.33E-02	9.34E-04	Fraction cardiac output going to other well-perfused tissues
ALIVER	BIND	8.28E-04	7.63E-04	Maximum capacity of sites in red cells to bind Pb

Variable	Parameter	Child	Adult	Parameter Description
ALIVER	KBIND	8.44E-04	7.58E-04	Half-saturation concentration of Pb for binding by sites in red cells
ALIVER	RAD7	3.63E-05	7.57E-04	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
ALIVER	A5	0.00E+00	6.67E-04	Constant 5 for bone formation rate algorithm
ALIVER	PW	2.11E-03	6.09E-04	Well-perfused/plasma partition coefficient
ALIVER	A2	3.08E-03	1.98E-04	Constant 2 for bone formation rate algorithm
ALIVER	QBONEC	8.66E-03	1.62E-04	Fraction cardiac output going to bone
ALIVER	G	8.74E-03	1.60E-04	Linear parameter for unbound lead in red cells
ALIVER	PP	8.13E-05	1.14E-04	Poorly perfused/plasma partition coefficient
ALIVER	PK	3.61E-05	2.25E-05	Kidney/plasma partition coefficient
ALIVER	QCC	0.00E+00	0.00E+00	Cardiac output in the adult

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1 **TABLE 4-12. AALM-OF STANDARDIZED SENSITIVITY COEFFICIENTS FOR KIDNEY PB**
 2 **IN CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
AKIDNEY	C1	2.39E+00	9.28E+00	Constant 1 for urinary clearance of Pb as a fraction of GFR
AKIDNEY	C2	1.38E+00	7.56E+00	Constant 2 for urinary clearance of Pb as a fraction of GFR
AKIDNEY	PK	1.00E+00	9.99E-01	Kidney/plasma partition coefficient
AKIDNEY	P0	5.73E-03	6.19E-02	Permeability constant for diffusion from canaliculi to bone
AKIDNEY	R0	4.99E-03	5.60E-02	Permeability constant for diffusion from bone to canaliculi
AKIDNEY	RAD8	4.29E-03	3.98E-02	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	CON	7.53E-04	2.51E-02	Fraction of bone blood flow to trabecular bone
AKIDNEY	D0	1.00E-03	1.07E-02	Diffusion constant
AKIDNEY	BASE	1.73E-04	9.04E-03	Base bone formation rate in bone growth algorithm
AKIDNEY	C3	4.48E-01	7.12E-03	Constant 3 for urinary clearance of Pb as a fraction of GFR
AKIDNEY	S	8.29E-04	6.69E-03	Surface area of canaliculi
AKIDNEY	RAD1	6.69E-04	5.11E-03	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	RAD2	3.68E-04	2.85E-03	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	RAD3	2.28E-04	2.16E-03	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	PL	1.13E-02	2.10E-03	Liver/plasma partition coefficient
AKIDNEY	RAD4	1.51E-04	1.89E-03	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	RAD5	1.05E-04	1.65E-03	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	RAD6	6.96E-05	1.29E-03	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	EXPO	7.19E-03	1.12E-03	Exponent constant for bone volume participating in adult-type bone remodeling
AKIDNEY	QKC	1.47E-03	1.05E-03	Fraction cardiac output going to kidney
AKIDNEY	A1	9.32E-03	1.01E-03	Constant 1 for bone formation rate algorithm
AKIDNEY	A3	4.22E-03	9.37E-04	Constant 3 for bone formation rate algorithm
AKIDNEY	QWC	1.33E-02	9.34E-04	Fraction cardiac output going to other well-perfused tissues
AKIDNEY	QLC	1.32E-02	9.19E-04	Fraction cardiac output going to liver

Variable	Parameter	Child	Adult	Parameter Description
AKIDNEY	RAD7	3.63E-05	7.57E-04	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
AKIDNEY	A5	0.00E+00	6.67E-04	Constant 5 for bone formation rate algorithm
AKIDNEY	BIND	3.64E-04	6.52E-04	Maximum capacity of sites in red cells to bind Pb
AKIDNEY	KBIND	3.85E-04	6.47E-04	Half-saturation concentration of Pb for binding by sites in red cells
AKIDNEY	PW	2.05E-03	6.09E-04	Well-perfused/plasma partition coefficient
AKIDNEY	A2	3.08E-03	1.98E-04	Constant 2 for bone formation rate algorithm
AKIDNEY	QBONEC	8.68E-03	1.62E-04	Fraction cardiac output going to bone
AKIDNEY	G	8.77E-03	1.60E-04	Linear parameter for unbound lead in red cells
AKIDNEY	PP	8.05E-05	1.13E-04	Poorly perfused/plasma partition coefficient
AKIDNEY	QCC	0.00E+00	0.00E+00	Cardiac output in the adult

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1 **TABLE 4-13. AALM-OF STANDARDIZED SENSITIVITY COEFFICIENTS FOR POORLY**
 2 **PERFUSED TISSUES PB IN CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
APOOR	C1	2.39E+00	9.28E+00	Constant 1 for urinary clearance of Pb as a fraction of GFR
APOOR	C2	1.38E+00	7.56E+00	Constant 2 for urinary clearance of Pb as a fraction of GFR
APOOR	PP	1.00E+00	1.00E+00	Poorly perfused/plasma partition coefficient
APOOR	P0	5.73E-03	6.19E-02	Permeability constant for diffusion from canaliculi to bone
APOOR	R0	4.99E-03	5.60E-02	Permeability constant for diffusion from bone to canaliculi
APOOR	RAD8	4.29E-03	3.98E-02	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
APOOR	CON	7.54E-04	2.51E-02	Fraction of bone blood flow to trabecular bone
APOOR	D0	1.00E-03	1.07E-02	Diffusion constant
APOOR	BASE	1.73E-04	9.03E-03	Base bone formation rate in bone growth algorithm
APOOR	C3	4.48E-01	7.12E-03	Constant 3 for urinary clearance of Pb as a fraction of GFR
APOOR	S	8.29E-04	6.69E-03	Surface area of canaliculi
APOOR	RAD1	6.69E-04	5.11E-03	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
APOOR	RAD2	3.68E-04	2.85E-03	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone
APOOR	RAD3	2.28E-04	2.16E-03	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
APOOR	PL	1.13E-02	2.08E-03	Liver/plasma partition coefficient
APOOR	RAD4	1.51E-04	1.89E-03	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
APOOR	RAD5	1.05E-04	1.65E-03	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
APOOR	RAD6	6.96E-05	1.29E-03	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
APOOR	EXPO	7.19E-03	1.12E-03	Exponent constant for bone volume participating in adult-type bone remodeling
APOOR	QKC	1.55E-03	1.12E-03	Fraction cardiac output going to kidney
APOOR	A1	9.13E-03	1.01E-03	Constant 1 for bone formation rate algorithm
APOOR	A3	4.22E-03	9.48E-04	Constant 3 for bone formation rate algorithm
APOOR	QWC	1.34E-02	9.34E-04	Fraction cardiac output going to other well-perfused tissues
APOOR	QLC	1.33E-02	9.19E-04	Fraction cardiac output going to liver

Variable	Parameter	Child	Adult	Parameter Description
APOOR	RAD7	3.63E-05	7.57E-04	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
APOOR	BIND	6.34E-04	7.16E-04	Maximum capacity of sites in red cells to bind Pb
APOOR	KBIND	6.52E-04	7.11E-04	Half-saturation concentration of Pb for binding by sites in red cells
APOOR	A5	0.00E+00	6.67E-04	Constant 5 for bone formation rate algorithm
APOOR	PW	2.74E-03	6.15E-04	Well-perfused/plasma partition coefficient
APOOR	A2	3.08E-03	1.98E-04	Constant 2 for bone formation rate algorithm
APOOR	QBONEC	7.84E-03	1.62E-04	Fraction cardiac output going to bone
APOOR	G	7.92E-03	1.60E-04	Linear parameter for unbound lead in red cells
APOOR	PK	3.62E-05	2.25E-05	Kidney/plasma partition coefficient
APOOR	QCC	0.00E+00	0.00E+00	Cardiac output in the adult

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1 **TABLE 4-14. AALM-OF STANDARDIZED SENSITIVITY COEFFICIENTS FOR WELL-**
 2 **PERFUSED TISSUES PB IN CHILDREN (5 YEARS) AND ADULTS (30 YEARS)**

Variable	Parameter	Child	Adult	Parameter Description
AWELL	C1	2.39E+00	9.28E+00	Constant 1 for urinary clearance of Pb as a fraction of GFR
AWELL	C2	1.38E+00	7.56E+00	Constant 2 for urinary clearance of Pb as a fraction of GFR
AWELL	PW	1.00E+00	1.00E+00	Well-perfused/plasma partition coefficient
AWELL	P0	5.73E-03	6.19E-02	Permeability constant for diffusion from canaliculi to bone
AWELL	R0	4.99E-03	5.60E-02	Permeability constant for diffusion from bone to canaliculi
AWELL	RAD8	4.29E-03	3.98E-02	Radius of shell 8 of bone in the canalicular diffusion region of deeper bone
AWELL	CON	7.53E-04	2.51E-02	Fraction of bone blood flow to trabecular bone
AWELL	D0	1.00E-03	1.07E-02	Diffusion constant
AWELL	BASE	1.73E-04	9.05E-03	Base bone formation rate in bone growth algorithm
AWELL	C3	4.48E-01	7.12E-03	Constant 3 for urinary clearance of Pb as a fraction of GFR
AWELL	S	8.29E-04	6.69E-03	Surface area of canaliculi
AWELL	RAD1	6.69E-04	5.11E-03	Radius of shell 1 of bone in the canalicular diffusion region of deeper bone
AWELL	RAD2	3.68E-04	2.85E-03	Radius of shell 2 of bone in the canalicular diffusion region of deeper bone
AWELL	RAD3	2.28E-04	2.16E-03	Radius of shell 3 of bone in the canalicular diffusion region of deeper bone
AWELL	PL	1.11E-02	2.08E-03	Liver/plasma partition coefficient
AWELL	RAD4	1.51E-04	1.89E-03	Radius of shell 4 of bone in the canalicular diffusion region of deeper bone
AWELL	RAD5	1.05E-04	1.65E-03	Radius of shell 5 of bone in the canalicular diffusion region of deeper bone
AWELL	RAD6	6.96E-05	1.29E-03	Radius of shell 6 of bone in the canalicular diffusion region of deeper bone
AWELL	EXPO	7.19E-03	1.12E-03	Exponent constant for bone volume participating in adult-type bone remodeling
AWELL	QKC	1.09E-03	1.12E-03	Fraction cardiac output going to kidney
AWELL	A1	9.45E-03	1.01E-03	Constant 1 for bone formation rate algorithm
AWELL	QWC	1.32E-02	9.34E-04	Fraction cardiac output going to other well-perfused tissues
AWELL	A3	4.21E-03	9.30E-04	Constant 3 for bone formation rate algorithm
AWELL	QLC	1.31E-02	9.19E-04	Fraction cardiac output going to liver

Variable	Parameter	Child	Adult	Parameter Description
AWELL	RAD7	3.63E-05	7.57E-04	Radius of shell 7 of bone in the canalicular diffusion region of deeper bone
AWELL	BIND	6.34E-04	7.16E-04	Maximum capacity of sites in red cells to bind Pb
AWELL	KBIND	6.52E-04	7.11E-04	Half-saturation concentration of Pb for binding by sites in red cells
AWELL	A5	0.00E+00	6.67E-04	Constant 5 for bone formation rate algorithm
AWELL	A2	3.08E-03	1.98E-04	Constant 2 for bone formation rate algorithm
AWELL	QBONEC	9.15E-03	1.64E-04	Fraction cardiac output going to bone
AWELL	G	9.14E-03	1.60E-04	Linear parameter for unbound lead in red cells
AWELL	PP	8.05E-05	1.13E-04	Poorly perfused/plasma partition coefficient
AWELL	PK	3.61E-05	2.25E-05	Kidney/plasma partition coefficient
AWELL	QCC	0.00E+00	0.00E+00	Cardiac output in the adult

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1 **TABLE 4-15. DOMINANT PARAMETERS INFLUENCING MAJOR DIFFERENCES IN**
 2 **PREDICTIONS FROM AALM-LG AND AALM-OF**

Predicted Variable	Model Difference	Dominant Parameters	
		AALM-LG	AALM-OF
Child blood Pb	AALM-OF < AALM-LG	TEVF TORBC TOSOF0 RRBC TOLVR1 H1TOBL TBONE	C1 C2 BIND KBIND
Child bone Pb	AALM-OF < AALM-LG	TEVF TORBC TBONE TOSOF0 FLONG RCS2DF TOLVR1 H1TOBL RTS2DF	C1 C2 R0 RAD8
Liver Pb	AALM-OF < AALM-LG	TEVF TORBC TOSOF0 TOLVR1 H1TOH2 RLVR2 H1TOBL RLVR1	C1 C2 PL
Kidney Pb	AALM-OF < AALM-LG	TEVF TORBC TOSOF0 RKDN1 TOKDN1 TOKDN2 RKDN2	C1 C2 PK
Other soft tissues	AALM-OF < AALM-LG	TEVF TORBC TOSOF0 RSOF2 TOSOF2 TOLVR1 H1TOBL TOSOF1 RSOF1	C1 C2 PP PW

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1 **TABLE 4-16. STRATEGY USED FOR SEQUENTIAL OPTIMIZATION OF AALM**
 2 **BIOKINETICS MODEL**

Step	Objective	Observation Data Sources
1	Unify parameter values for GI absorption and growth	(O'Flaherty, 1995, 1993)
2	Optimize plasma/RBC ratio	(Smith et al., 2002; Bergdahl et al., 1999; Bergdahl et al., 1998; Hernandez-Avila et al., 1998; Bergdahl et al., 1997; Schutz et al., 1996)
3	Optimize plasma(blood)-to-urine clearance	(Rentschler et al., 2012; Dewoskin and Thompson, 2008; Manton and Cook, 1984; Manton and Malloy, 1983; Chamberlain et al., 1978)
4	Optimize soft tissue (kidney, liver, muscle)/bone ratios	(Gerhardsson et al., 1995; Barry, 1981, 1975; Gross et al., 1975)
5	Optimize plasma(blood)/bone ratios	(Hernandez-Avila et al., 1998; Cake et al., 1996)
6	Optimize bone Pb elimination kinetics	(Nilsson et al., 1991)
7	Evaluate blood Pb elimination kinetics – adults	(Rabinowitz et al., 1976)
8	Evaluate blood Pb elimination kinetics – infants	(Sherlock and Quinn, 1986; Ryu et al., 1983)

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1 **TABLE 4-17. COMPARISON OF PREDICTED AND OBSERVED PLASMA PB/BONE PB**
 2 **SLOPES**

Model	Study	Bone	Predicted Slope	Observed Slope	SE	95%CL	Residual
AALM-LG	CA96	Cortical	0.037	0.052	0.013	0.027, 0.077	-1.16
AALM-LG	CA96	Trabecular	0.040	0.041	0.007	0.027, 0.054	-0.16
AALM-LG	HE98	Cortical	0.037	0.036	0.011	0.014, 0.058	0.12
AALM-LG	HE98	Trabecular	0.040	0.025	0.004	0.017, 0.033	3.67
AALM-OF	CA96	Cortical	0.042	0.052	0.013	0.027, 0.077	-0.81
AALM-OF	CA96	Trabecular	0.060	0.041	0.007	0.027, 0.054	2.70
AALM-OF	HE98	Cortical	0.042	0.036	0.011	0.014, 0.058	0.53
AALM-OF	HE98	Trabecular	0.060	0.025	0.004	0.017, 0.033	8.68

CA96, [Coke et al. \(1996\)](#); HE98, [Hernandez-Avila et al. \(1998\)](#)

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1 **TABLE 4-18. CHANGES TO (O'FLAHERTY, 1995, 1993) AND (LEGGETT, 1993) MODELS**
 2 **INCORPORATED INTO AALM**

Model Component	Parameter Change	AALM-LG	AALM-OF
Growth	Body and tissue growth as functions of age and body weight	X	
Respiratory tract	Simulation of deposition, mucociliary clearance and absorption of inhaled Pb based on ICRP HRTM	X	X
GI tract	Age-dependent absorption calculated with a continuous function rather than age array variable	X	
GI tract	Infant GI absorption fractions optimized	X	X
GI tract	Absorption fraction adjustable by user-specified media-specific relative bioavailability fractions	X	X
Tissue Pb	Age-dependent values for tissue-blood partition coefficients		X
Tissue Pb	Bone, kidney and liver concentrations calculated from Pb masses and tissue weights	X	
Neonate	Neonatal model which sets Pb masses in blood and tissues at birth as a function of maternal Pb concentration	X	X
RBC	Parameters for plasma-RBC binding and uptake optimized	X	X
GFR	Parameters for GFR adjusted to predict adult GFR of 170 L/day/1.73m ² (120 mL/min/1.73m ²) and 30% of adult in infants (<1 year)		X
Urine Pb	Parameters for Pb transfer to urine optimized	X	X

GFR, glomerular filtration rate; GI, gastrointestinal; ICRP, International Commission of Radiological Protection; RBC, red blood cell

1 **TABLE 4-19. COMPARISON OF AALM-LG AND AALM-OF PREDICTIONS OF BLOOD AND**
 2 **TISSUE PB CONCENTRATIONS**

Dose ($\mu\text{g}/\text{day}$)	Age (year)	Sex	Tissue	Unit	AALM-LG	AALM-OF
5	2	M	Blood	$\mu\text{g}/\text{dL}$	1.86	2.39
5	2	M	Bone	$\mu\text{g}/\text{g}$	0.88	0.43
5	2	M	Kidney	$\mu\text{g}/\text{g}$	0.06	0.08
5	2	M	Liver	$\mu\text{g}/\text{g}$	0.14	0.09
5	40	M	Blood	$\mu\text{g}/\text{dL}$	0.28	0.50
5	40	M	Bone	$\mu\text{g}/\text{g}$	0.14	0.15
5	40	M	Kidney	$\mu\text{g}/\text{g}$	0.005	0.010
5	40	M	Liver	$\mu\text{g}/\text{g}$	0.008	0.012
5	2	F	Blood	$\mu\text{g}/\text{dL}$	1.95	2.39
5	2	F	Bone	$\mu\text{g}/\text{g}$	0.93	0.43
5	2	F	Kidney	$\mu\text{g}/\text{g}$	0.07	0.08
5	2	F	Liver	$\mu\text{g}/\text{g}$	0.15	0.09
5	40	F	Blood	$\mu\text{g}/\text{dL}$	0.36	0.50
5	40	F	Bone	$\mu\text{g}/\text{g}$	0.20	0.15
5	40	F	Kidney	$\mu\text{g}/\text{g}$	0.006	0.010
5	40	F	Liver	$\mu\text{g}/\text{g}$	0.010	0.012

F, female; M, male

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1 **TABLE 4-20. COMPARISON OF ADULT LEAD METHODOLOGY, AALM-LG AND AALM-**
 2 **OF PREDICTIONS OF BLOOD PB CONCENTRATIONS IN ADULTS**

Parameter	Description	Units	ALM	AALM-LG	AALM-OF
PbS	Soil lead concentration	µg/g or ppm	1000	1000	1000
BKSF	Biokinetic Slope Factor	µg/dL per µg/day	0.4	NA	NA
PbB ₀	Baseline Blood Pb	µg/dL	1.5	1.5	1.5
IR _S	Soil Ingestion Rate	g/day	0.050	0.05	0.05
AF _{S, D}	Absorption Fraction	--	0.12	0.048	0.048
EF _{S, D}	Exposure Frequency	days/yr	219	219	219
AT _{S, D}	Averaging Time	days/yr	365	365	365
PbB _{adult}	Blood Pb Concentration	µg/dL	2.9	3.1	4.6

ALM, Adult Lead Methodology

3

1 **TABLE 4-21. COMPARISON OF AALM-LG AND AALM-OF PREDICTIONS OF BLOOD AND**
 2 **TISSUE PB CONCENTRATIONS AFTER CALIBRATING RBC PARAMETER VALUES TO**
 3 **THE IEUBK MODEL OUTPUT**

Dose ($\mu\text{g}/\text{day}$)	Age (year)	Sex	Tissue	Unit	AALM-LG	AALM-OF
5	2	M	Blood	$\mu\text{g}/\text{dL}$	1.6	1.2
5	2	M	Bone	$\mu\text{g}/\text{g}$	1.33	0.43
5	2	M	Kidney	$\mu\text{g}/\text{g}$	0.10	0.08
5	2	M	Liver	$\mu\text{g}/\text{g}$	0.21	0.09
5	40	M	Blood	$\mu\text{g}/\text{dL}$	0.28	0.50
5	40	M	Bone	$\mu\text{g}/\text{g}$	0.15	0.15
5	40	M	Kidney	$\mu\text{g}/\text{g}$	0.005	0.010
5	40	M	Liver	$\mu\text{g}/\text{g}$	0.008	0.012
5	2	F	Blood	$\mu\text{g}/\text{dL}$	1.7	1.2
5	2	F	Bone	$\mu\text{g}/\text{g}$	1.42	0.46
5	2	F	Kidney	$\mu\text{g}/\text{g}$	0.10	0.08
5	2	F	Liver	$\mu\text{g}/\text{g}$	0.23	0.10
5	40	F	Blood	$\mu\text{g}/\text{dL}$	0.36	0.55
5	40	F	Bone	$\mu\text{g}/\text{g}$	0.20	0.14
5	40	F	Kidney	$\mu\text{g}/\text{g}$	0.006	0.012
5	40	F	Liver	$\mu\text{g}/\text{g}$	0.010	0.014

F, female; M, male

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1 **TABLE 4-22. CHANGES MADE TO THE ([LEGGETT, 1993](#)) MODEL TO CREATE AALM-**
 2 **LG.CSL**

LEGGETT	AALM-LG	Output/Functionality Affected
Age-dependent blood volume	Age-dependent blood volume based on O'Flaherty (1995, 1993)	Age-dependent RBC and plasma volumes
Constant hematocrit	Age-dependent hematocrit based on O'Flaherty (1995, 1993)	Age-dependent RBC and plasma volumes
Adult bone mass	Age-dependent bone mass based on O'Flaherty (1995, 1993)	Age-dependent cortical and trabecular bone Pb concentration
Adult kidney mass	Age-dependent kidney mass based on O'Flaherty (1995, 1993)	Age-dependent kidney Pb concentration
NA	Age-dependent liver mass based on O'Flaherty (1995, 1993)	Age-dependent liver Pb concentration
Age-dependent absorption fraction (<i>FI</i>): <ul style="list-style-type: none"> • birth: 0.45 • 0.27 y: 0.45 • 1 y: 0.30 • 5 y: 0.30 • 10 y: 0.30 • 15 y: 0.30 • ≥25 y: 0.15 	Age-dependent absorption fraction (<i>FI</i>): <ul style="list-style-type: none"> • birth: 0.39 • 0.27 y: 0.39 • 1 y: 0.38 • 5 y: 0.17 • ≥10 y: 0.12 	Absorption fraction for ingested Pb
Absorption fraction for ingested Pb not adjusted for RBA	Absorption fraction adjusted for media-specific RBA	Absorption fraction of ingested Pb
RBC Pb saturation threshold: 60 µg/dL blood) Maximum: 350 µg/dL RBC	RBC Pb saturation threshold: 20 µg/dL blood) Maximum: 350 µg/dL RBC	Plasma-RBC Pb relationship
Transfer rate from (d ⁻¹) RBC to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.462 • 0.27 y: 0.462 • 1 y: 0.462 • 5 y: 0.277 • ≥10 y: 0.139 	Transfer rate from (d ⁻¹) from RBC to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.462 • 0.27 y: 0.462 • 1 y: 0.785 • 5 y: 0.499 • 10 y: 0.195 • ≥15 y: 0.139 	Plasma-RBC Pb relationship
Deposition fraction from diffusible plasma to RBC (0.24)	Deposition fraction from diffusible plasma to RBC (0.25)	Plasma-RBC relationship
Deposition fraction from diffusible plasma to urine (30)	Deposition fraction from diffusible plasma to urine (0)	Plasma to urine clearance

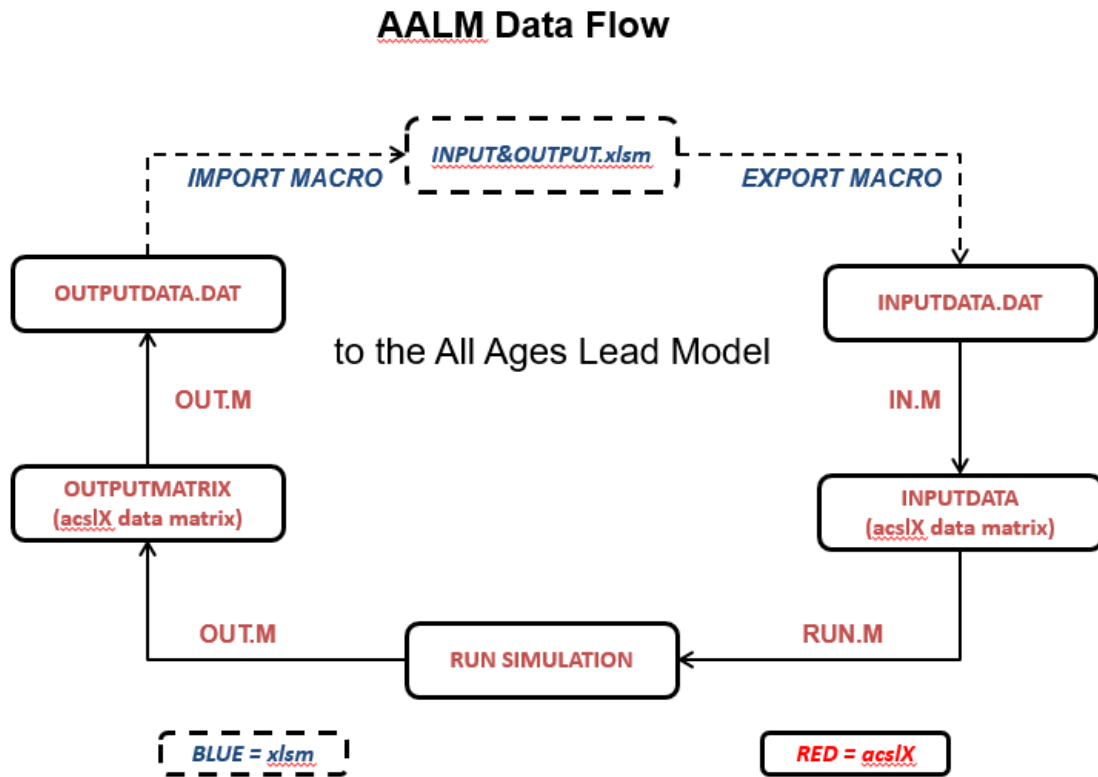
LEGGETT	AALM-LG	Output/Functionality Affected
Transfer rate (d^{-1}) from liver to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.00693 • 0.27 y: 0.00693 • 1 y: 0.00693 • 5 y: 0.00693 • 10 y: 0.00190 • 15 y: 0.00190 • ≥ 25 y: 0.00190 	Transfer rate (d^{-1}) from liver to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.00693 • 0.27 y: 0.00693 • 1 y: 0.00693 • 5 y: 0.00139 • 10 y: 0.000570 • 15 y: 0.000570 • 25 y: 0.000570 • 30 y: 0.00142 • 40 y: 0.00304 • 60 y: 0.00342 • 90 y: 0.00380 	Plasma to liver Pb kinetics
Deposition fraction from diffusible plasma to kidney (40)	Deposition fraction from diffusible plasma to kidney (50)	Urinary clearance of plasma Pb
Transfer rate (d^{-1}) from kidney to diffusible plasma (RKDN2): <ul style="list-style-type: none"> • birth: 0.00693 • 0.27 y: 0.00693 • 1 y: 0.00693 • 5 y: 0.00693 • 10 y: 0.00190 • 15 y: 0.00190 • ≥ 25 y: 0.00190 	Transfer rate (d^{-1}) from kidney to diffusible plasma (RKDN2): <ul style="list-style-type: none"> • birth: 0.000693 • 0.27 y: 0.000693 • 1 y: 0.000693 • 5 y: 0.000693 • 10 y: 0.000190 • 15 y: 0.000190 • 25 y: 0.000190 • 30 y: 0.000950 • ≥ 40 y: 0.00190 	Plasma to kidney Pb kinetics
Fraction of total transfer from exchangeable bone to nonexchangeable bone (0.2)	Fraction of total transfer from exchangeable bone to nonexchangeable bone (0.6)	Bone Pb retention
Transfer rate (d^{-1}) from non-exchangeable cortical bone to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.00822 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00154 • 10 y: 0.000890 • 15 y: 0.000512 • ≥ 25 y: 0.0000822 	Transfer rate (d^{-1}) from non-exchangeable cortical bone to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.0204 • 0.27 y: 0.0164 • 1 y: 0.00576 • 5 y: 0.00308 • 10 y: 0.00178 • 15 y: 0.00102 • ≥ 25 y: 0.000164 	Bone to plasma Pb kinetics

LEGGETT	AALM-LG	Output/Functionality Affected
Transfer rate (d^{-1}) from non-exchangeable trabecular bone to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.00822 • 0.27 y: 0.00822 • 1 y: 0.00288 • 5 y: 0.00181 • 10 y: 0.00132 • 15 y: 0.000956 • ≥ 25 y: 0.000493 	Transfer rate (d^{-1}) from non-exchangeable trabecular bone to diffusible plasma: <ul style="list-style-type: none"> • birth: 0.0102 • 0.27 y: 0.01644 • 1 y: 0.00576 • 5 y: 0.00362 • 10 y: 0.00264 • 15 y: 0.00192 • ≥ 25 y: 0.000986 	Bone-to-plasma Pb transfer kinetics

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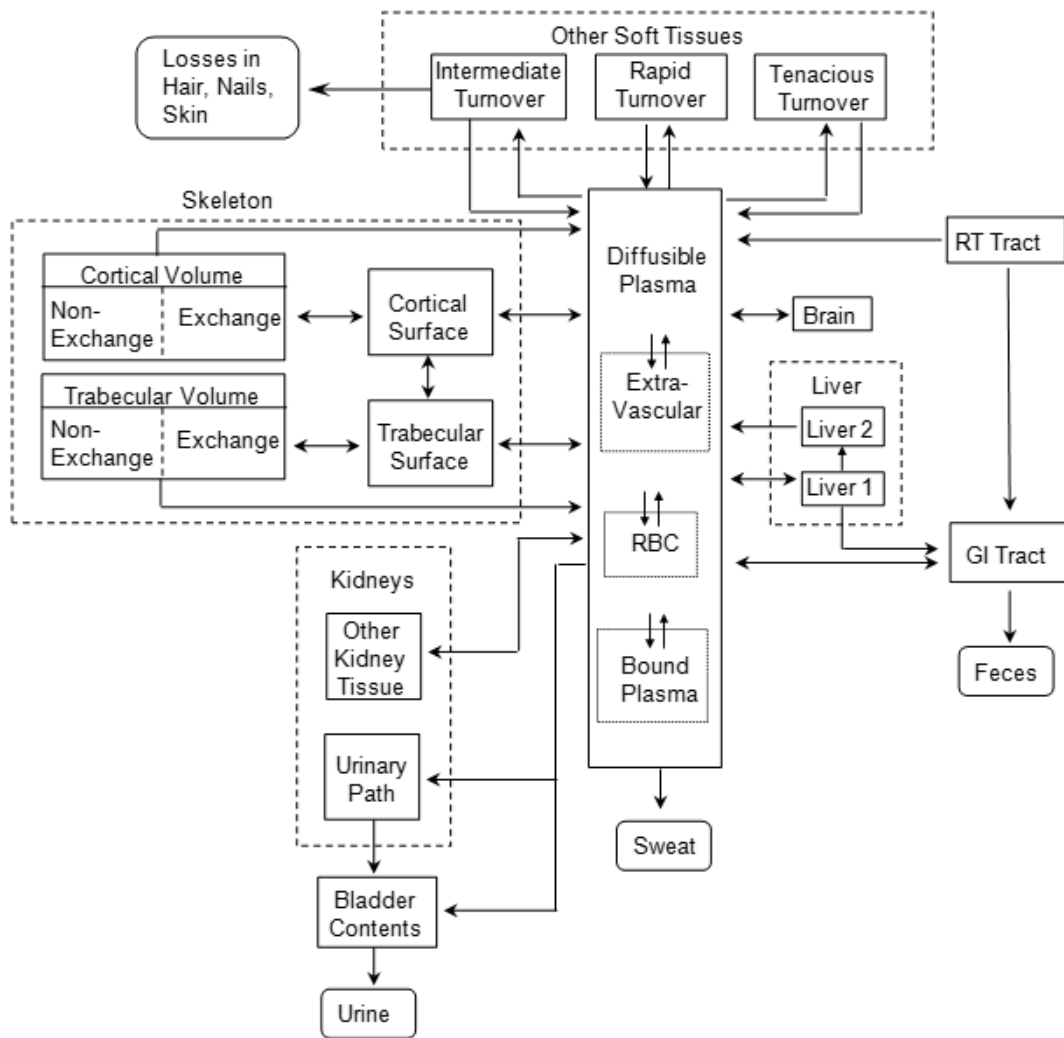
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1 **FIGURE 4-1. DATA FLOW DIAGRAM FOR AALM.**



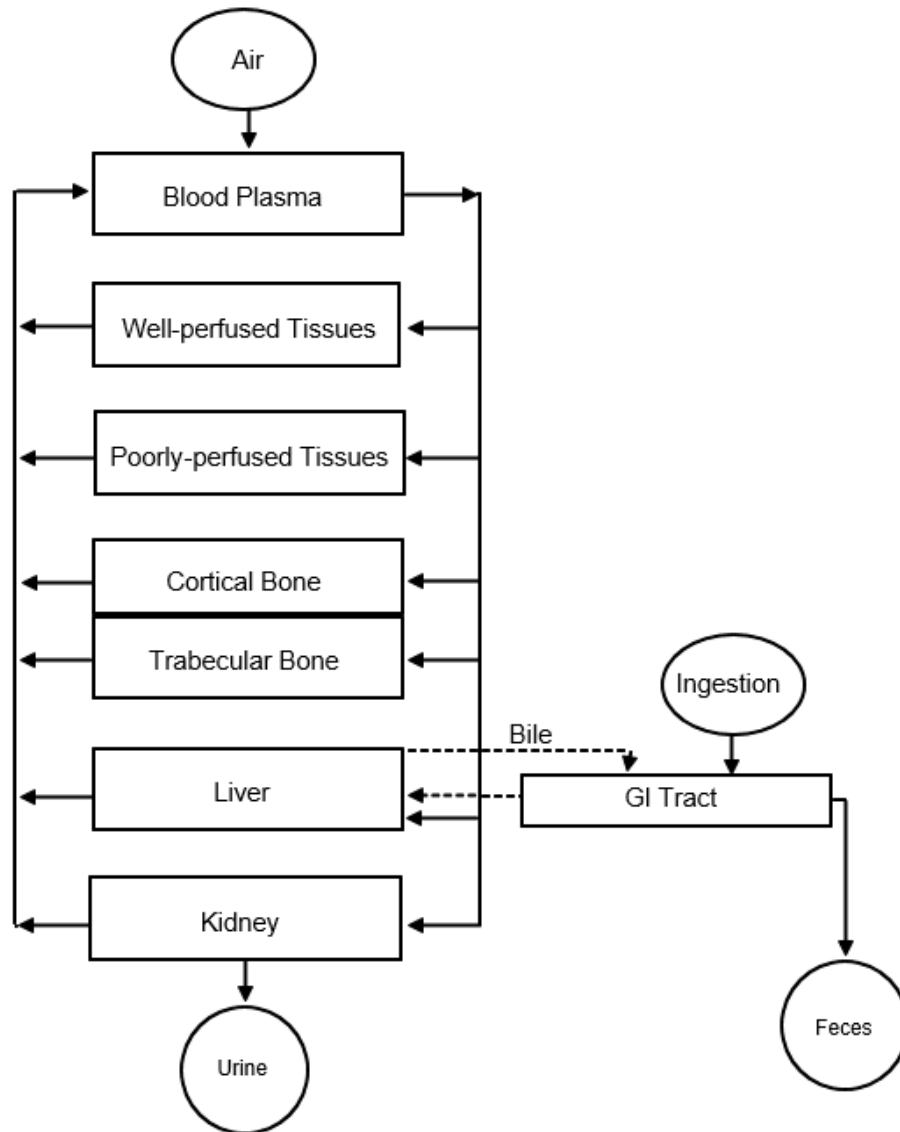
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1 **FIGURE 4-2. STRUCTURE OF AALM-LG MODEL.**



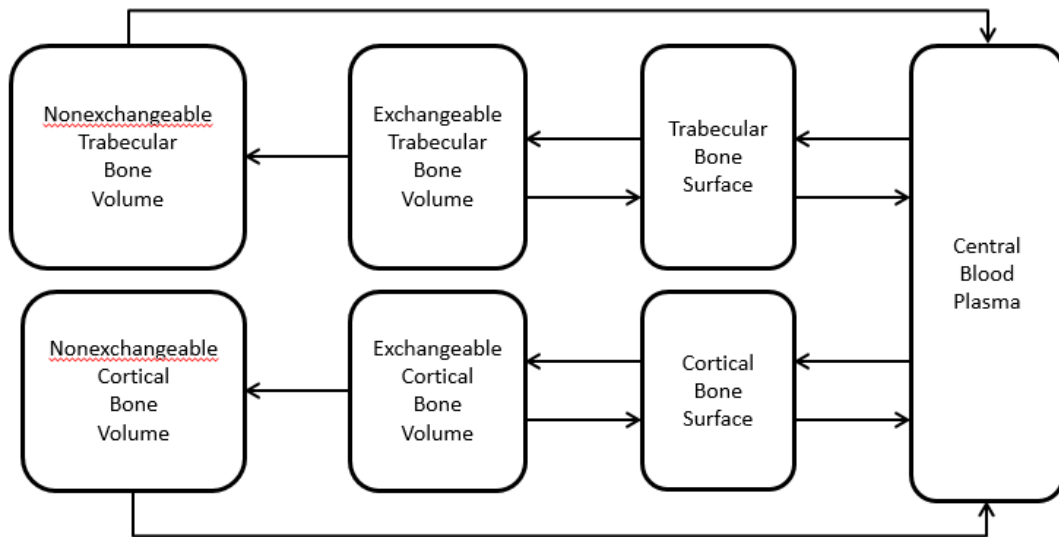
2
3 Figure is based on [Leggett \(1993\)](#).
4

1 **FIGURE 4-3. STRUCTURE OF AALM-OF MODEL.**



2
3 Figure is based on [O'Flaherty \(1993\)](#) .
4

1 **FIGURE 4-4. STRUCTURE OF AALM-LG BONE MODEL.**

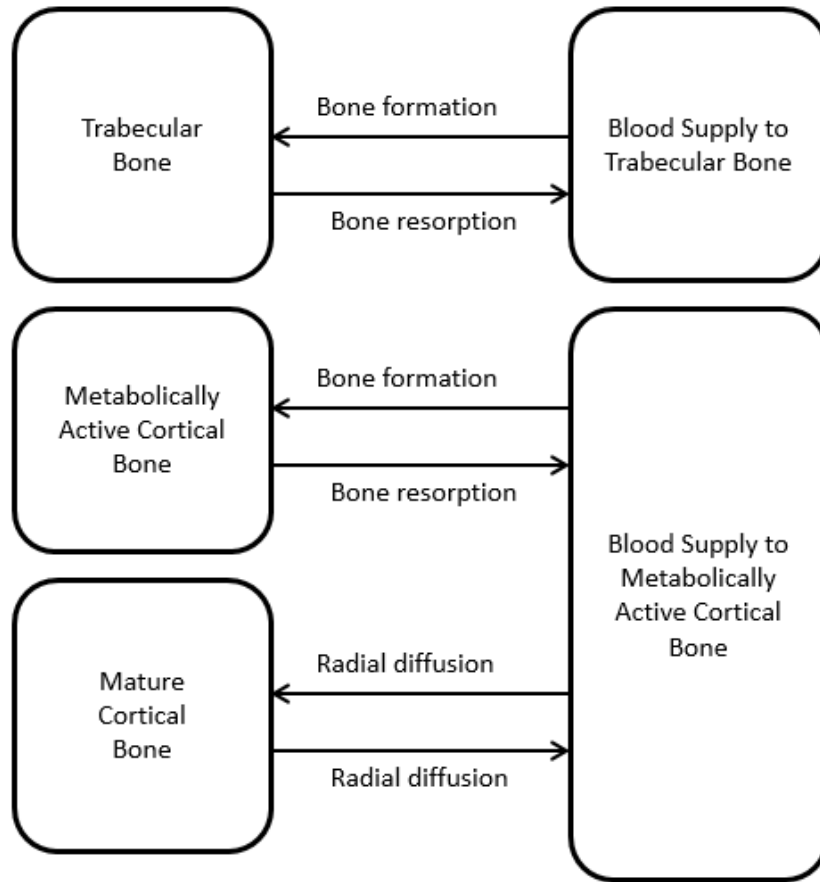


2

3 Figure is based on [Leggett \(1993\)](#).

4

1 **FIGURE 4-5. STRUCTURE OF AALM-OF BONE MODEL.**

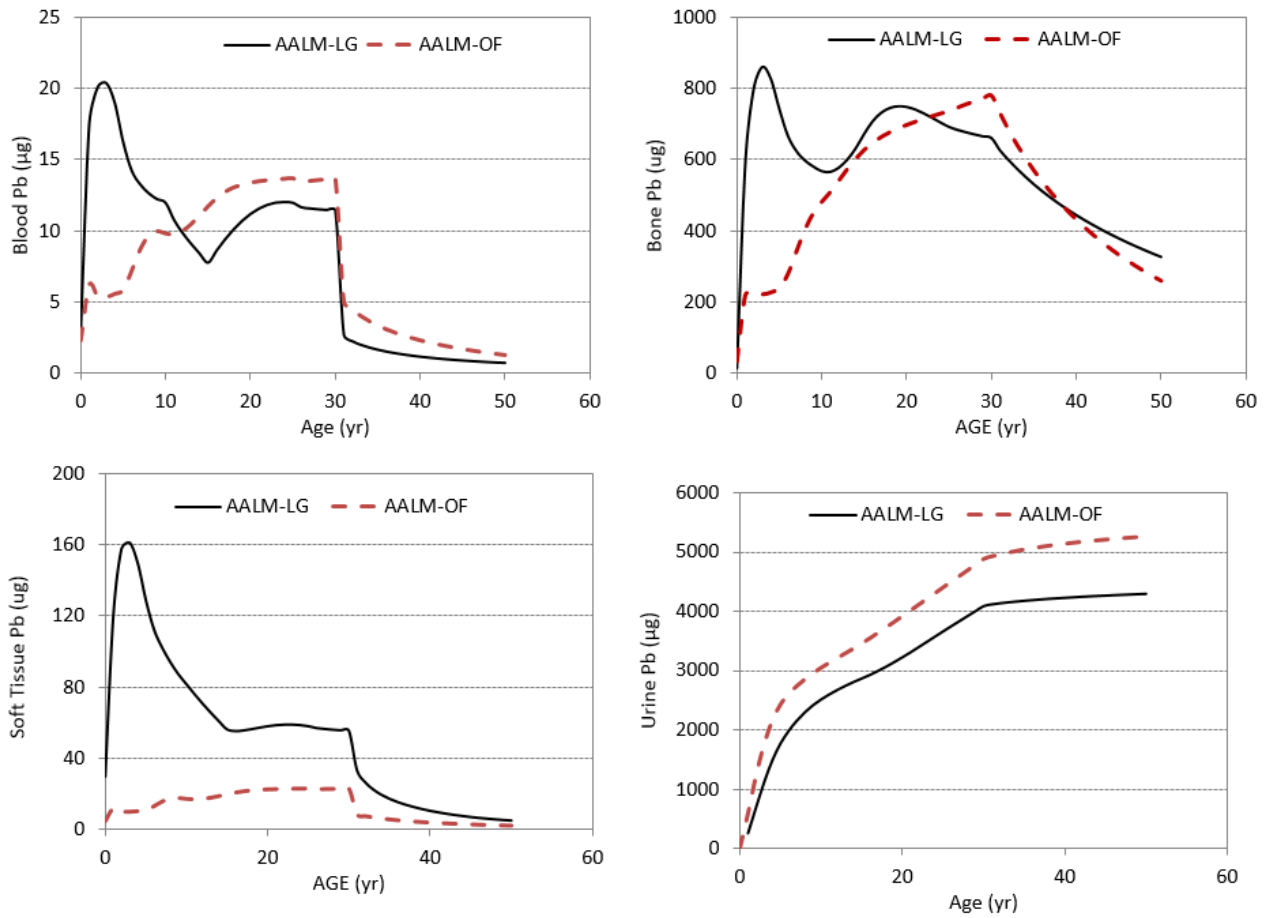


2

3 Figure is based on [O'Flaherty \(1993\)](#).

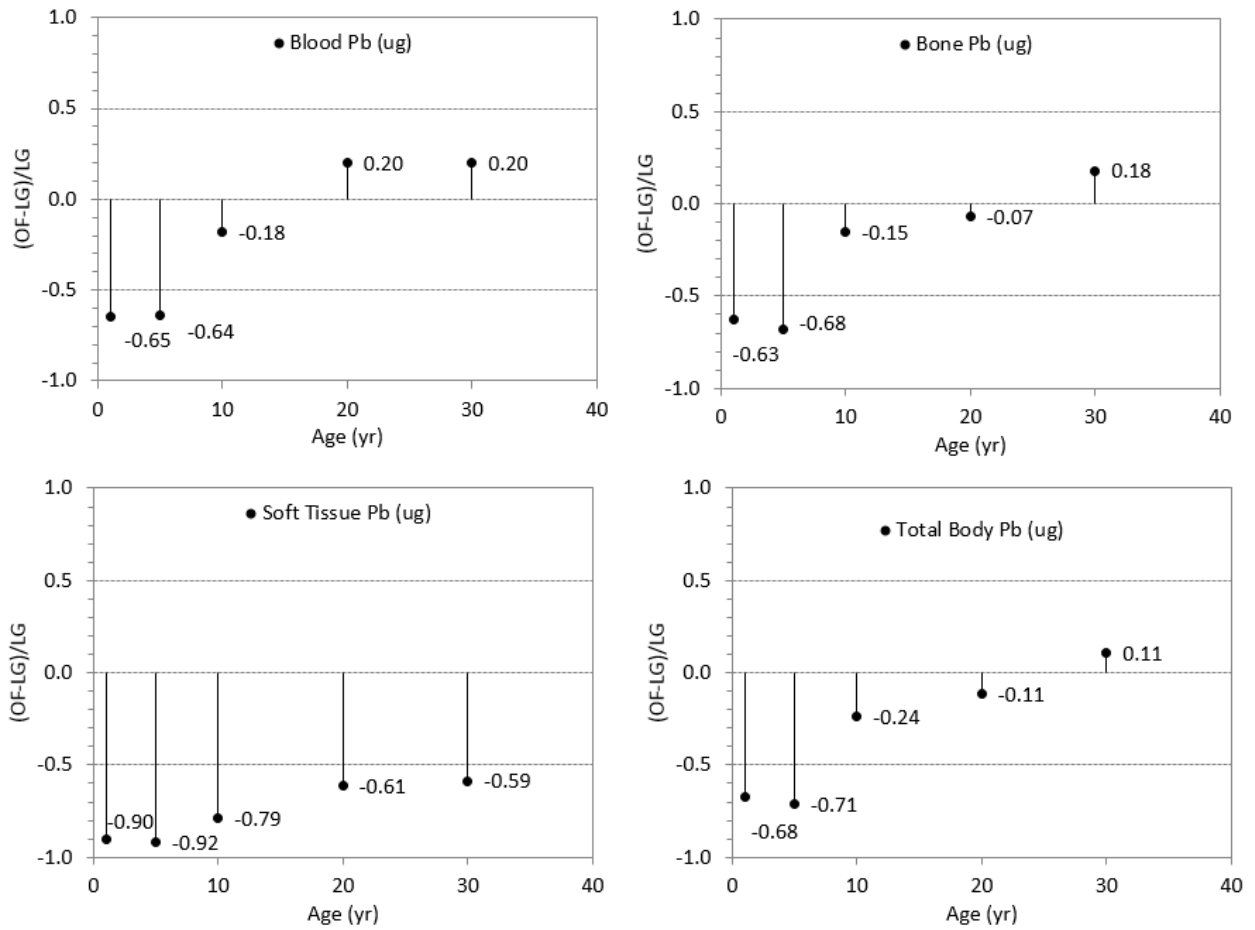
4

1 **FIGURE 4-6. COMPARISON OF PB (μG) LEVELS PREDICTED FROM AALM-OF AND**
2 **AALM-LG FOR A CONSTANT INGESTION OF 5 μG PB/DAY FOR AGES 0 TO 30 YEARS.**



3
4

1 **FIGURE 4-7. DIFFERENCES IN PB LEVELS PREDICTED FROM AALM-LG AND AALM-OF.**

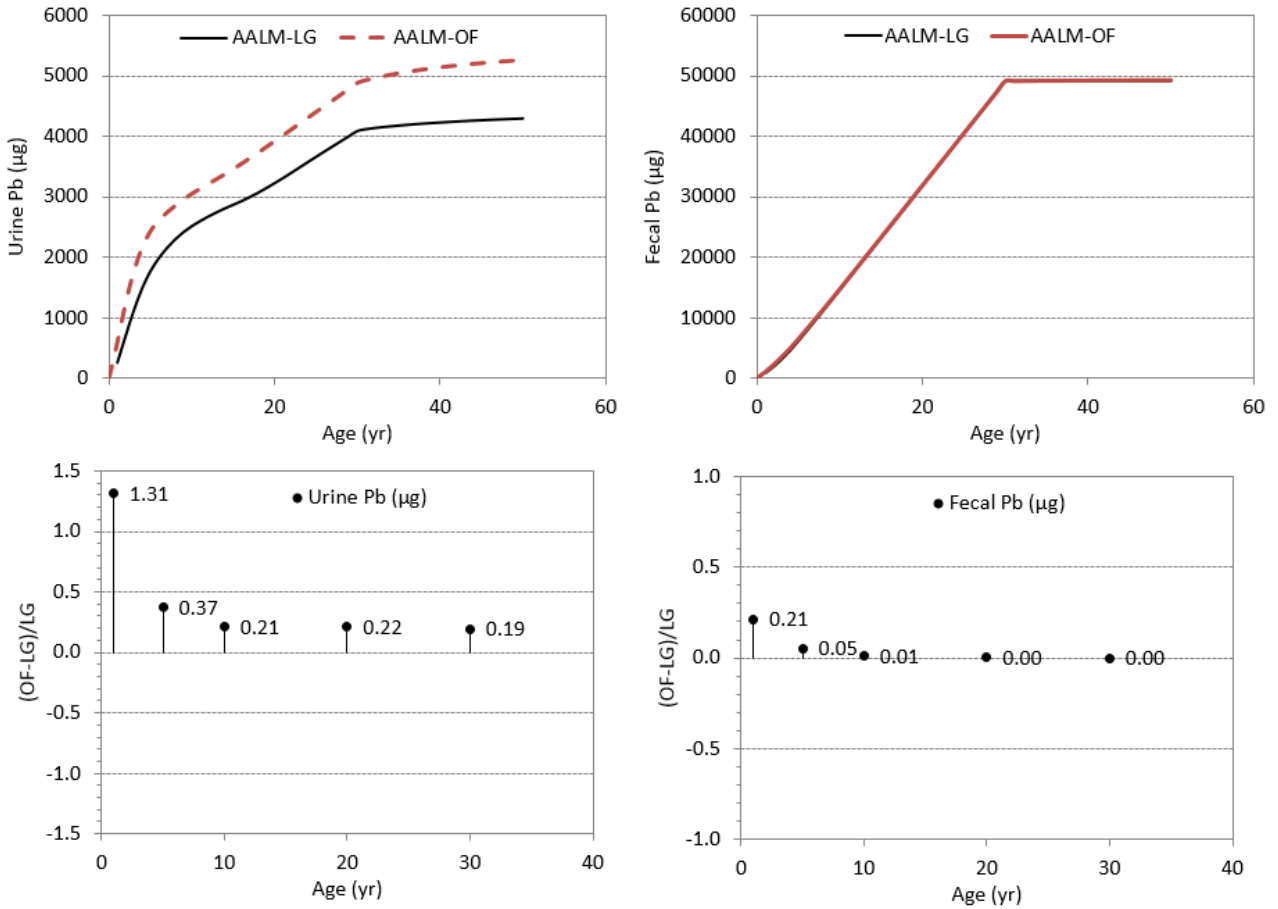


2

3 Differences are expressed relative to the prediction from AALM-LG.

4

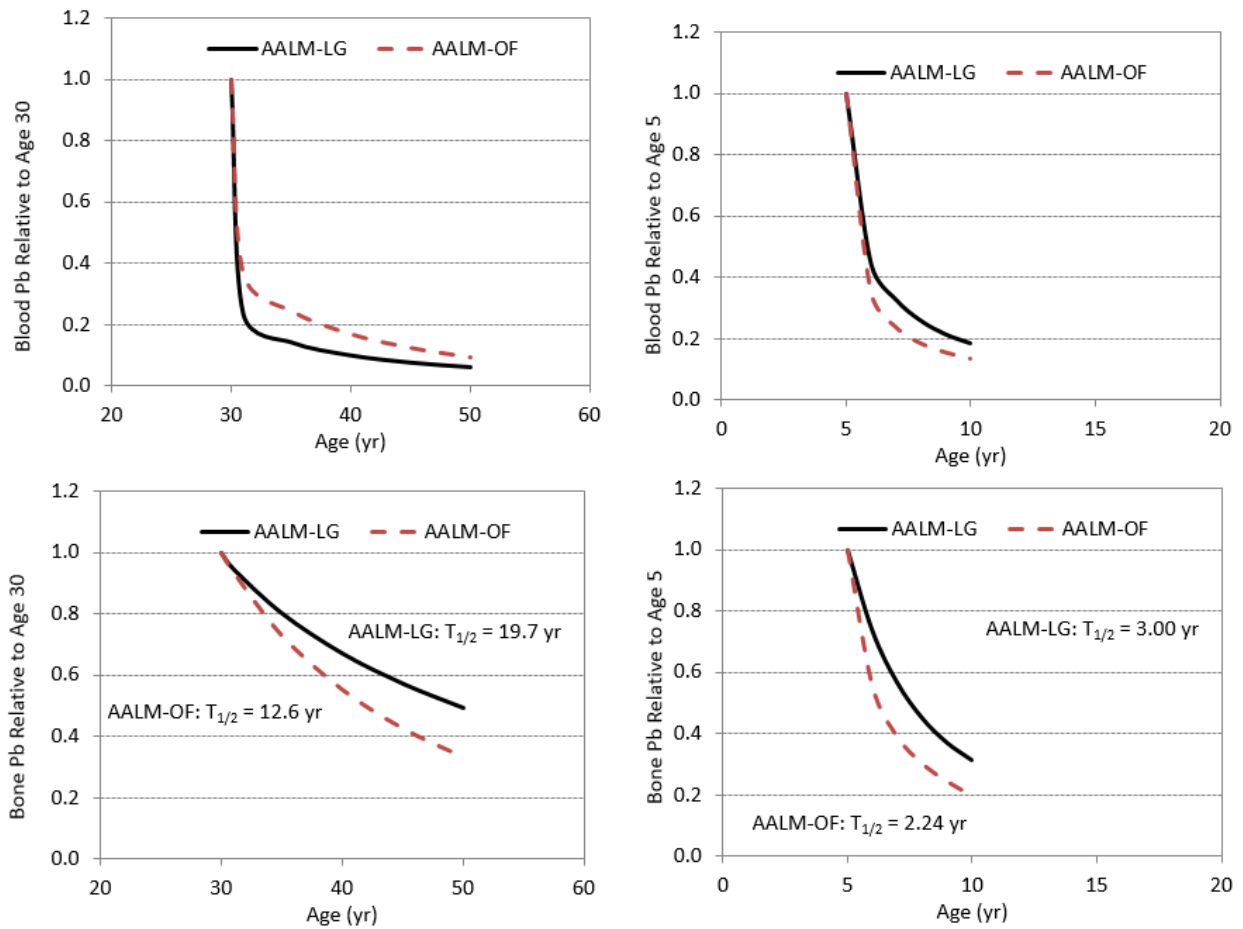
1 **FIGURE 4-8. COMPARISON OF CUMULATIVE URINARY AND FECAL PB EXCRETION**
 2 **(μG) LEVELS PREDICTED FROM AALM-OF AND AALM-LG FOR A CONSTANT**
 3 **INGESTION OF 5 μG PB/DAY FOR AGES 0 TO 30 YEARS.**



4

5

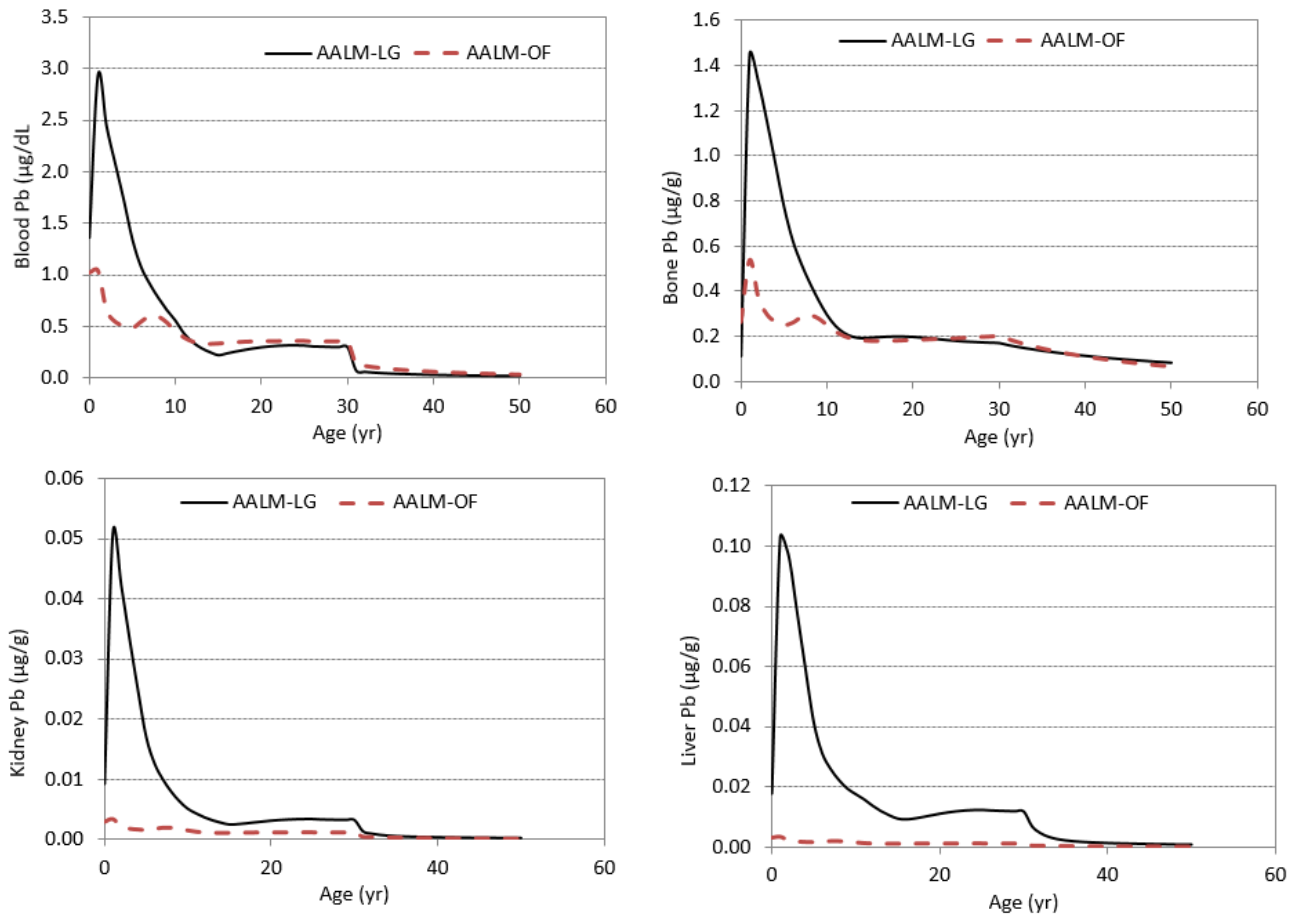
1 **FIGURE 4-9. DECLINE IN PB LEVELS FOLLOWING CESSATION OF EXPOSURE**
 2 **PREDICTED FROM AALM-LG AND AALM-OF FOR AGES 5 AND 30 YEARS.**



3
 4 Half-times are based on applying a single exponential model to the predicted time series (i.e., $Pb_{t=i} = Pb_{t=0} \times e^{-kt}$). The decline in blood Pb has multiple rates. In adults, the half-time for the first 50 days following
 5 cessation of exposure is approximately 36 days in AALM-LG and 46 days in AALM-OF. The half-time
 6 for the period 5–20 years following cessation of exposure is 12.7 years in AALM-LG and 10.9 years in
 7 AALM-OF.
 8

9

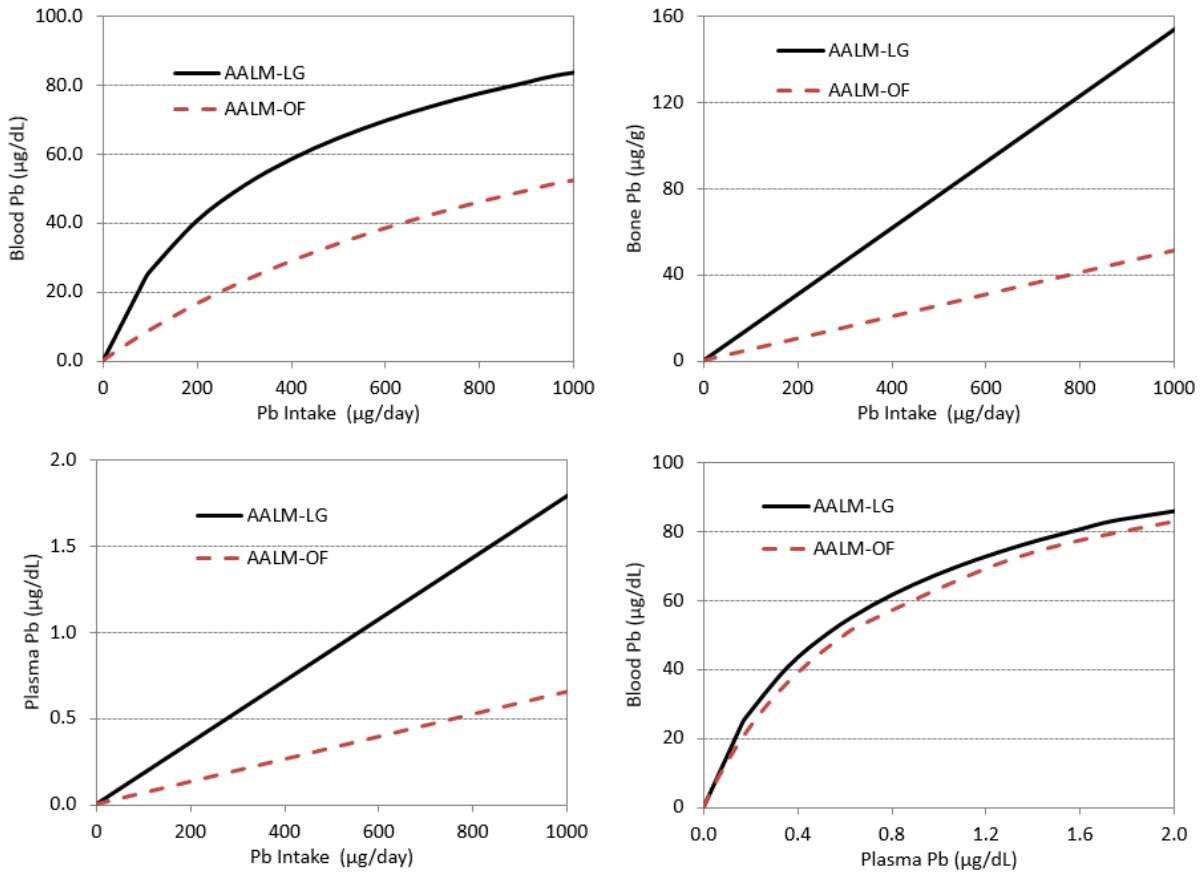
1 **FIGURE 4-10. COMPARISON OF PB CONCENTRATIONS PREDICTED FROM AALM-LG**
2 **AND AALM-OF FOR A CONSTANT INGESTION OF 5 μ G PB/DAY FOR AGES 0 TO 30**
3 **YEARS.**



4

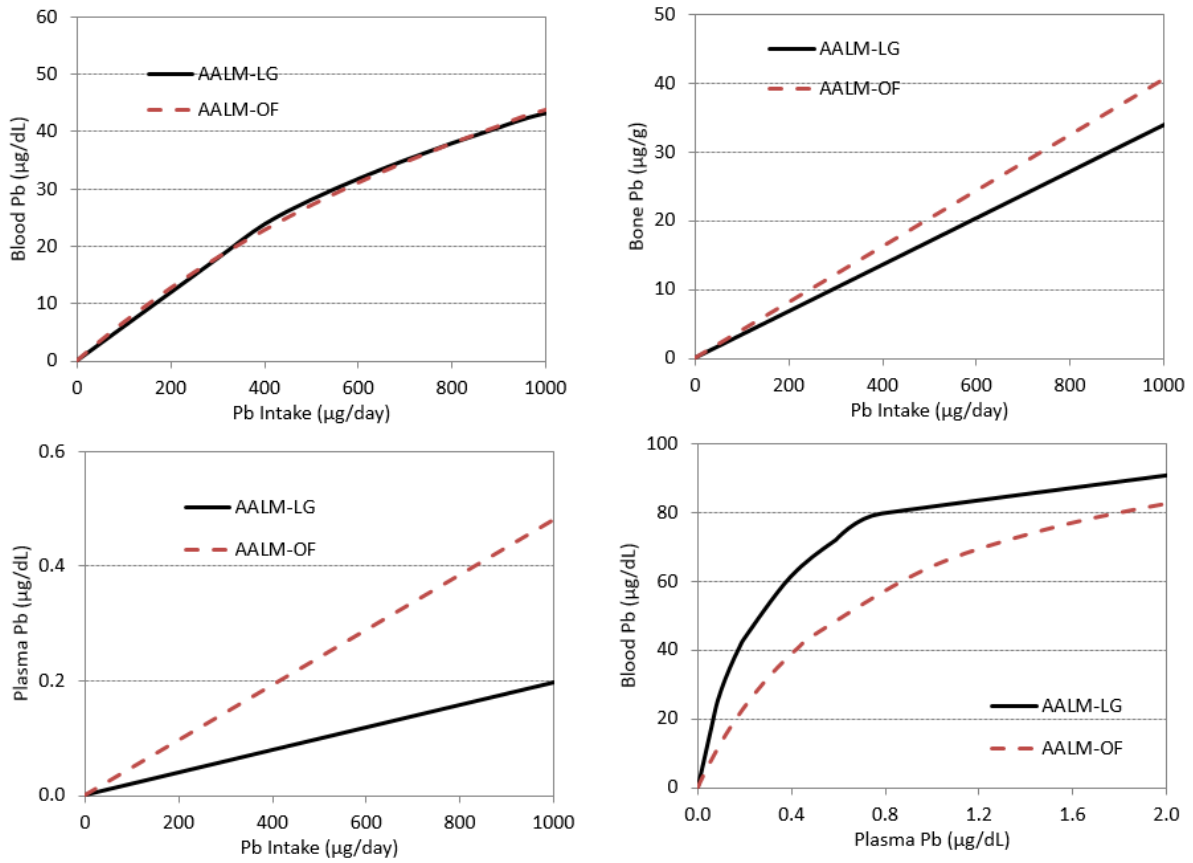
5

1 **FIGURE 4-11. DOSE-RESPONSE RELATIONSHIP FOR PB LEVELS AT AGE 5 YEARS**
2 **PREDICTED FROM AALM-LG AND AALM-OF.**



3
4
5

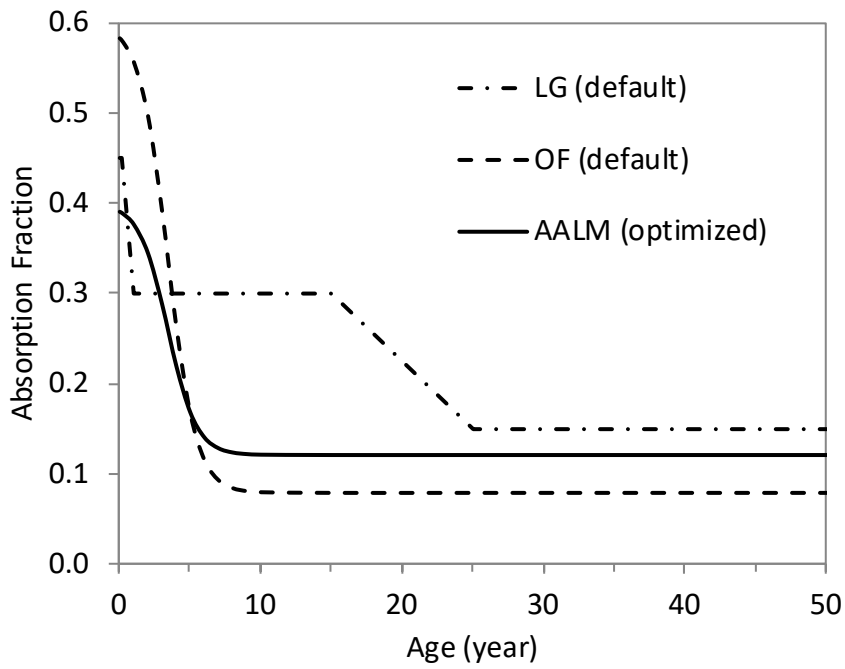
1 **FIGURE 4-12. DOSE-RESPONSE RELATIONSHIP FOR PB LEVELS AT AGE 30 YEARS**
2 **PREDICTED FROM AALM-LG AND AALM-OF.**



3

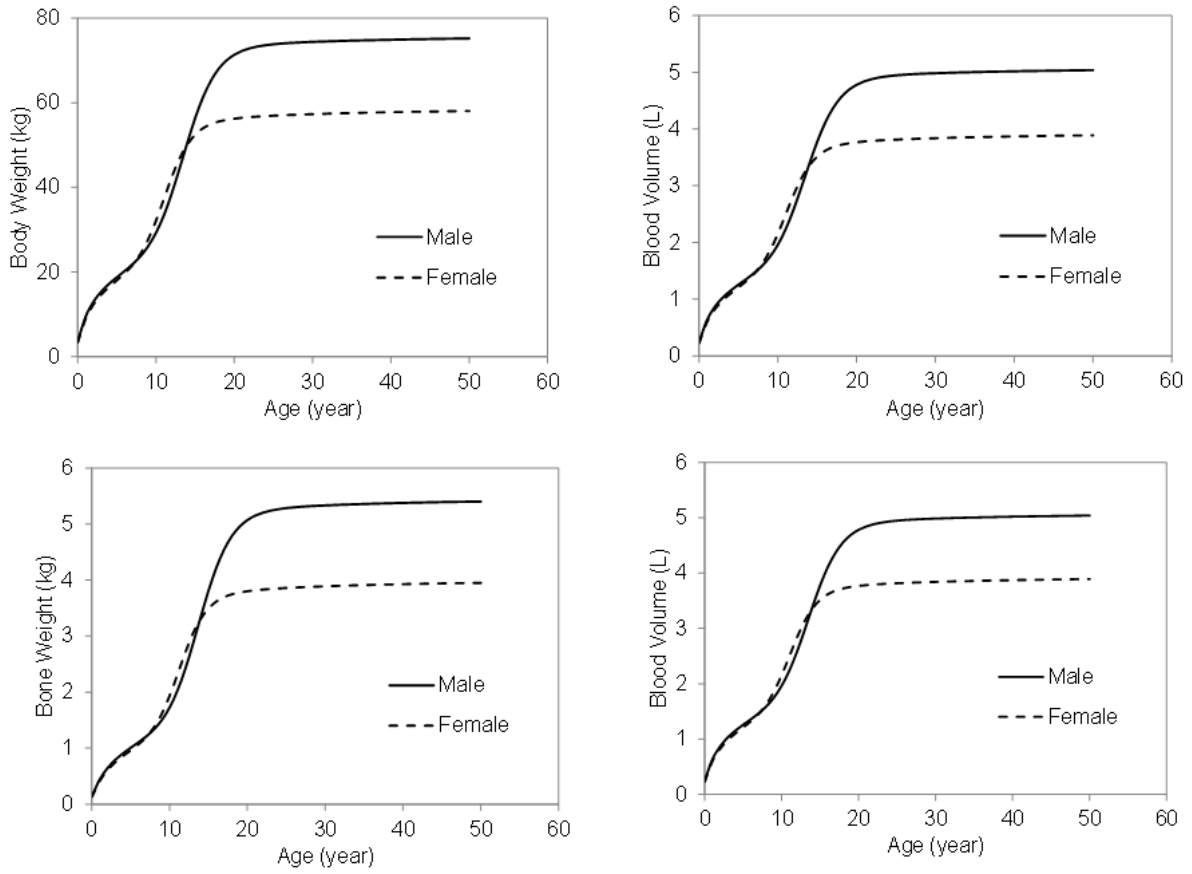
4

1 **FIGURE 4-13. GASTROINTESTINAL ABSORPTION OF PB IN THE O'FLAHERTY MODEL**
2 **(OF) AND LEGGETT MODEL (OF) AND AALM, OPTIMIZED TO [\(RYU ET AL., 1983\)](#).**



3

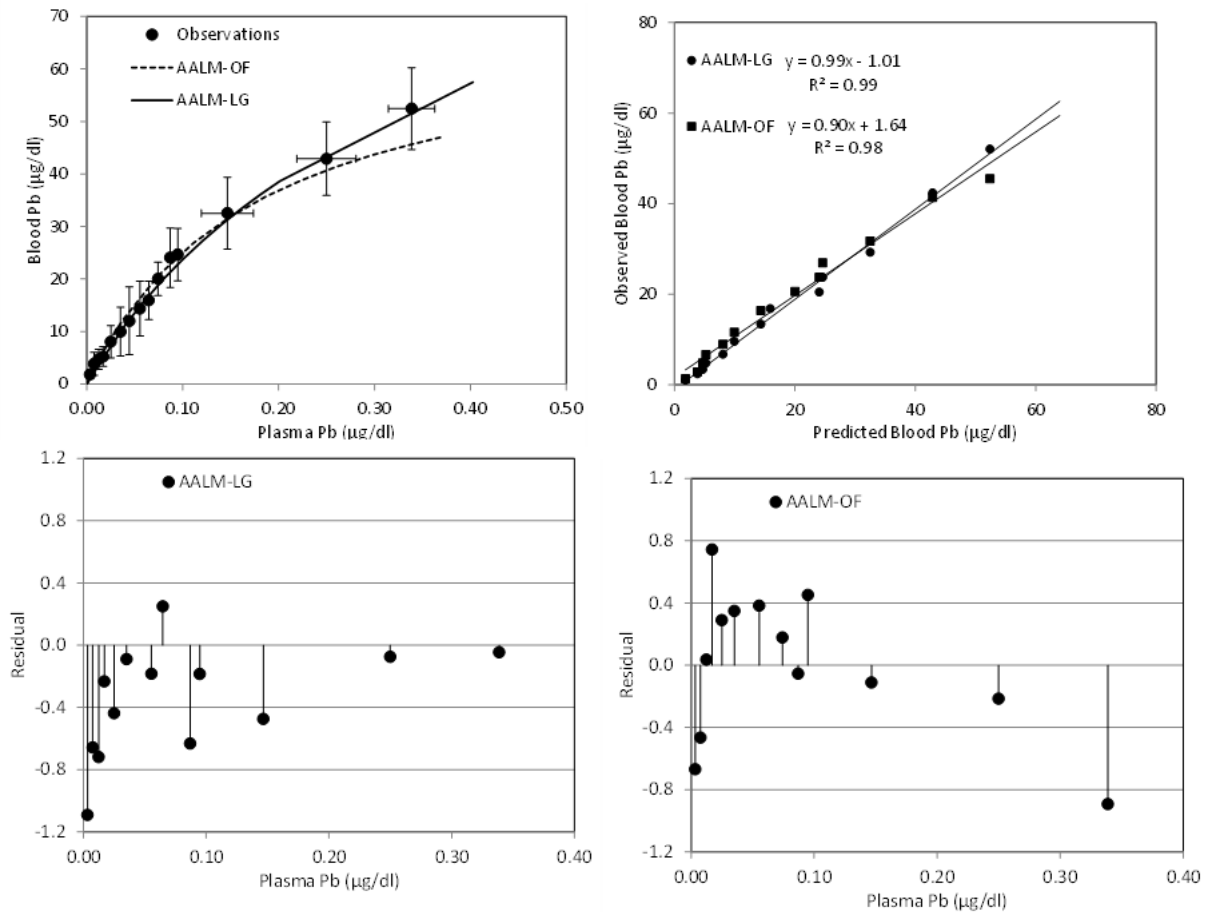
1 **FIGURE 4-14. BODY AND TISSUE GROWTH IN AALM.**



2

3

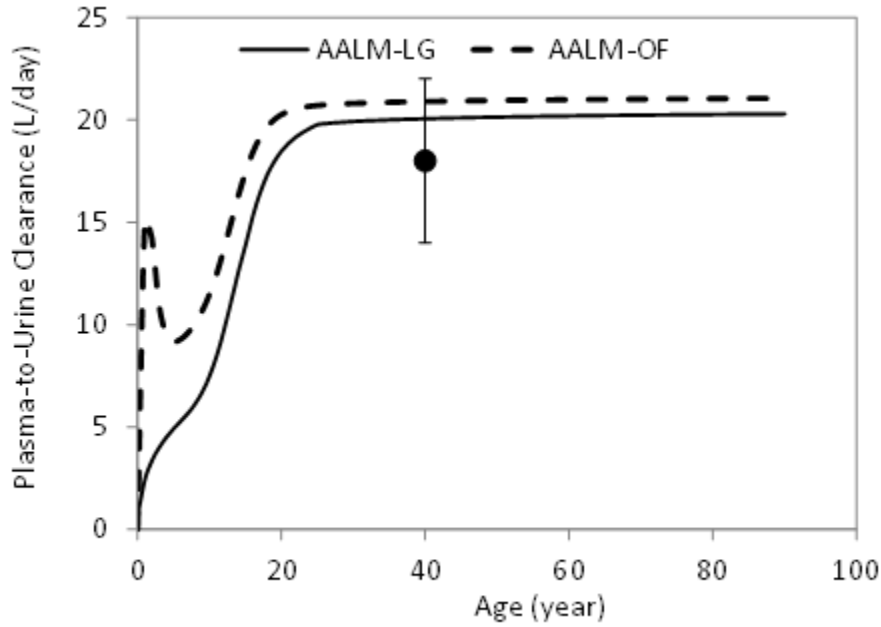
1 **FIGURE 4-15. SIMULATION OF WHOLE BLOOD AND PLASMA PB IN ADULTS** ([SMITH ET](#)
 2 [AL., 2002](#); [BERGDAHL ET AL., 1999](#); [BERGDAHL ET AL., 1998](#); [HERNANDEZ-AVILA ET](#)
 3 [AL., 1998](#); [BERGDAHL ET AL., 1997](#); [SCHUTZ ET AL., 1996](#)).



4
 5 Combined data for individuals (N = 406) from all studies were quantized into ranges of plasma Pb; shown
 6 are mean and standard deviations for ranges. Upper right panel shows linear regression for predicted and
 7 observed blood Pb concentrations. Lower panels show residuals for predictions
 8 ([predicted-observed]/standard deviation).

9

1 **FIGURE 4-16. SIMULATION OF PLASMA-TO-URINE CLEARANCE.**

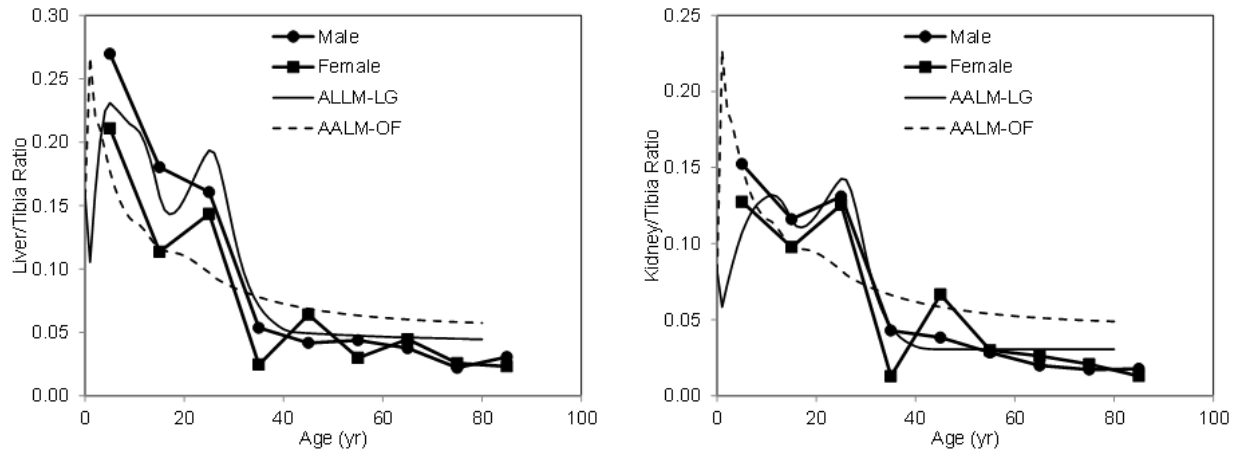


2

3 Data point is mean and standard deviation for four estimates based on 32 (normal) adults ([Araki et al.,](#)
4 [1986](#); [Manton and Cook, 1984](#); [Manton and Malloy, 1983](#); [Chamberlain et al., 1978](#)).

5

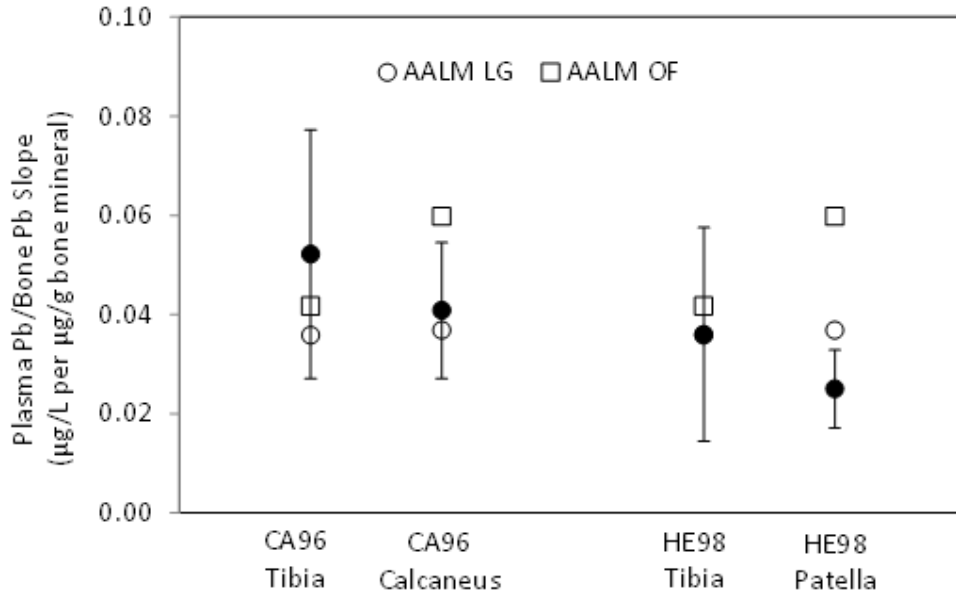
1 **FIGURE 4-17. SIMULATION OF POST-MORTEM SOFT TISSUE/TIBIA PB RATIOS.**



2
3 Shown are group means for kidney (n = 8) and for liver (n = 9), based on [Barry \(1975\)](#).

4

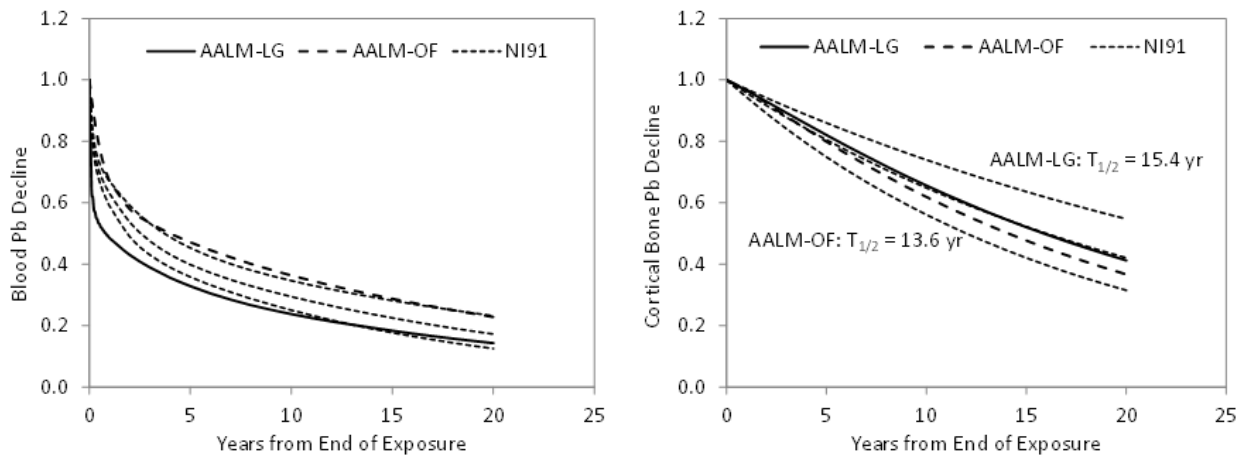
1 **FIGURE 4-18. SIMULATION OF PLASMA PB/BONE PB RATIO IN ADULTS.**



2
3 Observations are means and 95% CIs, based on CA96, [Cake et al. \(1996\)](#); and HE98, [Hernandez-Avila et](#)
4 [al. \(1998\)](#).

5

1 **FIGURE 4-19. SIMULATION OF ELIMINATION KINETICS OF PB FROM BLOOD (LEFT**
2 **PANEL) AND BONE (RIGHT PANEL).**

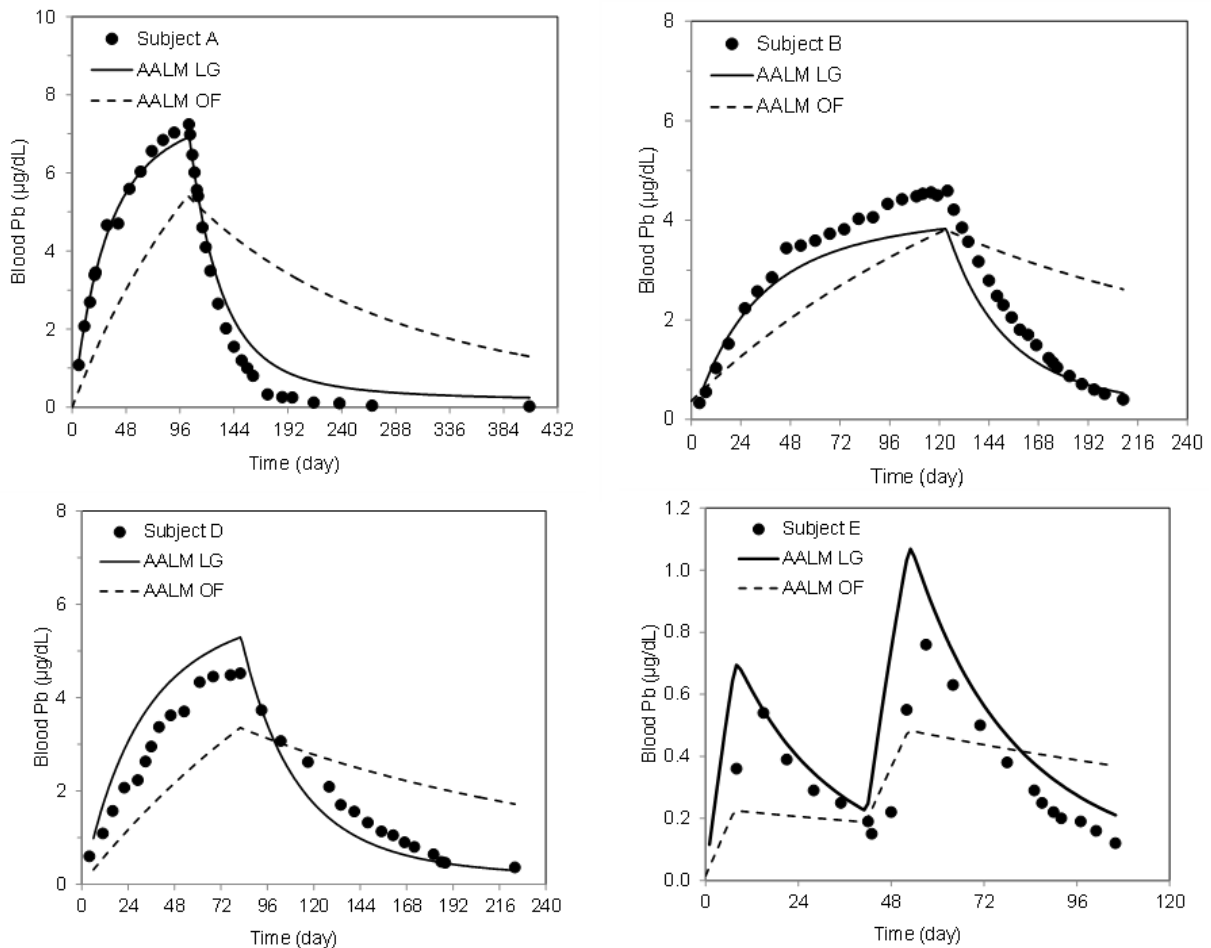


3

4 Dotted lines show the elimination from based on the median and upper and lower 95% confidence limits
5 of the tri-exponential model retired Pb workers (n = 14, median age 60 years at time of retirement)
6 reported in [Nilsson et al. \(1991\)](#).

7

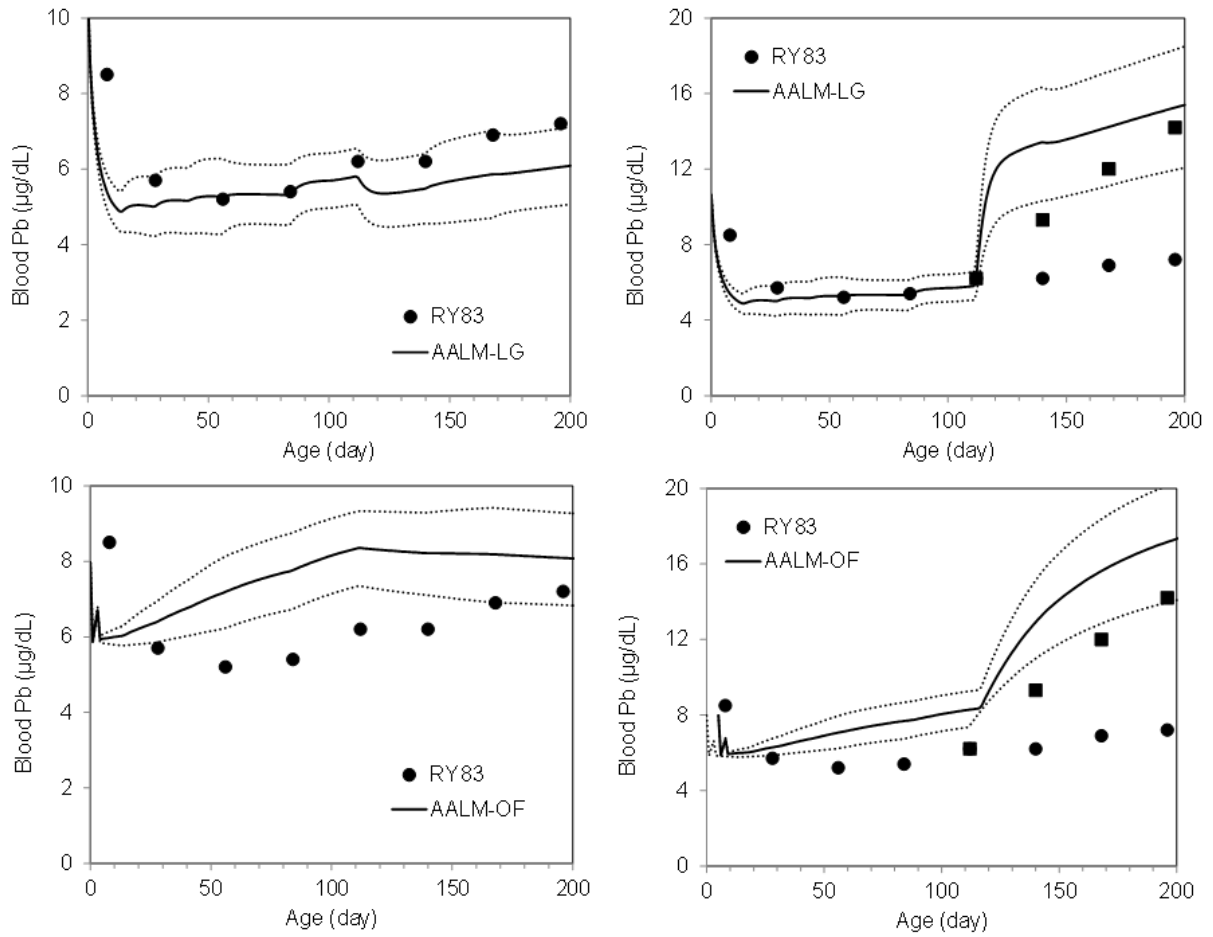
1 **FIGURE 4-20. COMPARISON OF OBSERVED AND PREDICTED BLOOD PB**
 2 **CONCENTRATIONS IN INDIVIDUALS WHO RECEIVED INGESTION DOSES OF [202PB]-**
 3 **NITRATE ([RABINOWITZ ET AL., 1976](#)).**



4
 5 Subject A received 204 µg/day for 104 days, Subject B received 185 µg/day for 124 days, Subject D
 6 received 105 µg/day for 83 days, and Subject E received 99 µg/day for on days 1–8 and days 42–51.
 7 Estimated absorption fractions were 8.5% for Subject A, 6.5% for Subject B, 10.9% for Subject D and
 8 9.1% for Subject E.

9

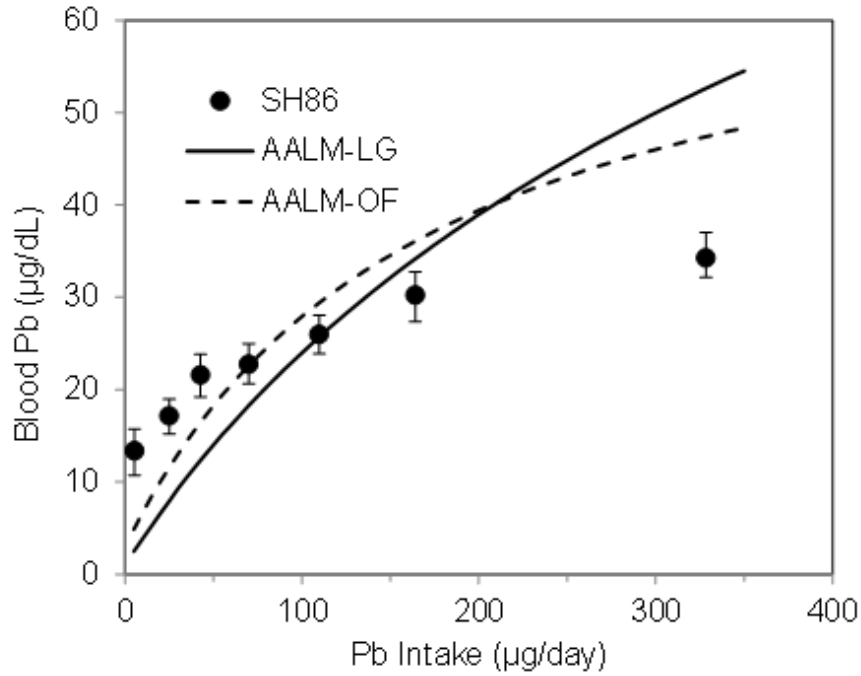
1 **FIGURE 4-21. SIMULATION OF FORMULA-FED INFANTS FROM (RYU ET AL., 1983).**



2
 3 Data in left panels are from 25 infants fed formula from cartons (12–20 µg/day) from age 8–196 days.
 4 Data in right panels are show a subset (n = 7) that were switched to formula from cans at age 112 days
 5 (60–63 µg/day). Solid lines show simulations of the mean Pb intakes; dotted lines show simulations of
 6 ±1 SD of mean intakes.

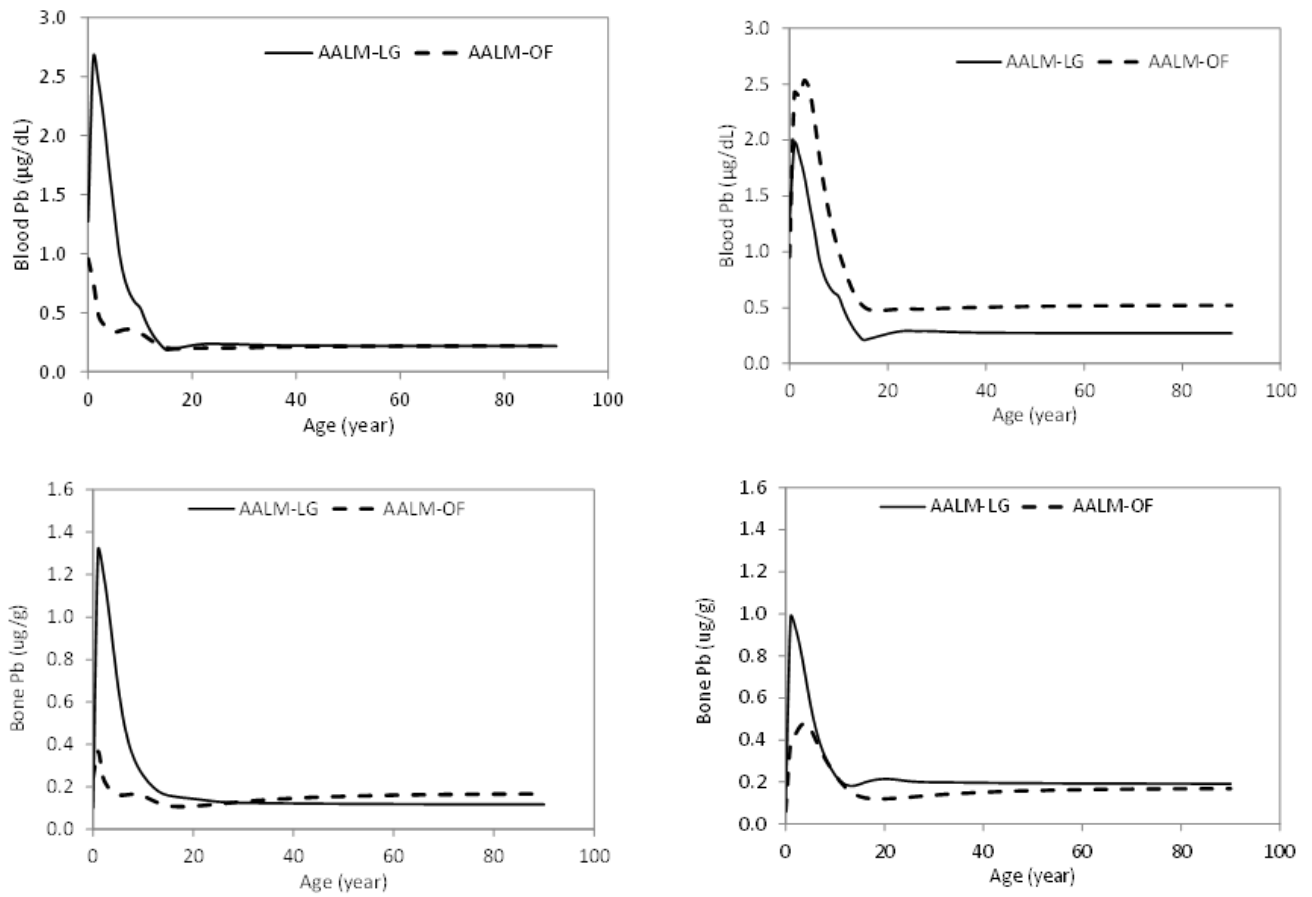
7

1 **FIGURE 4-22. SIMULATION OF FORMULA-FED INFANTS (N = 131, AGE 91 DAYS) FROM**
2 **(SHERLOCK AND QUINN, 1986).**



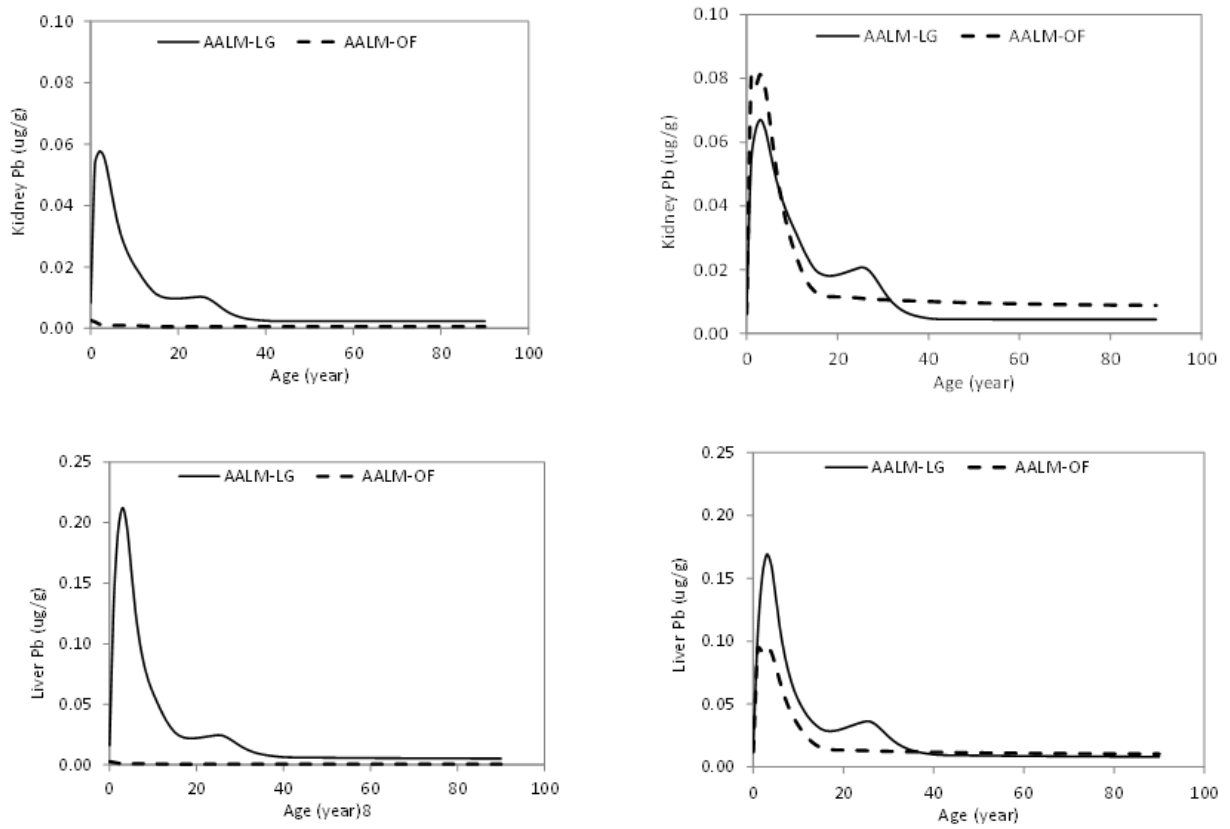
3
4 Blood Pb were measured and Pb intakes were estimated from duplicate diets assessed at age 91 days.
5

1 **FIGURE 4-23. COMPARISON OF INITIAL AND OPTIMIZED AALM-LG AND AALM-OF**
2 **MODELS FOR CONTINUOUS PB INTAKE OF 5 μ G/DAY.**



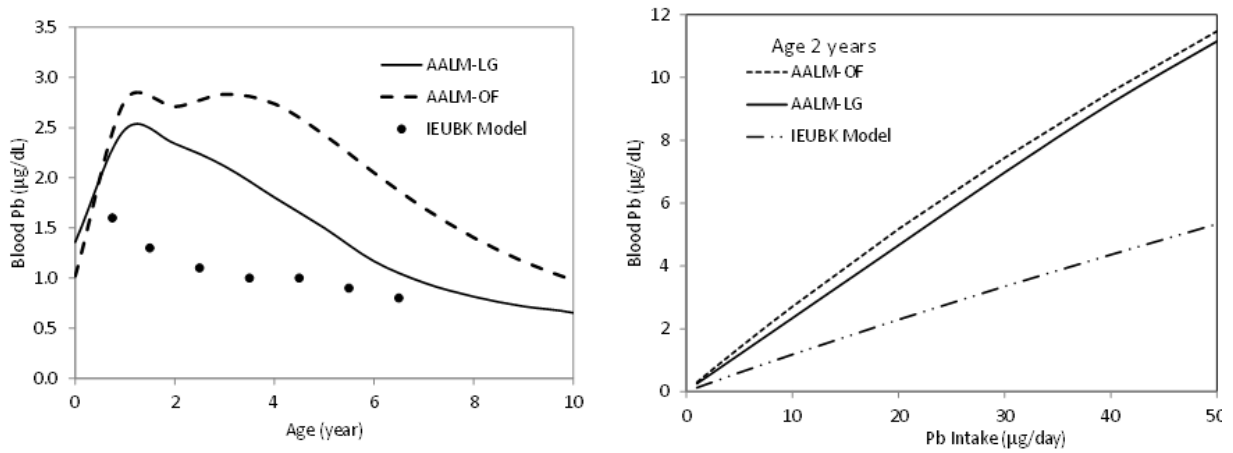
3
4 Right panels show optimized models.
5

1 **FIGURE 4-24. COMPARISON OF INITIAL AND OPTIMIZED AALM-LG AND AALM-OF**
2 **MODELS FOR CONTINUOUS PB INTAKE OF 5 μ G/DAY.**



3
4 Right panels show optimized models.
5

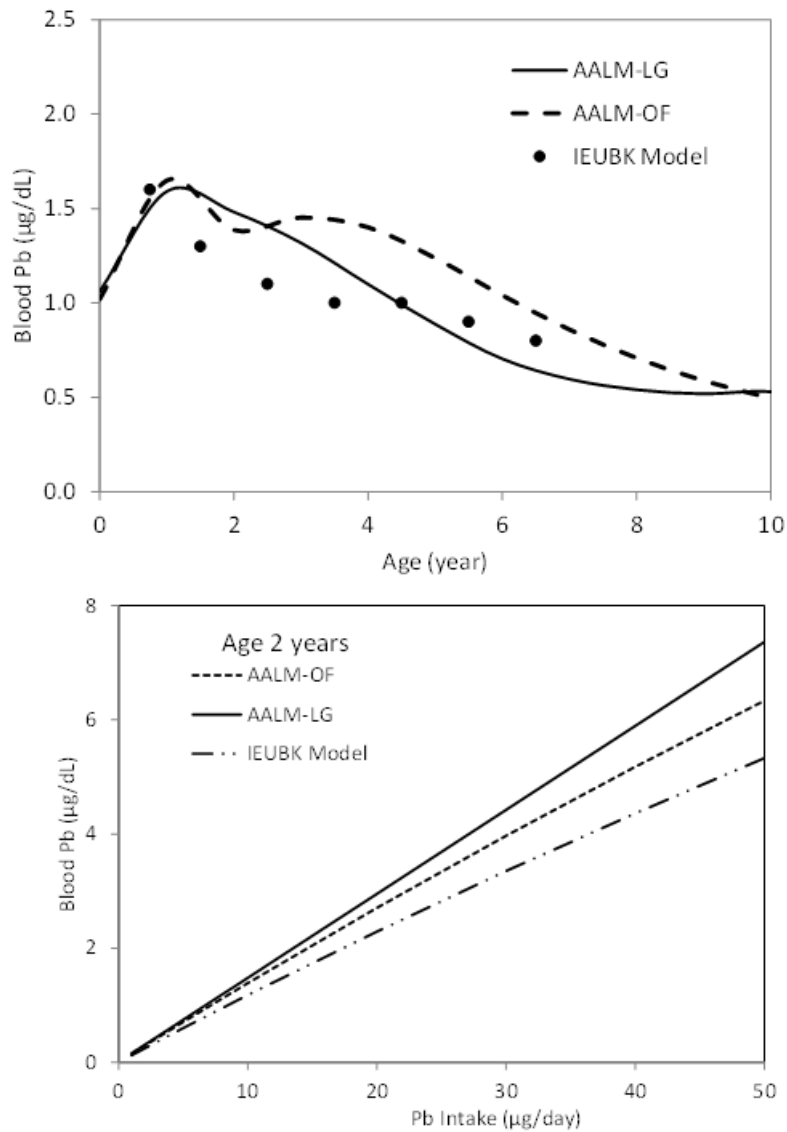
1 **FIGURE 4-25. COMPARISON OF BLOOD Pb PREDICTIONS OF AALM AND IEUBK**
 2 **MODEL.**



3
 4 Left panel shows simulations of continuous intake of 10 µg Pb/day in dust. Right panel shows
 5 relationship between dust Pb intake and blood Pb concentration at 2 years of age. In both models, the
 6 RBA for Pb in dust was assumed to be 60%. This corresponds to an absolute bioavailability of
 7 approximately 20% at age 2 years in the AALM and 30% in the IEUBK model.

8

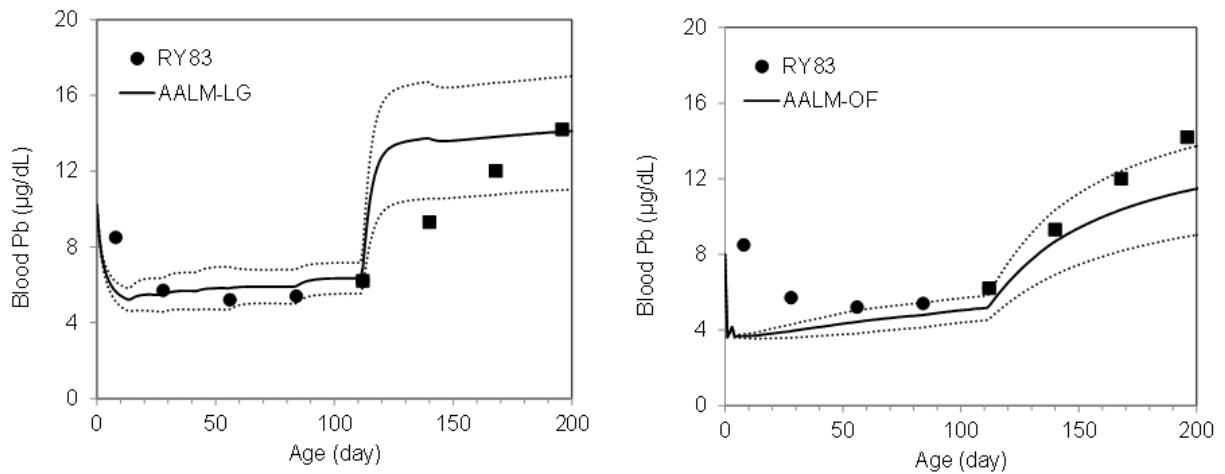
1 **FIGURE 4-26. COMPARISON OF BLOOD Pb PREDICTIONS OF AALM AND IEUBK MODEL**
 2 **AFTER ADJUSTMENT OF RED BLOOD CELL PARAMETERS (RRBC IN AALM-LG, KBIND**
 3 **IN AALM-OF).**



4
 5 Upper panel shows simulations of continuous intake of 10 µg Pb/day in dust. Lower panel shows
 6 relationship between dust Pb intake and blood Pb concentration at 2 years of age. In both models, the
 7 RBA for Pb in dust was assumed to be 60%. This corresponds to an absolute bioavailability of
 8 approximately 20% at age 2 years in the AALM and 30% in the IEUBK model.

9

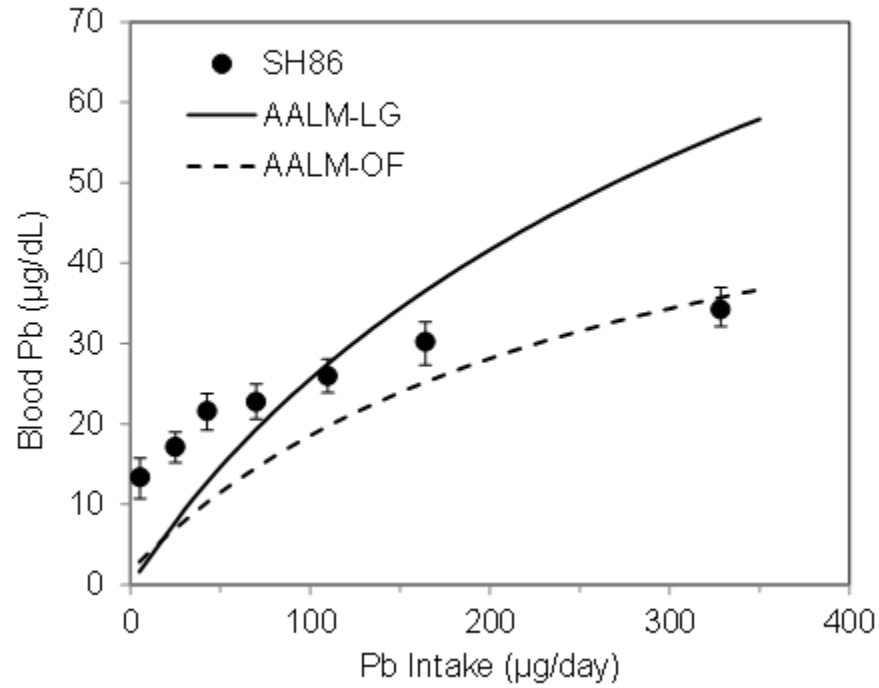
1 **FIGURE 4-27. SIMULATION OF FORMULA-FED INFANTS FROM (RYU ET AL., 1983)**
2 **AFTER ADJUSTMENT OF RED BLOOD CELL (RRBC IN AALM-LG, KBIND IN AALM-OF).**



3
4 Data in left panels are from 25 infants fed formula from cartons (12–20 µg/day) from age 8–196 days
5 (closed circles) and then a subset (n = 7) that were switched to formula from cans at age 112 days (60–63
6 µg/day, closed squares). Solid lines show simulations of the mean Pb intakes; dotted lines show
7 simulations of ±1 SD of mean intakes.

8

1 **FIGURE 4-28. SIMULATION OF FORMULA-FED INFANTS (N = 131, AGE 91 DAYS) FROM**
2 **([SHERLOCK AND QUINN, 1986](#)) AFTER ADJUSTMENT OF RED BLOOD CELL (RRBC IN**
3 **AALM-LG, KBIND IN AALM-OF).**



4
5 Blood Pb were measured and Pb intakes were estimated from duplicate diets assessed at age 91 days.
6

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1 APPENDIX A – EQUATIONS IN AALM.FOR

2 TABLE A-1. EQUATIONS OF THE ALL AGES LEAD MODEL (AALM.FOR)

Model	Submodel	Equation
Daily lead intake rate from air (µg/day)		
Exposure	Air	For each discrete age: $Air_{TWA_{discrete}} = Air_1 * f_{Air_1} + Air_2 * f_{Air_2} + Air_3 * f_{Air_3}$
Exposure	Air	For each discrete age: $f_{Air_3} = 1 - (f_{Air_1} + f_{Air_2})$
Exposure	Air	For each discrete age: $INair_{discrete} = Air_{TWA_{discrete}} * V_{air}$
Exposure	Air	For each pulse: $INair_{pulse_{sum}} = (Air_{baseline} + Air_{pulse}) * V_{air}$
Exposure	Air	For combined discrete and pulse: $INair_{Total} = INair_{discrete} * (1 - f_{pulse_{air}}) + INair_{pulse} * f_{pulse_{air}}$
Daily lead intake rate from indoor dust (µg/day)		
Exposure	Dust	For each discrete age: $Dust_{TWA_{discrete}} = Dust_1 * f_{Dust_1} + Dust_2 * f_{Dust_2} + Dust_3 * f_{Dust_3}$
Exposure	Dust	For each discrete age: $f_{Dust_3} = 1 - (f_{Dust_1} + f_{Dust_2})$
Exposure	Dust	For each discrete age: $INdust_{discrete} = Dust_{TWA_{discrete}} * IR_{Dust} * RBA_{Dust}$

Model	Submodel	Equation
Exposure	Dust	For each pulse: $INdust_{pulse_{sum}} = (Dust_{baseline} + Dust_{pulse}) * IR_{Dust} * RBA_{Dust}$
Exposure	Dust	For combined discrete and pulse: $INdust_{Total} = INdust_{discrete} * (1 - f_{pulse}) + INdust_{pulse} * f_{pulse}$
Exposure	Dust	For each discrete age: $Dust_{TWA_{discrete}} = Dust_1 * f_{Dust_1} + Dust_2 * f_{Dust_2} + Dust_3 * f_{Dust_3}$
Exposure	Dust	$IR_{Dust} = IR_{SD} * (1 - f_{IR_{Soil}})$
Daily lead intake rate from soil (µg/day)		
Exposure	Soil	For each discrete age: $Soil_{TWA_{discrete}} = Soil_1 * f_{Soil_1} + Soil_2 * f_{Soil_2} + Soil_3 * f_{Soil_3}$
Exposure	Soil	For each discrete age: $f_{Soil_3} = 1 - (f_{Soil_1} + f_{Soil_2})$
Exposure	Soil	For each discrete age: $INsoil_{discrete} = Soil_{TWA_{discrete}} * IR_{Soil} * RBA_{Doil}$
Exposure	Soil	For each pulse: $INsoil_{pulse_{sum}} = (Soil_{baseline} + Soil_{pulse}) * IR_{Soil} * RBA_{Soil}$
Exposure	Soil	For combined discrete and pulse: $INsoil_{Total} = INsoil_{discrete} * (1 - f_{pulse}) + INsoil_{pulse} * f_{pulse}$
Exposure	Soil	$IR_{Soil} = IR_{SD} * f_{IR_{Soil}}$

Model	Submodel	Equation
Daily lead intake rate from water (µg/day)		
Exposure	Water	For each discrete age: $Water_{TWA_{discrete}} = Water_1 * f_{Water_1} + Water_2 * f_{Water_2} + Water_3 * f_{Water_3}$
Exposure	Water	For each discrete age: $f_{Water_3} = 1 - (f_{Water_1} + f_{Water_2})$
Exposure	Water	For each discrete age: $INwater_{discrete} = Water_{TWA_{discrete}} * IR_{water} * RBA_{water}$
Exposure	Water	For each pulse: $INwater_{pulse_{sum}} = (Water_{baseline} + Water_{pulse}) * IR_{water} * RBA_{water}$
Exposure	Water	For combined discrete and pulse: $INwater_{Total} = INwater_{discrete} * (1 - f_{pulse_{water}}) + INwater_{pulse} * f_{pulse_{water}}$
Daily lead intake rate from food (µg/day)		
Exposure	Food	For each discrete age: $Food_{Total_{discrete}} = Food_1 + Food_2 + Food_3$
Exposure	Food	For each discrete age: $INfood_{discrete} = Food_{Total_{discrete}} * RBA_{food}$
Exposure	Food	For each pulse: $INfood_{pulse_{sum}} = (Food_{baseline} + Food_{pulse}) * RBA_{food}$
Exposure	Food	For combined discrete and pulse: $INfood_{Total} = INfood_{discrete} * (1 - f_{pulse}) + INfood_{pulse} * f_{pulse}$

Model	Submodel	Equation
Daily lead intake rate from other sources (µg/day)		
Exposure	Other	For each discrete age: $Other_{Totaldiscrete} = Other_1 + Other_2 + Other_3$
Exposure	Other	For each discrete age: $IN_{Otherdiscrete} = Other_{Totaldiscrete} * RBA_{Other}$
Exposure	Other	For each pulse: $IN_{Otherpulse_{sum}} = (Other_{baseline} + Other_{pulse}) * RBA_{Other}$
Exposure	Other	For combined discrete and pulse: $IN_{OtherTotal} = IN_{Otherdiscrete} * (1 - f_{pulse}) + IN_{Otherpulse} * f_{pulse}$
Daily lead intake from all sources (µg/day)		
Exposure	Inhaled	For input to biokinetics: $BRETH = IN_{airtotal}$
Exposure	Ingested	For combined ingestion pathways: $IN_{Ingestiontotal} = IN_{water} + IN_{dust} + IN_{food} + IN_{Other}$
Exposure	Ingested	For input to biokinetics: $EAT = IN_{Ingestiontotal}$
BioKinetics Equations (including absorption processes)		
Growth and tissue volumes (L or dL) and masses (kg)		

Model	Submodel	Equation
Biokinetics	Growth	$WBODY = WBIRTH + \frac{WCHILD * HOWOLD}{HALF + HOWOLD} + \frac{WADULT}{1 + KAPPA * e^{(LAMBDA * WADULT * HOWOLD)}}$
Biokinetics	Growth	$AMTBLD = VBLC * WBODY * 10$
Biokinetics	Growth	$PLSVOL = AMTBLD * (1 - BLDHCT)$
Biokinetics	Growth	$RBCVOL = AMTBLD * BLDHCT$
Biokinetics	Growth	$BLDHCT_{HOWOLD \leq 0.01} = 0.52 + HOWOLD * 14$ $BLDHCT_{HOWOLD > 0.01} = HCTA * (1 + (0.66 - HCTA) * e^{-(HOWOLD - 0.01) * 13.9})$
Biokinetics	Growth	$VK = 1000 * VKC * (WBIRTH + WCHILD + WADULT) * \left(\frac{WBODY}{WBIRTH + WCHILD + WADULT} \right)^{0.84}$
Biokinetics	Growth	$KIDWT = VK * 1.05$
Biokinetics	Growth	$VL = 1000 * VLC * (WBIRTH + WCHILD + WADULT) * \left(\frac{WBODY}{WBIRTH + WCHILD + WADULT} \right)^{0.85}$
Biokinetics	Growth	$LIVWT = VL * 1.05$
Biokinetics	Growth	$TSKELWT = 1000 * 0.058 * WBODY^{1.21}$
Biokinetics	Growth	$WBONE = 1000 * 0.029 * WBODY^{1.21}$

Model	Submodel	Equation
Biokinetics	Growth	$VBONE = 1000 * 0.0168 * WBODY^{1.188}$
Biokinetics	Growth	$CVBONE = 0.8 * VBONE$
Biokinetics	Growth	$TVBONE = VBONE - CVBONE$
Biokinetics	Growth	$CORTWT = \frac{WBONE * CVBONE}{VBONE}$
Biokinetics	Growth	$TRABWT = \frac{WBONE * TVBONE}{VBONE}$
Deposition fractions (DF, unitless) of lead from diffusible plasma to tissue compartments		
Biokinetics	DF	$AGESCL = \frac{1.0 - TEVF - TBONE}{1.0 - TEVF - ATBONE}$
Biokinetics	DF	$TURIN = AGESC * TOURIN$
Biokinetics	DF	$TSWET = AGESCL * TOSWET$
Biokinetics	DF	$TSOF0 = AGESCL * TOSOF0$
Biokinetics	DF	$TSOF1 = AGESCL * TOSOF1$

Model	Submodel	Equation
Biokinetics	DF	$TSOF2 = AGESCL * TOSOF2$
Biokinetics	DF	$TBRAN = AGESCL * TOBRAN$
Biokinetics	DF	$TLVR1 = AGESCL \cdot TOLVR1$
Biokinetics	DF	$TKDN1 = AGESCL * TOKDN1$
Biokinetics	DF	$TKDN2 = AGESCL * TOKDN2$
Biokinetics	DF	$TRBC = AGESCL * TORBC$
Biokinetics	DF	$TPROT = AGESCL * TOPROT$
Biokinetics	DF	$TOORBC = TRBC * \left(1 - \frac{RBCONC - RBCNL}{SATRAT - RBCNL}\right)^{POWER}$
Biokinetics	DF	$TSUM = TOORBC + TEVF + TPROT + TBONE + TURIN + TFECE + TSWET + TLVR1 + TKDN1 + TKDN2 + TSOFO + TSOF1 + TSOF2 + TBRAN$
Biokinetics	DF	$CF = \frac{1.0 - TOORBC}{1.0 - TRBC}$
Deposition fractions (DF, unitless) of lead from diffusible plasma to tissue compartments during chelation therapy		

Model	Submodel	Equation
Biokinetics	DF	$TEVF = (1 - CHLEFF) * TEVF$
Biokinetics	DF	$TFECE = (1 - CHLEFF) * TFECE$
Biokinetics	DF	$TSWET = (1 - CHLEFF) * TSWET$
Biokinetics	DF	$TSOF0 = (1 - CHLEFF) * TSOF0$
Biokinetics	DF	$TSOF1 = (1 - CHLEFF) * TSOF1$
Biokinetics	DF	$TSOF2 = (1 - CHLEFF) * TSOF2$
Biokinetics	DF	$TBRAN = (1 - CHLEFF) * TBRAN$
Biokinetics	DF	$TLVR1 = (1 - CHLEFF) * TLVR1$
Biokinetics	DF	$TKDN1 = (1 - CHLEFF) * TKDN1$
Biokinetics	DF	$TPROT = (1 - CHLEFF) * TPROT$
Biokinetics	DF	$TBONE = (1 - CHLEFF) * TBONE$

Model	Submodel	Equation
Biokinetics	DF	$TOORBC = (1 - CHLEFF) * TOORBC$
Biokinetics	DF	$TURIN = 1 - (TOORBC + TEVF + TPROT + TBONE + TURIN + TFECE + TSWET + TLVR1 + TKDN1 + TKDN2 + TSOFO + TSOF1 + TSOF2 + TBRAN)$
Transfer rates (day⁻¹)		
Biokinetics	Plasma	$RPLS = TSUM * RPLAS$
Biokinetics	Plasma	$BTEMP = RPLS * YPLS_w$
Biokinetics	Growth	$REVF = \frac{TEVF * RPLS}{SIZEVF}$
Biokinetics	RBC	$CF = \frac{1.0 - TOORBC}{1.0 - TRBC}$
Amount of lead (µg) in compartment at start of each integration step (Y₀) and amount integrated over the step (Y_w)		

Model	Submodel	Equation
Biokinetics	Lung	<p>IF DELT*OUTRATE >50:</p> $YR1_0 = \frac{INRATE}{RDECAY + BR1}$ <p>IF DELT*OUTRATE ≤50:</p> $YR1_0 = \left(YR1_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR1₀ = R1 CHRONIC: INRATE = R1 * BR1CRN OUTRATE = BR1 + RDECAY</p>
Biokinetics	Lung	<p>IF DELT*OUTRATE>50:</p> $YR1_w = \frac{1}{OUTRATE} * YR1_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR1_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OPUTRATE} * YR1_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR1 = R1 CHRONIC: INRATE = R1 * BR1CRN OUTRATE = BR1 + RDECAY</p>

Model	Submodel	Equation
Biokinetics	Lung	<p>IF DELT*OUTRATE >50:</p> $YR2_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR2_0 = \left(YR2_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR2 = R2 CHRONIC: INRATE = R2 * BR2CRN OUTRATE = BR2 + RDECAY</p>
Biokinetics	Lung	<p>IF DELT*OUTRATE >50:</p> $YR2_w = \frac{1}{OUTRATE} * YR2_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR2_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YR2_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR2 = R2 CHRONIC: INRATE = R2 * BR2CRN OUTRATE = BR2 + RDECAY</p>

Model	Submodel	Equation
Biokinetics	Lung	<p>IF DELT*OUTRATE >50:</p> $YR3_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR3_0 = \left(YR3_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR3 = R3 CHRONIC: INRATE = R3 * BRTCRN OUTRATE = BR3 + RDECAY</p>
Biokinetics	Lung	<p>IF DELT*OUTRATE >50:</p> $YR3_w = \frac{1}{OUTRATE} * YR3_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR3_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YR3_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR3 = R3 CHRONIC: INRATE = R3 * BRTCRN OUTRATE = BR3 + RDECAY</p>

Model	Submodel	Equation
Biokinetics	Lung	<p>IF DELT*OURTATE >50:</p> $YR4_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR4_0 = \left(YR4_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR4 = R4 CHRONIC: INRATE = R4 * BRTCRN OUTRATE = BR4 + RDECAY</p>
Biokinetics	Lung	<p>IF DELT*OUTRATE >50:</p> $YR4_w = \frac{1}{OUTRATE} * YR4_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YR4_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YR4_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ <p>ACUTE: INRATE = 0, YR4 = R4 CHRONIC: INRATE = R4 * BRTCRN OUTRATE = BR4 + RDECAY</p>

Model	Submodel	Equation
Biokinetics	GI Tract	$F_1 = AF_{C1} - \frac{AF_{C2}}{1 + 30 * e^{-HOWOLD}}$ <p>(calculated outside of Fortran code)</p>
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YRSTMC_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSTMC_0 = \left(YSTMC_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ <p>ACUTE: INRATE = 0, YSTMC₀ = 1 CHRONIC (no inhalation): INRATE = EATCRN CHRONIC (COMBINATION): INRATE = EATCRN + CILIAR * $\frac{(BR1 * YR1_w + BR2 * YR2_w + BR3 * YR3_w + BR4 * YR4_w)}{DELT}$ OUTRATE = GSCALE * RSTMC + RDECAY</p>

Model	Submodel	Equation
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YSTMC_w = \frac{1}{OUTRATE} * YRSTMC_0 - \frac{INRATE}{OUTRATE} + INRATE * \frac{DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSTMC_w = \left(\frac{1 - e^{(OUTRATE*DELT)}}{OUTRATE} * YSTMC_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ <p>ACUTE: INRATE = 0, YSTMC₀ = 1 CHRONIC (no inhalation): INRATE = EATCRN</p> <p>CHRONIC (COMBINATION): INRATE = EATCRN + CILIAR * $\frac{(BR1 * YR1_w + BR2 * YR2_w + BR3 * YR3_w + BR4 * YR4_w)}{DELT}$</p> <p>OUTRATE = GSCALE * RSTMC + RDECAY</p>

Model	Submodel	Equation
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YSIC_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSIC_0 = \left(YSIC_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{(INRATE)}{OUTRATE}$ $INRATE = \frac{(GSCALE * RSTMC * YSTMC_W) + (H1TOSI * RLVR1 * YRLVR1_W) + (TFECE * CF * BTEMP)}{DELT}$ $OUTRATE = GSCALE * RSIC + RDECAY$
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YSIC_W = \frac{1}{OUTRATE} * YSIC_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSIC_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YSIC_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{(GSCALE * RSTMC * YSTMC_W) + (H1TOSI * RLVR1 * YRLVR1_W) + (TFECE * CF * BTEMP)}{DELT}$ $OUTRATE = GSCALE * RSIC + RSIC$

Model	Submodel	Equation
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YULIC_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YULIC_0 = \left(YULIC_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{-OUTRATE*DELT} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{(1.0 - F1) * GSCALE * RSIC * YSIC_W}{DELT}$ $OUTRATE = GSCALE * RULI + RDECAY$

Model	Submodel	Equation
Biokinetics	GI Tract	<p>IF DELT*OUTRATE>50:</p> $YULIC_W = \frac{1}{OUTRATE} * YULIC_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE≤50:</p> $YULIC_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YULIC_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{(1.0 - F1) * GSCALE * RSIC * YSIC_W}{DELT}$ $OUTRATE = GSCALE * RULI + RDECAY$

Model	Submodel	Equation
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YLLIC_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YLLIC_0 = \left(YLLIC_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{GSCALE * RULI * YULIC_W}{DELT}$ $OUTRATE = GSCALE * RLLI + RDECAY$

Model	Submodel	Equation
Biokinetics	GI Tract	<p>IF DELT*OUTRATE >50:</p> $YLLIC_W = \frac{1}{OUTRATE} * YULIC_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YLLIC_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YLLIC_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{GSCALE * RULI * YULIC_W}{DELT}$ $OUTRATE = GSCALE * RLLI + RDECAY$

Model	Submodel	Equation
Biokinetics	Plasma	<p>IF DELT*OUTRATE >50:</p> $YPLS_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YPLS_0 = \left(YPLS_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{(INRATE)}{OUTRATE}$ $INRATE = \begin{cases} ACUTE: INRATE_{TISSUE} \\ CHRONIC: INRATE_{TISSUE} + CRONIC \\ INHALATION: INRATE_{TISSUE} + \frac{(1.0 + CILIAR) * (BR1 * YR1_W + BR2 * YR2_W + BR3 * YR3_W + BR4 * YR4_W)}{DELT} \end{cases}$ $TISSUE\ RATES = RPROT * YPROT_W + RRBC * YRBC_W + REVF * YEVF_W + RSOF0 * YSOF0_W * (1 - S2HAIR) + RSOF1 * YSOF1_W + RSOF2 * YSOF2_W + H1TOBL * RLVR1 * YLVR1_W + RLVR2 * YLVR2_W + RKDN2 * YKDN2_W + RCS2B * YCSUR_W + RTS2B * YTSUR_W + RCORT * YCVOL_W + RTRAB * YTVOL_W + RBRAN * YBRAN_W + F1 * GSCALE * RSIC * YSIC_W$ $INRATE_{TISSUE} = \frac{TISSUE\ RATES}{DELT}$ $OUTRATE = RPLS + RDECAY$

Model	Submodel	Equation
Biokinetic	Plasma	<p>IF DELT*OUTRATE >50:</p> $YPLS_W = \frac{1}{OUTRATE} * YPLS_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YPLS_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{RDECAY + RPLS} * YPLS_0 - \frac{INRATE}{RDECAY + RPLS} \right) + \frac{INRATE * DELT}{OUTRATE}$ <p>INRATE =</p> $\begin{cases} \text{ACUTE: } INRATE_{TISSUE} \\ \text{CHRONIC: } INRATE_{TISSUE} + CRONIC \\ \text{INHALATION: } INRATE_{TISSUE} + \frac{(1.0 + CILIAR) * (BR1 * YR1_W + BR2 * YR2_W + BR3 * YR3_W + BR4 * YR4_W)}{DELT} \end{cases}$ <p>TISSUE RATES = RPROT * YPROT_W + RRBC * YRBC_W + REVF * YEVF_W + RSOF0 * YSOF0_W * (1 - S2HAIR) * RSOF1 * YSOF1_W + RSOF2 * YSOF2_W + H1TOBL * RLVR1 * YLVR1_W + RLVER2 * YLVR2_W + RKDN2 * YKDN2_W + RCS2B * YCSUR_W + RTS2B * YTSUR_W + RCORT * YCVOL_W + RTRAB * YTVOL_W + RBRAN * YBRAN_W + F1 * GSCALE * RSIC * YSIC_W</p> $INRATE_{TISSUE} = \frac{TISSUE RATES}{DELT}$ <p>OUTRATE = RPLS + RDECAY</p>

Model	Submodel	Equation
Biokinetics	Plasma Protein	<p>IF DELT*OUTRATE >50:</p> $YPROT_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YPROT_0 = \left(YPROT_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TPROT * CF * BTEMP}{DELT}$ $OUTRATE = RPROT + RDECAY$

Model	Submodel	Equation
Biokinetics	Plasma Protein	<p>IF DELT*OUTRATE >50:</p> $YPROT_W = \frac{1}{OUTRATE} * YPROT_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YPROT_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YPROT_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TPROT * CF * BTEMP}{DELT}$ $OUTRATE = RDECAY + RPROT$

Model	Submodel	Equation
Biokinetics	RBC	<p>IF DELT*OUTRATE >50:</p> $YRBC_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YRBC_0 = \left(YRBC_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TOORBC * BTEMP}{DELT}$ $OUTRATE = RRBC + RDECAY$

Model	Submodel	Equation
Biokinetics	RBC	<p>IF DELT*OUTRATE >50:</p> $YRBC_W = \frac{1}{OUTRATE} * YRBC_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YRBC_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YRBC_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TOORBC * BTEMP}{DELT}$ $OUTRATE = RRBC + RDECAY$

Model	Submodel	Equation
Biokinetics	EVF	<p>IF DELT*OUTRATE >50:</p> $YEVF_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YEVF_0 = \left(YEVF_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TEVF * CF * BTEMP}{DELT}$ $OUTRATE = REVF + RDECAY$

Model	Submodel	Equation
Biokinetics	EVF	<p>IF DELT*OUTRATE >50:</p> $YEVF_w = \frac{1}{OUTRATE} * YEVF_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YEVF_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YEVF_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TEVF * CF * BTEMP}{DELT}$ $OUTRATE = REVF + RDECAY$

Model	Submodel	Equation
Biokinetics	Brain	<p>IF DELT*OUTRATE >50:</p> $YBRAN_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YBRAN_0 = \left(YBRAN_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TBRAN * CF * BTEMP}{DELT}$ $OUTRATE = RBRAN + RDECAY$

Model	Submodel	Equation
Biokinetics	Brain	<p>IF DELT*OUTRATE >50:</p> $YBRAN_w = \frac{1}{OUTRATE} * YBRAN_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YBRAN_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YBRAN_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TBRAN * CF * BTEMP}{DELT}$ $OUTRATE = RBRAN + RDECAY$

Model	Submodel	Equation
Biokinetics	Kidney	<p>IF DELT*OUTRATE >50:</p> $YKDN1_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YKDN1_0 = \left(YKDN1_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TKDN1 * CF * BTEMP}{DELT}$ $OUTRATE = RKDN1 + RDECAY$

Model	Submodel	Equation
Biokinetics	Kidney	<p>IF DELT*OUTRATE >50:</p> $YKDN1_w = \frac{1}{OUTRATE} * YKDN1_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YKDN1_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YKDN1_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TKDN1 * CF * BTEMP}{DELT}$ $OUTRATE = RKDN1 + RDECAY$

Model	Submodel	Equation
Biokinetics	Kidney	<p>IF DELT*OUTRATE >50:</p> $YKDN2_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YKDN2_0 = \left(YKDN2_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TKDN2 * CF * BTEMP}{DELT}$ $OUTRATE = RKDN2 + RDECAY$

Model	Submodel	Equation
Biokinetics	Kidney	<p>IF DELT*OUTRATE >50:</p> $YKDN2_w = \frac{1}{OUTRATE} * YKDN2_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YKDN2_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YKDN2_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TKDN2 * CF * BTEMP}{DELT}$ $OUTRATE = RKDN2 + RDECAY$

Model	Submodel	Equation
Biokinetics	Bladder	<p>IF DELT*OUTRATE >50:</p> $YBLAD_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YBLAD_0 = \left(YBLAD_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TURIN * CF * BTEMP + RKDN1 * YKDN1_W}{DELT}$ $OUTRATE = RBLAD + RDECAY$

Model	Submodel	Equation
Biokinetics	Bladder	<p>IF DELT*OUTRATE >50:</p> $YBLAD_w = \frac{1}{OUTRATE} * YBLAD_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YBLAD_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YBLAD_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TURIN * CF * BTEMP + RKDN1 * YKDN1_w}{DELT}$ $OUTRATE = RBLAD + RDECAY$

Model	Submodel	Equation
Biokinetics	Liver	<p>IF DELT*OUTRATE >50:</p> $YLVR1_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YLVR1_0 = \left(YLVR1_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TLVR1 * CF * BTEMP}{DELT}$ $OUTRATE = RLVR1 + RDECAY$

Model	Submodel	Equation
Biokinetics	Liver	<p>IF DELT*OUTRATE >50:</p> $YLVR1_w = \frac{1}{OUTRATE} * YLVR1_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YLVR1_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YLVR1_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TLVR1 * CF * BTEMP}{DELT}$ $OUTRATE = RLVR1 + RDECAY$

Model	Submodel	Equation
Biokinetics	Liver	<p>IF DELT*OUTRATE >50:</p> $YLVR2_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YLVR2_0 = \left(YLVR2_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{H1TOH2 * RLVR1 * YLVR1_w}{DELT}$ $OUTRATE = RLVR2 + RDECAY$

Model	Submodel	Equation
Biokinetics	Liver	<p>IF DELT*OUTRATE >50:</p> $YLVR2_w = \frac{1}{OUTRATE} * YLVR2_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YLVR2_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YLVR2_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{H1TOH2 * RLVR1 * YLVR1_w}{DELT}$ $OUTRATE = RLVR2 + RDECAY$

Model	Submodel	Equation
Biokinetics	Soft Tissue	<p>IF DELT*OUTRATE >50:</p> $Y_{SOFO_0} = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $Y_{SOFO_0} = \left(Y_{SOFO_0} - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TSOFO * CF * BTEMP}{DELT}$ $OUTRATE = RSOFO + RDECAY$

Model	Submodel	Equation
Biokinetics	Soft Tissue	<p>IF DELT*OUTRATE >50:</p> $YSOF0_w = \frac{1}{OUTRATE} * YSOF0_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSOF0_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YSOF0_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TSOF0 * CF * BTEMP}{DELT}$ $OUTRATE = RSOFO + RDECAY$

Model	Submodel	Equation
Biokinetics	Soft Tissue	<p>IF DELT*OUTRATE >50:</p> $YSOF1_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSOF1_0 = \left(YSOF1_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TSOF01 * CF * BTEMP}{DELT}$ $OUTRATE = RSOF1 + RDECAY$

Model	Submodel	Equation
Biokinetics	Soft Tissue	<p>IF DELT*OUTRATE >50:</p> $YSOF1_w = \frac{1}{OUTRATE} * YSOF1_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSOF1_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YSOF1_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TSOF1 * CF * BTEMP}{DELT}$ $OUTRATE = RSOF1 + RDECAY$

Model	Submodel	Equation
Biokinetics	Soft Tissue	<p>IF DELT*OUTRATE >50:</p> $YSOF2_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSOF2_0 = \left(YSOF2_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TSOF02 * CF * BTEMP}{DELT}$ $OUTRATE = RSOF2 + RDECAY$

Model	Submodel	Equation
Biokinetics	Soft Tissue	<p>IF DELT*OUTRATE >50:</p> $YSOF2_w = \frac{1}{OUTRATE} * YSOF2_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YSOF2_w = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YSOF2_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TSOF2 * CF * BTEMP}{DELT}$ $OUTRATE = RSOF2 + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YCDIF_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YCDIF_0 = \left(YCDIF_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{RCS2DF * YCSUR_W}{DELT}$ $OUTRATE = RDF2CS + RDF2DC + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YCDIF_W = \frac{1}{OUTRATE} * YCDIF_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YCDIF_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YCDIF_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{RCS2DF * YCSUR_W}{DELT}$ $OUTRATE = RDF2CS + RDF2DC + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YCSUR_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YCSUR_0 = \left(YCSUR_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{(TBONE * (1.0 - TFRAC) * CF * BTEMP * RDF2CS * YCDIF_W)}{DELT}$ $OUTRATE = RCS2B + RCS2DF + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YCSUR_W = \frac{1}{OUTRATE} * YCSUR_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YCSUR_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YCSUR_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{(TBONE * (1.0 - TFRAC) * CF * BTEMP * RDF2CS * YCDIF_W)}{DELT}$ $OUTRATE = RCS2B + RCS2DF + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YCVOL_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YCVOL_0 = \left(YCVOL_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{RDF2DC * YCDIF_W}{DELT}$ $OUTRATE = RCORT + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YCVOL_W = \frac{1}{OUTRATE} * YCVOL_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YCVOL_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YCVOL_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{RDF2DC * YCDIF_W}{DELT}$ $OUTRATE = RCORT + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YTDIF_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YTDIF_0 = \left(YTDIF_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{RTS2DF * YTSUR_W}{DELT}$ $OUTRATE = RDF2TS + RDF2DT + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YTDIF_W = \frac{1}{OUTRATE} * YTDIF_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YTDIF_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YTDIF_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{RTS2DF * YTSUR_W}{DELT}$ $OUTRATE = RDF2TS + RDF2DT + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YTSUR_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YTSUR_0 = \left(YTSUR_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{TBONE * TFRAC * CF * BTEMP * RDF2TS * YTDIF_W}{DELT}$ $OUTRATE = RTS2B + RTS2DF + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YTSUR_W = \frac{1}{OUTRATE} * YTSUR_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YTSUR_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YTSUR_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{TBONE * TFRAC * CF * BTEMP * RDF2TS * YTDIF_W}{DELT}$ $OUTRATE = RTS2B + RTS2DF + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YTVOL_0 = \frac{INRATE}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YTVOL_0 = \left(YTVOL_0 - \left(\frac{INRATE}{OUTRATE} \right) \right) * e^{(-OUTRATE*DELT)} + \frac{INRATE}{OUTRATE}$ $INRATE = \frac{RDF2DT * YTDIF_W}{DELT}$ $OUTRATE = RTRAB + RDECAY$

Model	Submodel	Equation
Biokinetics	Bone	<p>IF DELT*OUTRATE >50:</p> $YTVOL_W = \frac{1}{OUTRATE} * YTVOL_0 - \frac{INRATE}{OUTRATE} + \frac{INRATE * DELT}{OUTRATE}$ <p>IF DELT*OUTRATE ≤50:</p> $YTVOL_W = \left(\frac{1 - e^{(-OUTRATE*DELT)}}{OUTRATE} * YTVOL_0 - \frac{INRATE}{OUTRATE} \right) + \frac{INRATE * DELT}{OUTRATE}$ $INRATE = \frac{RDF2DT * YTDIF_W}{DELT}$ $OUTRATE = RTRAB + RDECAY$
Lead Masses in Tissues at Birth		
Biokinetics	Blood	$YRBC = RBCIN * \frac{BLDMOT * BRATIO * 3}{RBCIN}$
Biokinetics	Brain	$YBRAN = BRANIN * \frac{BLDMOT * BRATIO * 3}{RBCIN}$

Model	Submodel	Equation
Biokinetics	Kidney	$YKDN2 = RENIN * \frac{BLDMOT * BRATIO * 3}{RBCIN}$
Biokinetics	Liver	$YLVR2 = HEPIN * \frac{BLDMOT * BRATIO * 3}{RBCIN}$
Biokinetics	Soft Tissue	$YSOF2 = SOFIN * \frac{BLDMOT * BRATIO * 3}{RBCIN}$
Biokinetics	Bone	$YCVOL = 0.8 * \frac{BLDMOT * BRATIO * 3}{RBCIN}$
Biokinetics	Bone	$YTVOL = 0.2 * \frac{BLDMOT * BRATIO * 3}{RBCIN}$
Composite lead masses in tissues		
Biokinetics	Blood	$YBLUD = YPLAS + YRBC$
Biokinetics	Plasma	$YPLAS = YPLS + YPROT$

Model	Submodel	Equation
Biokinetics	Plasma	$YPLAS_W = YPLS_W + YPROT_W$
Biokinetics	RBC	$SUMRBC = SUMRBC + YRBC_W$
Biokinetics	Kidney	$YKDNE = YKDNI + YKDN2$
Biokinetics	Liver	$YLIVR = YLVR1 + YLVR2$
Biokinetics	Lung	$YLUNG = YR1 + YR2 + YR3 + YR4$
Biokinetics	Soft Tissue	$YSOFT = YSOF0 + YSOF1 + YSOF2$
Biokinetics	Bone	$YCORT = YCSUR + YCDIF + YCVOL$
Biokinetics	Bone	$YTRAB = YRSUR + YTDIF + YTVOL$
Biokinetics	Bone	$YSKEL = YCVOL + YTVOL + YCSUR + YTSUR + YCDIF + YTDIF$
Biokinetics	Body	$TBODY1 = YPLAS + YRBC + YEVF + YSOF0 + YSOF1 + YSOF2 + YBRAN + YCVOL + YTVOL + YCSUR + YTSUR + YCDIF + YTDIF + YKDNE + YLIVR$
Biokinetics	Body	$TBODY2 = TBODY1 + YR1 + YR2 + YR3 + YR4 + YBLAD + YSTMC + YSIC + YULIC + YLLIC$

Model	Submodel	Equation
Fraction of lead in tissues relative to total body burden or blood		
Biokinetics	Blood	$BLDFRC = \frac{YBLUD}{TBODY1}$
Biokinetics	Plasma	$PLSRBC = \frac{YPLAS}{YBLUD}$
Biokinetics	Plasma	$PCENT = \frac{100 * YPLAS}{YBLUD}$
Biokinetics	Brain	$BRNFRC = \frac{YBRN}{TBODY1}$
Biokinetics	Kidney	$RENFRC = \frac{YKDNE}{TBODY1}$
Biokinetics	Liver	$HEPFRC = \frac{YLIVR}{TBODY1}$
Biokinetics	Soft Tissue	$OTHFRC = \frac{YSOFT}{TBODY1}$
Biokinetics	Bone	$BONFRC = \frac{YSKEL}{TBODY1}$
Tissue-specific lead concentrations ($\mu\text{g/g}$ or $\mu\text{g/dL}$)		
Biokinetics	Blood	$BLCONC = \frac{YBLUD}{AMTBLD}$
Biokinetics	Plasma	$DECPLS = \frac{YPLAS}{PLSVOL}$

Model	Submodel	Equation
Biokinetics	RBC	$RBCONC = \frac{YRBC}{BLDHCT * AMTBLD}$
Biokinetics	Kidney	$RENCON = \frac{YKDNE}{KIDWT}$
Biokinetics	Liver	$LIVCON = \frac{YLIVR}{LIVWT}$
Biokinetics	Bone	$CRTCON = \frac{YCORT}{CORTWT}$
Biokinetics	Bone	$TRBCON = \frac{YTRAB}{TRABWT}$
Biokinetics	Bone	$ASHCON = \frac{YSKEL}{TSKELWT}$
Biokinetics	Bone	$CRTCONBM = \frac{CRTCON}{0.55}$
Biokinetics	Bone	$TRBCONBM = \frac{TRBCON}{0.5}$
Lead excretion (µg or µg/day)		
Biokinetics	Urine	$YURIN = YURIN_0 + INRATE * DELT$ $INRATE = \frac{RBLAD * YBLAD_w}{DELT}$ $URIN = YURIN - YURIN_0$

Model	Submodel	Equation
Biokinetics	Feces	$YFECE = YFECE_0 + INRATE * DELT$ $INRATE = \frac{GSCALE * RLLI * YLLIC_W}{DELT}$
Biokinetics	Sweat	$YSWET = YSWET_0 + INRATE * DELTT$ $INRATE = \frac{TSWET * CF * BTEMP}{DELT}$
Biokinetics	Other	$YHAIR = YHAIR_0 + INRATE * DELT$ $INRATE = \frac{S2HAIR * RSOF1 * YSOF1_W}{DELT}$
Biokinetics	Total	$TOTEXC = YURIN + YFECE + YSWET + YHAIR$
Clearance (day⁻¹)		
Biokinetics	Urine	$CLEAR = \frac{URINE}{DELT} * \frac{1}{YPLAS}$
Biokinetics	Blood	$BCLEAR = 100 * \frac{URIN}{DELT} * \frac{1}{YBLUD}$

1 **APPENDIX B – ALL AGES LEAD MODEL (AALM.FOR) PARAMETERS**2 **TABLE B-1. ALL AGES LEAD MODEL PARAMETER DESCRIPTIONS**

Variable	Units	Form	Type	Explanation
EXPOSURE MODEL PARAMETERS				
Age_air_discrete	day	A	F	Age for discrete air Pb concentration
Age_air_V	day	A	F	Age for air ventilation rate
Age_dust_discrete	day	A	F	Age for discrete dust Pb concentration
Age_dust_IR	day	A	F	Age for dust ingestion rate
Age_food_discrete	day	A	F	Age for discrete food Pb concentration
Age_other_discrete	day	A	F	Age for discrete other Pb concentration
Age_soil_discrete	day	A	F	Age for discrete soil Pb concentration
Age_soil_IR	day	A	F	Age for indoor soil ingestion rate
Age_water_discrete	day	A	F	Age for discrete water Pb concentration
Age_water_IR	day	A	F	Age for water ingestion rate
Air_baseline	$\mu\text{g}/\text{m}^3$	C	F	Baseline air Pb concentration used in exposure pulse train
Air_i; i= 1, 2,3	$\mu\text{g}/\text{m}^3$	A	F	Air Pb concentrations for discrete exposures
Air_pulse	$\mu\text{g}/\text{m}^3$	C	F	Air Pb concentration used in exposure pulse train
Air_discrete_weighted	$\mu\text{g}/\text{m}^3$	V	F	Weighted average air Pb concentrations for discrete exposures
Dust_baseline	$\mu\text{g}/\text{g}$	C	F	Baseline dust Pb concentration used in exposure pulse train
Dust_i; i= 1, 2,3	$\mu\text{g}/\text{g}$	A	F	Dust Pb concentrations for discrete exposures
Dust_pulse	$\mu\text{g}/\text{g}$	C	F	Dust Pb concentration used in exposure pulse train
Dust_discrete_weighted	$\mu\text{g}/\text{g}$	V	F	Weighted average dust Pb concentrations for discrete exposures
f_Air_i; i= 1,2,3	unitless	A	F	Fraction of discrete Air_i contributing to daily air Pb exposure
f_Dust_i; i= 1,2	unitless	A	F	Fraction of discrete Dust_i contributing to daily dust Pb exposure
f_IR_soil	unitless	C	F	Soil fraction of soil and dust ingestion rate (IR_sd)
f_Other_i; i= 1,2,3	unitless	A	F	Fraction of discrete Other_i contributing to daily other Pb exposure
f_pulse_air	unitless	C	F	Fraction of air daily air exposure from pulse train
f_pulse_dust	unitless	C	F	Fraction of daily dust exposure from pulse train
f_pulse_other	unitless	C	F	Fraction of daily other exposure from pulse train

Variable	Units	Form	Type	Explanation
f_pulse_soil	unitless	C	F	Fraction of daily soil exposure from pulse train
f_pulse_water	unitless	C	F	Fraction of daily water exposure from pulse train
f_Soil_i; i= 1,2	unitless	A	F	Fraction of discrete Soil_i contributing to daily soil Pb exposure
f_Water_i; i= 1,2,3	unitless	A	F	Fraction of discrete Water_i contributing to daily water Pb exposure
Food_baseline	µg/day	C	F	Baseline food Pb intake used in exposure pulse train
Food_i; i= 1, 2,3	µg/day	A	F	Food Pb intakes for discrete exposures
Food_pulse	µg/day	C	F	Food Pb intake used in exposure pulse train
Food_total_discrete	µg/day	V	F	Total food Pb intakes for discrete exposures
IN_air_discrete	µg/day	V	F	Pb intake from discrete exposures to air
IN_air_pulse	µg/day	V	F	Pb intake from pulse train exposures to air
IN_air_total	µg/day	V	F	Pb intake from combined discrete and pulse train exposures to air
IN_dust_discrete	µg/day	V	F	Pb intake from discrete exposures to dust
IN_dust_pulse	µg/day	V	F	Pb intake from pulse train exposures to dust
IN_dust_total	µg/day	V	F	Pb intake from combined discrete and pulse train exposures to dust
IN_food_discrete	µg/day	V	F	Pb intake from discrete exposures to food
IN_food_pulse	µg/day	V	F	Pb intake from pulse train intakes from food
IN_food_total	µg/day	V	F	Pb intake from combined discrete and pulse train exposures to food
IN_ingestion_total	µg/day	V	F	Pb intake from all ingestion exposures combined (dust, soil, food, water, other)
IN_other_discrete	µg/day	V	F	Pb intake from discrete exposures to other sources
IN_other_pulse	µg/day	V	F	Pb intake from pulse train intakes from other sources
IN_other_total	µg/day	V	F	Pb intake from combined discrete and pulse train exposures to other sources
IN_soil_discrete	µg/day	V	F	Pb intake from discrete exposures to soil
IN_soil_pulse	µg/day	V	F	Pb intake from pulse train exposures to soil
IN_soil_total	µg/day	V	F	Pb intake from combined discrete and pulse train exposures to soil
IN_water_discrete	µg/day	V	F	Pb intake from discrete exposures to water
IN_water_pulse	µg/day	V	F	Pb intake from pulse train exposures to water
IN_water_total	µg/day	V	F	Pb intake from combined discrete and pulse train exposures to water

Variable	Units	Form	Type	Explanation
IR_dust	g/day	C	F	Dust ingestion rate for dust Pb exposures
IR_soil	g/day	C	F	Dust ingestion rate for soil Pb exposures
IR_sd	g/day	A	F	Combined soil and dust ingestion rate for Pb exposures
IR_water	L/day	C	F	Dust ingestion rate for water Pb exposures
Other_baseline	µg/day	C	F	Baseline other Pb intake used in exposure pulse train
Other_i; i= 1, 2,3	µg/day	A	F	Food Pb intakes for discrete exposures
Other_pulse	µg/day	C	F	Other Pb intake used in exposure pulse train
Other_total_discrete	µg/day	V	F	Total other Pb intakes for discrete exposures
Pulse_i_period_air; i=1,2	day	C	F	Period for pulse train exposure to air
Pulse_i_period_dust ; i=1,2	day	C	F	Period for pulse train exposure to dust
Pulse_i_period_food ; i=1,2	day	C	F	Period for pulse train exposure to food
Pulse_i_period_oth er; i=1,2	day	C	F	Period for pulse train exposure to other
Pulse_i_period_soil; i=1,2	day	C	F	Period for pulse train exposure to soil
Pulse_i_period_wate r; i=1,2	day	C	F	Period for pulse train exposure to water
Pulse_i_width_air; i=1,2	day	C	F	Width for pulse train exposure to air
Pulse_i_width_dust; i=1,2	day	C	F	Width for pulse train exposure to dust
Pulse_i_width_food; i=1,2	day	C	F	Width for pulse train exposure to food
Pulse_i_width_oth er; i=1,2	day	C	F	Width for pulse train exposure to other
Pulse_i_width_soil; i=1,2	day	C	F	Width for pulse train exposure to indoor soil
Pulse_i_width_wate r; i=1,2	day	C	F	Width for pulse train exposure to water
Pulse_start_air	day	C	F	Start age for pulse train exposure to air
Pulse_start_dust	day	C	F	Start age for pulse train exposure to dust
Pulse_start_food	day	C	F	Start age for pulse train exposure to food
Pulse_start_oth er	day	C	F	Start age for pulse train exposure to other
Pulse_start_soil	day	C	F	Start age for pulse train exposure to indoor soil

Variable	Units	Form	Type	Explanation
Pulse_start_water	day	C	F	Start age for pulse train exposure to water
Pulse_stop_air	day	C	F	Stop age for pulse train exposure to air
Pulse_stop_dust	day	C	F	Stop age for pulse train exposure to dust
Pulse_stop_food	day	C	F	Stop age for pulse train exposure to food
Pulse_stop_other	day	C	F	Stop age for pulse train exposure to other
Pulse_stop_soil	day	C	F	Stop age for pulse train exposure to soil
Pulse_stop_water	day	C	F	Stop age for pulse train exposure to water
RBA_dust	unitless	C	F	Relative bioavailability of dust Pb
RBA_food	unitless	C	F	Relative bioavailability of food Pb
RBA_other	unitless	C	F	Relative bioavailability of other Pb
RBA_soil	unitless	C	F	Relative bioavailability of soil Pb
RBA_water	unitless	C	F	Relative bioavailability of water Pb
Sex	unitless	C	S	Female of male
Soil_baseline	µg/g	C	F	Baseline dust Pb concentration used in exposure pulse train
Soil_i; i= 1, 2,3	µg/g	A	F	Soil Pb concentrations for discrete exposures
Soil_pulse	µg/g	C	F	Soil Pb concentration used in exposure pulse train
Soil_discrete_weighted	µg/g	V	F	Weighted average soil Pb concentrations for discrete exposures
Water_baseline	µg/L	C	F	Baseline water Pb concentration used in exposure pulse train
Water_i; i= 1, 2,3	µg/L	A	F	Water Pb concentrations for discrete exposures
Water_pulse	µg/L	C	F	Water Pb concentration used in exposure pulse train
Water_discrete_weighted	µg/L	V	F	Weighted average water Pb concentrations for discrete exposures
V_air	m ³ /day	A	F	Ventilation rate for air Pb exposures
BIOKINETIC MODEL PARAMETERS				
AF1	unitless	A	F	Fractional absorption of Pb from small intestine – age array (see F1)
AGESCAL	unitless	A	F	Age scaling factor for gastrointestinal transfers – age array (see GSCALE)
AGEYEAR	year	V	F	Age from birth in years
AMTBLD	dL	V	F	Amount of blood at time(t)
ARBLAD	day ⁻¹	A	F	Rate coefficient for Pb transfer from urinary bladder to urine – age array (see RBLAD)

Variable	Units	Form	Type	Explanation
ARBRAN	day ⁻¹	A	F	Rate coefficient for Pb transfer from brain to diffusible plasma – age array (see RBRAN)
ARCORT	day ⁻¹	A	F	Rate coefficient for Pb transfer from non-exchangeable cortical bone to diffusible plasma – age array (see RCORT)
ARCS2B	day ⁻¹	A	F	Rate coefficient for Pb transfer from cortical bone surface to diffusible plasma – age array (see RCS2B)
ARCSDF	day ⁻¹	A	F	Rate coefficient for Pb transfer from cortical bone surface to exchangeable cortical bone – age array (see RCS2DF)
ARD2CS	day ⁻¹	A	F	Rate coefficient for Pb transfer from exchangeable cortical bone to cortical bone surface – age array (see RDF2CS)
ARD2DC	day ⁻¹	A	F	Rate coefficient for Pb transfer from exchangeable cortical bone to non-exchangeable cortical bone – age array (see RDF2DC)
ARD2DT	day ⁻¹	A	F	Rate coefficient for Pb transfer from exchangeable trabecular bone to non-exchangeable trabecular bone – age array (see RDF2DT)
ARD2TS	day ⁻¹	A	F	Rate coefficient for Pb transfer from exchangeable trabecular bone to trabecular bone surface – age array (see RDF2DS)
ARKDN2	day ⁻¹	A	F	Rate coefficient for transfer from kidney compartment 2 to diffusible plasma – age array (see RKDN2)
ARLVR2	day ⁻¹	A	F	Rate coefficient for Pb transfer from the slow liver compartment 2 to diffusible plasma – age array (see RLVR2)
ARRBC	day ⁻¹	A	F	Rate coefficient for Pb transfer from RBC to diffusible plasma – age array (see RRBC)
ARTRAB	day ⁻¹	A	F	Rate coefficient for Pb transfer from non-exchangeable trabecular bone to diffusible plasma – age array (see RTRAB)
ARTS2B	day ⁻¹	A	F	Rate coefficient for Pb transfer from trabecular bone surface to diffusible plasma – age array (see RTS2B)
ARTSDF	day ⁻¹	A	F	Rate coefficient for Pb transfer from surface trabecular bone to exchangeable trabecular bone – age array (see RTS2DF)
ASHCON	µg/g	V	F	Pb concentration in skeletal mineral

Variable	Units	Form	Type	Explanation
ATBONE	unitless	A	F	Deposition fraction for Pb from diffusible plasma to surface bone – age array (see TBONE)
ATBRAN	unitless	A	F	Deposition fraction for Pb from diffusible plasma to brain – age array (see RBRAN)
ATFRAC	unitless	A	F	Fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone – age array (see TFRAC)
ATOSOF0	unitless	A	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 0 – age array (see TOSOF0)
ATOSOF1	unitless	A	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 1 – age array (see TOSOF1)
ATOSOF2	unitless	A	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 2 – age array (see TOSOF2)
BCLEAR	day ⁻¹	V	F	Clearance of Pb from blood to urine
BLCONC	µg/dL	V	D	Pb concentration in whole blood
BLDFRC	unitless	V	F	Amount of Pb in blood as a fraction of total body Pb
BLDHCT	unitless	V	F	Blood hematocrit
BLDMOT	µg/dL	C	F	Maternal blood Pb concentration
BLDVOL	dL	V	F	Blood volume as the sum of RBC and plasma volume
BONFRC	unitless	V	F	Amount of Pb in bone as a fraction of total body Pb
BR1	day ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 1 to diffusible plasma
BR2	day ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 2 to diffusible plasma
BR3	day ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 3 to diffusible plasma
BR4	day ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 4 to diffusible plasma
BRATIO	unitless	C	F	Child (at birth):maternal blood Pb concentration ratio
BRETH	µg/day	V	A	Pb intake rate age array from inhalation of Pb in air (see IN_air_total)
BRNFRC	unitless	V	F	Amount of Pb in brain as a fraction of total body Pb

Variable	Units	Form	Type	Explanation
BRTCRN	µg/day	V	F	Pb intake from inhalation exposure at each age range
BTEMP	µg/day	V	F	Total outflow of Pb from diffusible plasma to all compartments
CF	unitless	V	F	Factor for adjusting Pb deposition fractions from diffusible plasma to account for non-linear uptake of Pb in RBC
CHAGE	day	A	F	Ages at which biokinetics parameters are specified (for each NUMAGE)
CHEL1	unitless	C	I	First day of chelation therapy
CHEL2	unitless	C	I	Last day of chelation therapy
CHLEFF	unitless	C	I	Deposition change factor due to chelation therapy
CHR	µg	A	F	Chronic injection uptakes for each NCHRON
CILIAR	unitless	C	F	Fraction of inhaled Pb transferred to gastrointestinal tract
CORTWT	g	V	F	cortical bone weight
CRONIC	µg	V	F	Chronic injection intake at current integration time step
CRTCON	µg/g	V	F	Pb concentration in cortical bone
CRTCONBM	µg/g	V	F	Pb concentration in cortical bone mineral
CVBONE	mL	V	F	cortical bone volume
DECLTR	µg/dL	V	D	Pb concentration in total blood
DECPLS	µg/dL	V	D	Pb concentration in diffusible plasma
DECRBC	µg/dL	V	D	Pb concentration in RBCs
DELTO	day	C	F	Initial integration time step
DELTA	unitless	A	F	Numerical integration cycle lengths – age array
DELTA_i	day	A	F	Array of integration step sizes for each NDELT
EAT	µg/day	A	F	Pb intake rate age array from ingestion of Pb (see IN_ingestion_total)
EATCRN	µg/day	V	F	Pb intake from oral exposure at each age range
ENDDAY	day	C	F	Age and end of simulation
ENDPT	day	A	F	End days for chronic intakes for each NCHRON
EXPAGE	day	C	F	Age at start exposure
F1	unitless	V	F	Fractional absorption of Pb from small intestine at time(t) (see AF1)
FLONG	unitless	A	F	Fraction of total Pb transfer from the exchangeable bone to non-exchangeable bone

Variable	Units	Form	Type	Explanation
GSCALE	unitless	V	F	Age scaling factor for gastrointestinal transfers at time(t) (see AGSCL)
HALF	year	C	F	Age at which body weight is half of WCHILD
HCTA	unitless	C	F	Adult hematocrit
H1TOBL	unitless	C	F	Fraction of Pb transfer out of liver compartment 1 that goes to diffusible plasma
H1TOH2	unitless	C	F	Fraction of Pb transfer out of liver compartment 1 that goes to liver compartment 2
H1TOSI	unitless	C	F	Fraction of Pb transfer out of liver compartment 1 that goes to the small intestine
HEPFRC	unitless	V	F	Amount of Pb in liver as a fraction of total body Pb
IACUTE	unitless	C	I	Switch for acute (1) or chronic array (2) uptakes
ICHEL	unitless	C	I	Switch for chelation simulation off (0) or on (1)
ICYC_i	unitless	A	F	Number of numerical integration cycles for each NDELTA
IFETAL	unitless	C	I	Switch for fetal simulation on (1) or off (0)
INMODE	unitless	C	I	Switch for injection (0), inhalation (1), ingestion (2), or combination (3)
IRBC	unitless	C	I	Switch for linear (0) or non-linear (1) RBC uptake
ISKIP	day	C	F	Communication interval
KAPPA	unitless	C	F	Logistic body growth parameter
KIDWT	g	V	F	Kidney weight
LAMBDA	unitless	C	F	Logistic body growth parameter
LINPUT	unitless	C	I	Switch for manual input (0) or array input (1)
LIVCON	µg/g	V	F	Pb concentration in liver
LIVWT	g	V	F	Liver weight
NCHRON	unitless	C	F	Number of different chronic intakes
NCYCLE	unitless	C	F	Maximum number of numerical integration cycles
NDELTA	unitless	C	F	Number of times the integration step changes
NUMAGE	unitless	C	F	Number of ages at which biokinetics parameter values are specified
OTHFRC	unitless	V	F	Amount of Pb in other soft tissue as a fraction of total body Pb
PCENT	percent	V	F	Percent of whole blood Pb in plasma
PLSRBC	unitless	V	F	Plasma fraction of Pb in whole blood
PLSVOL	dL	V	F	Plasma volume
POWER	unitless	C	F	Exponent for non-linear deposition of Pb from diffusible plasma to RBC

Variable	Units	Form	Type	Explanation
R1	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 1
R2	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 2
R3	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 3
R4	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 4
RBCIN	unitless	V	F	Amount of Pb in RBC as a fraction of body Pb, at birth
RBCNL	$\mu\text{g/dL}$	C	F	Threshold Pb concentration in RBC for non-linear deposition of Pb from diffusible plasma to RBC
RBCON	$\mu\text{g/dL}$	V	F	Concentration of Pb in RBC
RBCVOL	dL	V	F	RBC volume
RBLAD	day^{-1}	V	F	Rate coefficient for Pb transfer from urinary bladder to urine at time(t) (see ARBLAD)
RBRAN	day^{-1}	V	F	Rate coefficient for Pb transfer from brain to diffusible plasma at time(t) (see ABRAN)
RCORT	day^{-1}	V	F	Rate coefficient for Pb transfer from non-exchangeable cortical bone to diffusible plasma at time(t) (see ACORT)
RCS2B	day^{-1}	V	F	Rate coefficient for Pb transfer from cortical bone surface to diffusible plasma at time(t) (see ARCS2B)
RCS2DF	day^{-1}	V	F	Rate coefficient for Pb transfer from cortical bone surface to exchangeable cortical bone at time(t) (see ARCS2DF)
RDECAY	day^{-1}	C	F	Rate coefficient for radioactive decay
RDF2CS	day^{-1}	V	F	Rate coefficient for Pb transfer from exchangeable cortical bone to cortical bone surface at time(t) (see ARD2CS)
RDF2DC	day^{-1}	V	F	Rate coefficient for Pb transfer from exchangeable cortical bone to non-exchangeable cortical bone at time(t) (see ARD2DC)
RDF2DT	day^{-1}	V	F	Rate coefficient for Pb transfer from exchangeable trabecular bone to non-exchangeable trabecular bone at time(t) (see ARD2DT)
RDF2TS	day^{-1}	V	F	Rate coefficient for Pb transfer from exchangeable trabecular bone to trabecular bone surface at time(t) (see ARD2TS)

Variable	Units	Form	Type	Explanation
RDIFF	day ⁻¹	A	F	Rate coefficient for Pb transfer from exchangeable bone (cortical or trabecular) to surface and non-exchangeable bone – age array (see FLONG for fraction to non-exchangeable)
RENCON	µg/g	V	F	Pb concentration in kidney
RENFRC	unitless	V	F	Amount of Pb in kidney as a fraction of total body Pb
REVF	day ⁻¹	V	F	Rate coefficient for transfer from diffusible plasma to the extravascular fluid
RKDN1	day ⁻¹	C	F	Rate coefficient for transfer from kidney compartment 1 to urinary pathway
RKDN2	day ⁻¹	V	F	Rate coefficient for transfer from kidney compartment 2 to diffusible plasma at time(t) (see ARKDN2)
RLLI	day ⁻¹	C	F	Rate coefficient for Pb transfer from lower large intestine to feces
RLVR1	day ⁻¹	C	F	Rate coefficient for Pb transfer from liver compartment 1 to small intestine or diffusible plasma
RLVR2	day ⁻¹	V	F	Rate coefficient for Pb transfer from the slow liver compartment 2 to diffusible plasma at time(t) (see ARLVR2)
RPLAS	day ⁻¹	C	F	Rate coefficient for Pb transfer from diffusible plasma to all compartments; Note: scaled to bone surface deposition (see RPLS)
RPLS	day ⁻¹	V	F	Rate coefficient for Pb transfer from diffusible plasma scaled to bone surface deposition (see RPLAS)
RPROT	day ⁻¹	C	F	Rate coefficient for Pb transfer from bound plasma to diffusible plasma
RRBC	day ⁻¹	V	F	Rate coefficient for Pb transfer from RBC to diffusible plasma at time(t) (see ARRBC)
RSIC	day ⁻¹	C	F	Rate coefficient for Pb transfer from small intestine to upper large intestine
RSOF0	day ⁻¹	C	F	Rate coefficient for Pb transfer from soft tissue compartment 0 to diffusible plasma
RSOF1	day ⁻¹	C	F	Rate coefficient for Pb transfer from soft tissue compartment 1 to diffusible plasma
RSOF2	day ⁻¹	C	F	Rate coefficient for Pb transfer from soft tissue compartment 2 to diffusible plasma
RSTMC	day ⁻¹	C	F	Rate coefficient for Pb transfer from stomach to small intestine

Variable	Units	Form	Type	Explanation
RTRAB	day ⁻¹	V	F	Rate coefficient for Pb transfer from non-exchangeable trabecular bone to diffusible plasma at time(t) (see ARTRAB)
RTS2B	day ⁻¹	V	F	Rate coefficient for Pb transfer from trabecular bone surface to diffusible plasma at time(t) (see ARTS2B)
RTS2DF	day ⁻¹	V	F	Rate coefficient for Pb transfer from surface trabecular bone to exchangeable trabecular bone at time(t) (see ARTSDF)
RULI	day ⁻¹	C	F	Rate coefficient for Pb transfer from upper large intestine to lower large intestine
S2HAIR	unitless	C	F	Deposition fraction for Pb from soft tissue compartment 1 to other excreta
SATRAT	µg/dL	C	F	Maximum (saturating) concentration of Pb in RBC
SIGMA	µg	V	F	Amount of Pb in all compartments
SIZEVF	unitless	C	F	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)
SOFIN	unitless	C	F	Amount of Pb in other soft tissue as a fraction of total body Pb, at birth
SUMRBC	µg	V	F	Cumulative amount of Pb in RBC over the simulation
TBODY1	µg	V	F	Pb mass in body, excluding bladder, GIT and RT
TBODY2	µg	V	F	Pb mass in body, including bladder, gastrointestinal tract, and RT
TBONE	unitless	V	F	Deposition fraction for Pb from diffusible plasma to surface bone at time(t) (see ATBONE)
TBRAN	unitless	V	F	Deposition fraction for Pb from diffusible plasma to brain at time(t) scaled to bone surface deposition (see TOBRAN)
TEVF	unitless	C	F	Deposition fraction for Pb from diffusible plasma to extravascular fluid
TFECE	unitless	V	F	Deposition fraction for Pb from diffusible plasma directly to the small intestine at time(t) scaled bone surface deposition (not including the transfer from biliary secretion, specified by RLVR1) (see TOFECE)
TFRAC	unitless	V	F	Fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone at time(t); 1-TFRAC is the fraction that goes to cortical surface bone

Variable	Units	Form	Type	Explanation
TKDN1	unitless	V	F	Deposition fraction for Pb from diffusible plasma to kidney compartment 1 scaled to bone surface deposition (see TOKDN1)
TKDN2	unitless	V	F	Deposition fraction for Pb from diffusible plasma to liver compartment 2 scaled to bone surface deposition (see TOKDN2)
TLVR1	unitless	V	F	Deposition fraction for Pb from diffusible plasma to liver compartment 1 scaled to bone surface deposition (see TOLVR1)
TOBRAN	unitless	A	F	Deposition fraction for Pb from diffusible plasma to brain at time(t) (not scaled for bone surface deposition – see TBRAN)
TOEVF	unitless	C	F	Deposition fraction for Pb from diffusible plasma to extravascular fluid
TOFECE	unitless	C	F	Deposition fraction for Pb from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by RLVR1, not scaled to bone surface deposition – see TFECE)
TOKDN1	unitless	C	F	Deposition fraction for Pb from diffusible plasma to kidney compartment 1 not scaled to bone surface deposition (see TKDN1)
TOKDN2	unitless	C	F	Deposition fraction for Pb from diffusible plasma to kidney compartment 2 not scaled to bone surface deposition (see TKDN2)
TOLVR1	unitless	C	F	Deposition fraction for Pb from diffusible plasma to liver compartment 2 not scaled to bone surface deposition (see TLVR1)
TOORBC	unitless	V	F	Deposition fraction for Pb from diffusible plasma to RBC adjusted for capacity-limited deposition in RBC and scaled to bone surface deposition
TOPROT	unitless	C	F	Deposition fraction for Pb from diffusible plasma to protein-bound plasma not scaled to bone surface deposition (see TPROT)
TORBC	unitless	C	F	Deposition fraction from diffusible plasma to RBC not scaled to bone surface (see TRBC)
TOSOF0	unitless	A	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 0 at time (t), not scaled to bone surface deposition (see TSOFO)
TOSOF1	unitless	A	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 1 at time (t), not scaled to bone surface deposition (see TSOFO)

Variable	Units	Form	Type	Explanation
TOSOF2	unitless	A	F	Deposition fraction from diffusible plasma to soft tissue compartment 2 at time (t), not scaled to bone surface deposition (see TSOFF2)
TOSWET	unitless	C	F	Deposition fraction for Pb from diffusible plasma to sweat not scaled to bone surface deposition (see TSWET)
TOTEXC	μg	V	F	Pb mass in urine, feces, sweat, hair, nails, and skin
TOURIN	unitless	C	F	Deposition fraction for Pb from diffusible plasma to urine not scaled to bone surface deposition (see TOURIN)
TPROT	unitless	V	F	Deposition fraction for Pb from diffusible plasma to protein-bound plasma scaled to bone surface deposition (see TOPROT)
TRABWT	g	F	F	Trabecular bone weight
TRBC	unitless	V	F	Deposition fraction for Pb from diffusible plasma to RBCs, below non-linear threshold, scaled to bone surface deposition (see TORBC)
TRBCON	μg/g	V	F	Pb concentration in trabecular bone
TRBCONBM	μg/g	V	F	Pb concentration in trabecular bone mineral
TSKELWT	g	V	F	Skeleton weight
TOSF0	unitless	V	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 0 at time (t), scaled to bone surface deposition (see TOSF0)
TOSF1	unitless	V	F	Deposition fraction for Pb from diffusible plasma to soft tissue compartment 1 at time (t), scaled to bone surface deposition (see TOSF1)
TOSF2	unitless	V	F	Deposition fraction from diffusible plasma to soft tissue compartment 2 at time (t), scaled to bone surface deposition (see TOSF2)
TSUM	unitless	V	F	Sum of deposition fractions (TOORBC,TEVF,TPROT,TBONE,TURIN,TFECE,TSWET,TLVR1,TKDN1,TKDN2,TOSF0,TOSF1,TOSF2,TBRAN)
TSWET	unitless	V	F	Deposition fraction for Pb from diffusible plasma to sweat, scaled to bone surface deposition (see TOSWET)
TURIN	unitless	V	F	Deposition fraction for Pb from diffusible plasma to urine, scaled to bone surface deposition (see TOURIN)
TVBONE	mL	V	F	trabecular bone volume
URIN	μg	V	F	Amount of Pb excreted in urine during the integration time step

Variable	Units	Form	Type	Explanation
VBL	L	V	F	Whole blood volume
VBLC	L/kg	C	F	Blood volume fraction of body weight
VBONE	mL	V	F	bone volume
VK	mL	V	F	Kidney volume
VKC	L/kg	C	F	Kidney volume fraction of body weight
VL	mL	V	F	Liver volume
VLC	L/kg	C	F	Liver volume fraction of body weight
VLUC	L/kg	C	F	Lung volume fraction of body weight
VP	mL	V		Lung tissue volume
WADULT	kg	C	F	Maximum body weight
WBIRTH	kg	C	F	Weight at birth
WBODY	kg	V	F	Age-dependent body weight
WBONE	g	V	F	Bone weight
WCHLD	kg	C	F	Maximum body weight achieved during early hyperbolic growth phase.
XXAGE	day	C	F	End age for biokinetics parameter values array (max NUMAGE)
YBLOOD	μg	V	F	Amount of Pb in blood
YBRAN ₀	μg	V	F	Amount of Pb in brain at the beginning of each integration cycle
YBRAN _w	μg	V	F	Amount of Pb in the brain integrated over the time interval DELT
YCDIF ₀	μg	V	F	Amount of Pb in the exchangeable volume of cortical bone at the beginning of each integration cycle
YCDIF _w	μg	V	F	Amount of Pb in the exchangeable volume of cortical bone integrated over the time interval DELT
YCORT	μg	V	F	Amount of Pb in cortical bone
YCSUR ₀	μg	V	F	Amount of Pb in cortical bone surface at the beginning of each integration cycle
YCSUR _w	μg	V	F	Amount of Pb in the cortical bone surface integrated over the time interval DELT
YCVOL ₀	μg	V	F	Amount of Pb in non-exchangeable volume of cortical bone at the beginning of each integration cycle
YCVOL _w	μg	V	F	Amount of Pb in the non-exchangeable volume of cortical bone over the time interval DELT

Variable	Units	Form	Type	Explanation
YEVF ₀	μg	V	F	Amount of Pb in extravascular fluid at the beginning of each integration cycle
YEVF _w	μg			Amount of extravascular fluid in the brain integrated over the time interval DELT
YFECE	μg	V	F	Amount of Pb excreted in feces
YHAIR	μg	V	F	Amount of Pb excreted by routes other than feces, sweat and urine (e.g., hair, nails, and desquamated skin)
YKDN1 ₀	μg	V	F	Amount of Pb in fast-turnover kidney at the beginning of each integration cycle
YKDN2 ₀	μg	V	F	Amount of Pb in slow-turnover kidney at the beginning of each integration cycle
YKDN2 _w	μg	V	F	Amount of Pb in the slow-turnover over kidney the time interval DELT
YKIDN1 _w	μg	V	F	Amount of fast-turnover kidney in the brain integrated over the time interval DELT
YLLIC ₀	μg	V	F	Amount of Pb in lower portion of large intestine at the beginning of each integration cycle
YLLIC _w	μg	V	F	Amount of Pb in the lower portion of large intestine integrated over the time interval DELT
YLVR1 ₀	μg	V	F	Amount of Pb in fast-turnover liver at the beginning of each integration cycle
YLVR1 _w	μg	V	F	Amount of fast-turnover liver in the brain integrated over the time interval DELT
YLVR2 ₀	μg	V	F	Amount of Pb in slow-turnover liver at the beginning of each integration cycle
YLVR2 _w	μg			Amount of slow-turnover liver in the brain integrated over the time interval DELT
YPLAS	μg	V	F	Amount of Pb in plasma (diffusible plus protein bound)
YPLAS _w	μg	V	F	Amount of Pb in plasma (diffusible plus protein bound) integrated over the time interval DELT
YPLS ₀	μg	V	F	Amount of Pb in diffusible plasma ($0.69 \times$ YPLAS) at the beginning of each integration cycle
YPLS _w	μg	V	F	Amount of Pb in diffusible plasma ($0.69 \times$ YPLAS) integrated over the time interval DELT
YPROT ₀	μg	V	F	Amount of Pb in plasma protein at the beginning of each integration cycle
YPROT _w	μg	V	F	Amount of Pb in the plasma protein integrated over the time interval DELT

Variable	Units	Form	Type	Explanation
YR0 ₀	μg	V	F	Amount of Pb in RT region 1 at the beginning of each integration cycle
YR0 _w	μg	V	F	Amount of Pb in the RT region 1 integrated over the time interval DELT
YR1 ₀	μg	V	F	Amount of Pb in RT region 2 at the beginning of each integration cycle
YR1 _w	μg	V	F	Amount of Pb in the RT region 2 integrated over the time interval DELT
YR2 ₀	μg	V	F	Amount of Pb in RT region 3 at the beginning of each integration cycle
YR2 _w	μg	V	F	Amount of Pb in the RT region 3 integrated over the time interval DELT
YR3 ₀	μg	V	F	Amount of Pb in RT region 4 at the beginning of each integration cycle
YR3 _w	μg	V	F	Amount of Pb in the RT region 4 integrated over the time interval DELT
YRBC ₀	μg	V	F	Amount of Pb in RBCs at the beginning of each integration cycle
YRBC _w	μg	V	F	Amount of Pb in RBCs integrated over the time interval DELT
YSIC ₀	μg	V	F	Amount of Pb in small intestine at the beginning of each integration cycle
YSIC _w	μg	V	F	Amount of Pb in the small intestine integrated over the time interval DELT
YSKEL	μg	V	F	Amount of Pb in bone
YSOF0 ₀	μg	V	F	Amount of Pb in fast-turnover soft tissue at the beginning of each integration cycle
YSOF0 _w	μg	V	F	Amount of Pb in the fast-turnover soft tissue integrated over the time interval DELT
YSOF1 ₀	μg	V	F	Amount of Pb in intermediate-turnover soft tissue at the beginning of each integration cycle
YSOF1 _w	μg	V	F	Amount of Pb in the intermediate-turnover soft tissue integrated over the time interval DELT
YSOF2 ₀	μg	V	F	Amount of Pb in slow-turnover soft tissue at the beginning of each integration cycle
YSOF2 _w	μg	V	F	Amount of Pb in the slow-turnover soft tissue integrated over the time interval DELT
YSOFT	μg	V	F	Amount of Pb in soft tissues
YSTMC ₀	μg	V	F	Amount of Pb in stomach at the beginning of each integration cycle

Variable	Units	Form	Type	Explanation
YSTMC _w	μg	V	F	Amount of Pb in the stomach integrated over the time interval DELT
YSWET	μg	V	F	Amount of Pb excreted in sweat
YTDIF ₀	μg	V	F	Amount of Pb in exchangeable trabecular bone surface at the beginning of each integration cycle
YTDIF _w	μg	V	F	Amount of Pb in the exchangeable trabecular bone surface integrated over the time interval DELT
YTRAB	μg	V	F	Amount of Pb in brain at the beginning of each integration cycle
YTSUR ₀	μg	V	F	Amount of Pb in trabecular bone surface at the beginning of each integration cycle
YTSUR _w	μg	V	F	Amount of Pb in the trabecular bone surface integrated over the time interval DELT
YTVOL ₀	μg	V	F	Amount of Pb in non-exchangeable volume of trabecular bone at the beginning of each integration cycle
YTVOL _w	μg	V	F	Amount of Pb in the non-exchangeable volume of trabecular bone integrated over the time interval DELT
YULIC ₀	μg	V	F	Amount of Pb in upper portion of lower intestine at the beginning of each integration cycle
YULIC _w	μg	V	F	Amount of Pb in the upper portion of lower intestine integrated over the time interval DELT
YURIN	μg	V	F	Amount of Pb in excreted in urine

Abbreviations: A=array; C=constant; F=floating point; I=integer; S=switch; V=variable

1 **APPENDIX C – ALL AGES LEAD MODEL (AALM.FOR) EXPOSURE PARAMETER** 2 **VALUES**

3 The AALM.FOR exposure model includes parameters that are variables (i.e., computed in mathematical
4 expressions), and parameters that are assigned constants or are represented by age arrays. A list of
5 parameters that are assigned constants or are represented by age arrays are presented in Table C-1. The
6 bases for values assigned to each parameter are summarized below. Parameters are presented in
7 alphabetical order, according to the parameter name.

8 Exposure variables include variables that represent the concentration of Pb in air, indoor dust, soil, food
9 and water, and activity factors that represent the intensity of exposure to contaminated environmental
10 media (e.g., water consumption rates). All exposure variables that are accessible to the user are included
11 in Table C-1. Default values are intended to be central tendency estimates that are representative of the
12 U.S. population. Sources for the default values are provided along with a brief summary of the sources.
13 Some exposure variables were not assigned default values. Some of these variables were considered to be
14 inherently site-specific and assigning default values to them would therefore be arbitrary. For others,
15 reliable sources of data upon which to base a default value were not identified.

16 In general, the activity factors were taken from the Exposure Factors Handbook ([EFH; U.S. EPA, 2011](#)).
17 The EFH recommendations for default values for activity factors are based on thorough reviews of the
18 exposure science literature and independent analyses of exposure data from surveys performed by others.
19 The use of the EFH-recommended default values in the AALM.FOR, when appropriate, also promotes
20 consistency in risk assessments performed by or for the Agency. In some cases, default values were
21 based on recent studies that were not included in the EFH when the studies were deemed to be sufficiently
22 reliable.

23 A strong preference was placed on basing default values for environmental concentration variables and
24 activity factors on data from statistical surveys that were designed to provide data representative of the
25 entire U.S. Equally important was ensuring that analyses of data from these surveys were done properly
26 to produce unbiased estimates (i.e., properly used the sampling weights in calculating estimates and
27 considered the complex sampling design when calculating standard errors).

28 **AIR CONCENTRATION**

29 **AALM Variables:** Air_baseline, Air_i, Air_pulse

30 The AALM.FOR allows the user to define multiple exposures to Pb in air. These can include up to three
31 discrete (i.e., age-specific) exposure concentrations, a constant baseline concentration and up to two pulse
32 trains in which air Pb concentration can vary at inputted durations and periods. Multiple exposures could
33 be used to represent exposures to air Pb in various settings such as outdoor and indoor air; air at the home,
34 school, workplace, or recreational sites; or continuous exposure or intermittent exposures.

35 Concentrations of Pb in air can be expected to vary considerably by location, depending on proximity to
36 local sources ([U.S. EPA, 2013](#)). Based on analysis of data from U.S. national monitoring networks
37 collected during the period 2008-2010, air Pb concentrations were as follows ([U.S. EPA, 2013](#)):

	Source Oriented	Non-source Oriented
Mean	0.21	0.012
Median	0.079	0.010
95 th percentile	0.88	0.037

Units: $\mu\text{g}/\text{m}^3$

3-month rolling average, 2008-2010

Source-oriented monitors are within one mile of ≥ 0.5 ton/year emission non-airport source or near airports in which use of leaded aviation fuels are estimated to result in >1 tone/year emissions.

1

2 A detailed description the national monitoring networks and related data can be found in [U.S. EPA](#)
3 [\(2013\)](#).

4 **Recommendations.** Based on these data, $0.01 \mu\text{g}/\text{m}^3$ is recommended as a default value for the parameter
5 *Air_baseline* to represent average U.S. exposure concentrations distant from substantial emissions
6 sources. For simulations of populations living near emissions sources, the source-oriented average could
7 be used as a default for average air concentrations, however, it should be recognized that air Pb
8 concentrations near emission sources could vary considerably depending on the strength of the source and
9 other geographic and weather factors that would affect dispersion and deposition of emissions.

10 Although, the default values are based on measurements made of outdoor air, indoor and outdoor air Pb
11 concentrations are expected to be similar if indoor environments that do not have substantial indoor
12 sources of Pb ([Clayton et al., 1999](#); [Robertson et al., 1999](#)).

13 INDOOR DUST LEAD CONCENTRATION

14 **AALM Variables:** Dust_baseline, Dust_i, Dust_pulse

15 The AALM.FOR allows the user to define multiple exposures to Pb in indoor dusts. These can include up
16 to three discrete (i.e., age-specific) exposure concentrations, a constant baseline concentration and up to
17 three pulse trains in which dust Pb concentration can vary at inputted durations and periods. These could
18 be used to represent exposures to Pb in various sources of dust such dusts at various locations (e.g., at the
19 home, school, workplace, or recreational sites); or continuous exposure or intermittent exposures.

20 The National Human Exposure Assessment Surveys (NHEXAS) provides data on indoor dust Pb
21 concentrations in statistical samples from various locations. Based on data for approximately 250
22 residences in EPA Region 5 (Great Lakes region), the mean Pb concentrations were as follows ([Clayton](#)
23 [et al., 1999](#)):

Surface	Window Sill
463	954
(188, 738)	(481, 3164)

Units: $\mu\text{g}/\text{g}$ (95% CL)

24 Based on NHEXAS data for approximately 119 residences in Arizona, the median Pb concentration
25 (XRF) was $21 \mu\text{g}/\text{g}$ ([90th percentile: 122](#); [Robertson et al., 1999](#)).

26 Concentrations of Pb in dusts can be expected to vary considerably by location, depending on proximity
27 to local sources, presence in lead-based paint, and dust cleaning practices ([U.S. EPA, 2013](#)). The National

1 Survey of Lead and Allergens (NSLAH) conducted by the Department of Housing and Urban
 2 Development; ([Clickner et al., 2002](#)) provides data in Table 5.7 of their report on Pb in residential indoor
 3 dusts for a statistical sample of U.S. residences. Based on a sample of approximately 2000 homes, the
 4 mean Pb loading ($\mu\text{g}/\text{ft}^2$) were as follows:

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

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

5 Data on dust Pb loading on indoor surfaces ($\mu\text{g Pb}/\text{ft}^2$) provide additional sources estimated of
 6 indoor dust Pb concentration ([U.S. EPA, 2019](#)). An analysis of data on Pb loading collected as part of the
 7 American Healthy Housing Survey ([AHHS, Cox et al., 2011](#)) provided the following central estimates for
 8 residential Pb loading and concentration ([U.S. EPA, 2019](#)):

Loading ($\mu\text{g}/\text{ft}^2$)		Concentration ($\mu\text{g}/\text{g}$)	
Median	Mean	Median	Mean
0.8	1.2	107.8	175.0

9

10 **Recommendations.** Based on the above data, 175 $\mu\text{g}/\text{g}$ is recommended as a default value for the
 11 parameter *Dust_baseline* to represent average U.S. exposure concentrations distant from substantial
 12 current or historical emission sources (e.g., background) that could impact the indoor environment (e.g.
 13 track in from contaminated soil). A value of equal to the soil Pb concentration (see section on *Soil Lead*
 14 *Concentration*) is recommended for *Dust_baseline* for simulating residences where soil derived dust is
 15 the major source of indoor dust Pb (e.g. no other significant indoor sources such as paint or hobbies).
 16 Indoor dust Pb concentrations in residences impacted by Pb-based paint can be expected to vary
 17 considerably within and between residences and local exposure conditions should be considered to
 18 establish a representative estimate.

19 SOIL LEAD CONCENTRATION

20 **AALM Variables:** Soil_baseline, Soil_i, Soil_pulse

21 The AALM.FOR allows the user to define multiple exposures to Pb in soil. These can include up to three
 22 discrete (i.e., age-specific) exposure concentrations, a constant baseline concentration and up to three
 23 pulse trains in which dust Pb concentration can vary at inputted durations and periods. These could be
 24 used to represent exposures to Pb in various sources of surface soil such soils at various locations (e.g., at
 25 the home, school, workplace, or recreational sites); or continuous exposure or intermittent exposures.

26 Concentrations of Pb in soils can be expected to vary considerably by location, depending on proximity to
 27 local sources ([U.S. EPA, 2013](#)). A study conducted by the U.S. Geological Survey measured soil Pb
 28 concentrations along a 4000 km east-west transect of the U.S. ([Smith et al., 2013](#); [Reimann et al., 2011](#)).
 29 Sampling locations were selected to avoid local sources, including roads, buildings, power plants and
 30 smelters. The mean concentrations for samples collected a depth of 0–5 cm depth (sieved at 2 mm) were
 31 as follows:

Full Transect (n = 4841)	Statewide Average (n = 48)
25 (8, 44) ^a	30 (14, 68) ^b

Units: $\mu\text{g/g}$.

Statewide average is the average of state means.

^a5th-95th percentile range

^brange

- 1 Data for individual U.S. states and physiographic provinces are provided in [Smith et al. \(2013\)](#).
 2 NSLAH conducted by the Department of Housing and Urban Development; [Clickner et al. \(2002\)](#)
 3 provide data in Table 6.3 of their report on Pb in residential soil for a statistical sample of U.S. residences.
 4 Based on a sample of approximately 700 residential yards, the mean Pb concentrations ($\mu\text{g/g}$) were as
 5 follows:

Main Entryway	Dripline 1	Dripline 2	Midyard 1	Midyard 2
235±1094	243±818	404±1613	87±195	123±360

$\mu\text{g/g}$, mean \pm SD

- 6 Based on data from the AHHS ([Cox et al., 2011](#); [Clickner et al., 2002](#)), the following central estimates for
 7 soil Pb concentration were estimated ([U.S. EPA, 2019](#)):

Housing Stock	GM	GSD	Median	Mean
Pre-1940	113.4	3.58	113.4	246.8
1940-1977	28.6	2.9	28.6	50.0
Pre-1978	26.3	3.8	26.3	64.1

GM, geometric mean, $\mu\text{g/g}$; GSD, geometric standard deviation

8

- 9 **Recommendations.** Based on the above data, 25 $\mu\text{g/g}$ is recommended as a default value for the
 10 parameter *Soil_baseline* to represent average U.S. exposure concentrations distant from substantial
 11 current or historical emission sources (e.g., background). Means for individual U.S. states ranged 6 to 80
 12 $\mu\text{g/g}$. These estimates are based on measurements made in soils sieved to <2 mm and which may have
 13 underestimated Pb concentration in the fine fraction (e.g. <250 μm or <150 μm) that is typically used to
 14 represent the exposure term for the adherence to hand-to-mouth pathway used in risk assessment. The
 15 value 50 $\mu\text{g/g}$ is recommended as a value for yard soils associated with post 1940 housing stock and 250
 16 $\mu\text{g/g}$ for older housing stock.

17 WATER CONCENTRATION

18 AALM Variables: Water_baseline, Water_i, Water_pulse

- 19 The AALM.FOR allows the user to define multiple exposures to Pb in drinking water. These can include
 20 up to three discrete (i.e., age-specific) exposure concentrations, a constant baseline concentration and up
 21 to two pulse trains in which water Pb concentration can vary at inputted durations and periods. These
 22 could be used to represent exposures to Pb in various exposure settings such: home, school, workplace, or
 23 recreational sites; or continuous exposure or intermittent exposures.

1 Concentrations of Pb in drinking water can be expected to vary considerably by location, depending on
 2 water source, Pb in service lines and extent of plumbing corrosion ([U.S. EPA, 2007a](#)). In residences
 3 served by lines containing Pb, first-draw water that has been stagnant in plumbing will tend to have a
 4 higher Pb concentration than after the system has been flushed. The NHEXAS provides data on drinking
 5 water Pb concentrations in statistical samples from various locations. Based on data for approximately
 6 250 residences in EPA Region 5 (Great Lakes region), the mean Pb concentrations were as follows
 7 ([Clayton et al., 1999](#)):

First draw	Flushed
3.92	0.84
(3.06, 4.79)	(0.6, 1.07)

Units: $\mu\text{g/L}$ (95% CL)

8 Based on NHEXAS data for approximately 82 residences in Arizona, median, 75th and 90th percentile of
 9 Pb concentrations in flushed unfiltered tap water were 0.4, 0.9, and 1.3 $\mu\text{g/L}$, respectively ([O'Rourke et](#)
 10 [al., 1999](#)).

11 The EPA TRW analysed data tap water concentrations reported for the Six-Year Review-ICR
 12 dataset. This survey conducted during the period 1998-2005 measured first-draw tap water concentration
 13 in residences supplied by approximately 883 public water suppliers in the U.S. Based on this analysis, the
 14 mean tap water concentrations were as follows:

Sample Mean	Population Weighted Mean
4.89	0.89
(4.38, 5.39)	(0.78, 1.01)

Units: $\mu\text{g/L}$ (95% CL)

Population weighted mean is weighted for number of people served by each supplier.

15 Based on data in Supplemental Information from [Zartarian et al. \(2017\)](#), the average, 95th
 16 percentile and 99th percentile values from this dataset are 0.89, 2.25 and 13.27 $\mu\text{g/L}$, respectively. The
 17 following central estimates for water Pb concentration were estimated ([U.S. EPA, 2019](#)):

GM	GSD	Median	Mean
0.69	2.1	0.69	0.89

GM, geometric mean, $\mu\text{g/g}$; GSD, geometric standard deviation

18

19 **Recommendations.** Based on the above data, 0.9 $\mu\text{g/L}$ is recommended as a default value for the
 20 parameter *Water_baseline* to represent average U.S. exposure concentrations to tap water from public
 21 water supplies. This default value may not apply to local conditions that contribute to leaching of Pb into
 22 tap water (e.g. Pb service lines, Pb solder, corrosion).

23 FOOD LEAD INTAKE

24 **AALM Variables:** Food_baseline, Food_i, Food_pulse

25 The AALM.FOR allows the user to define multiple exposures to Pb in food. These can include up to three
 26 discrete (i.e., age-specific) food Pb intakes ($\mu\text{g/day}$), a constant baseline intake and up to two pulse trains

1 in which food Pb intake can vary at inputted durations and periods. These could be used to represent
 2 exposures to Pb in various diets or sources of food (e.g., market basket, home grown produce, local fish
 3 or game); or continuous exposure or intermittent exposures.

4 The rate of Pb intake from food can be expected to vary considerably depending on the diet and age. The
 5 NHEXAS provides data on food Pb intakes in statistical samples from various locations ([Clayton et al.,](#)
 6 [1999](#); [Thomas et al., 1999](#)). Based on a sample for 159 residences (children and adults), the mean food
 7 Pb intakes was 7.96 µg/day (95% CL: 4.2, 11.6; [Clayton et al., 1999](#)).

8 The EPA TRW estimated food Pb intakes in children based on data from the U.S. Food and Drug
 9 Administration Total Diet Studies performed between 1995–2005 ([FDA, 2007, 2006](#)) and food
 10 consumption data from the National Food Consumption Survey (NCFS) that was performed as part of the
 11 Third National Health and Nutrition Examination Survey (NHANES 2003–2006). Age category mean Pb
 12 intakes were as follows:

Age Category (months)	Dietary Pb Intake (µg/day)
0 to <12	2.26
12 to <24	1.96
24 to <36	2.13
36 to <48	2.04
40 to <60	1.95
60 to <72	2.05
72 to <84	2.22

13

14 **Recommendations.** Based on the above data, 10 µg/day is recommended as a default value for
 15 *Food_baseline* the food Pb intake in adults. This corresponds to an intake of approximately 0.14 µg/kg
 16 bw/day which, if extrapolated to children, yield estimates that are similar to those recommended by the
 17 EPA TRW, if AALM.FOR growth is assumed:

Age (year)	Female BW (kg)	Male BW (kg)	Female Pb Intake (µg/day)	Male Pb Intake (µg/day)
1	8.9	9.4	1.2	1.3
2	12.3	12.9	1.7	1.8
3	14.6	15.3	2.0	2.1
4	16.4	17.2	2.3	2.4
5	18.0	18.8	2.5	2.6
6	19.7	20.2	2.8	2.8
7	21.7	21.8	3.0	3.1
8	24.2	23.7	3.4	3.3
9	27.7	26.1	3.9	3.7
10	32.1	29.3	4.5	4.1
15	52.5	56.4	7.3	7.9

Age (year)	Female BW (kg)	Male BW (kg)	Female Pb Intake ($\mu\text{g}/\text{day}$)	Male Pb Intake ($\mu\text{g}/\text{day}$)
≥ 20	56.2	71.4	7.9	10.0

For intake 0.14 $\mu\text{g}/\text{kg}$ bw/day.

BW, body weight

1 The above age array of food Pb intakes are recommended default values for *Food_i*, where *i* would
2 represent age category baseline intakes for the average U.S. diet.

3 DUST AND SOIL INGESTION RATES

4 **AALM Variables:** IR_sd, f_IR_s, IR_dust, IR_soil

5 The EPA Exposure Factors Handbook ([U.S. EPA, 2017](#)) provides the following recommendations for
6 dust and soil ingestion rates to be used in U.S. EPA risk assessments.

7

Age Category	Dust (g/day)	Soil (g/day)	Dust + Soil (g/day)
<6 months	0.020	0.020	0.040
6 months to 1 year	0.040	0.030	0.070
1 to <2 years	0.050	0.040	0.090
2 to <6 years	0.030	0.030	0.060
1 to 6 years	0.040	0.040	0.080
6 to <12 years	0.030	0.030	0.060
>12 years	0.020	0.010	0.030

8

9 The EPA TRW estimated combined soil and dust ingestion rates in children based on the best fit model
10 from [von Lindern et al. \(2016\)](#) and supported by modelled estimates from [Ozkaynak et al. \(2011\)](#) and
11 [Wilson et al. \(2013\)](#). Age category mean ingestion rates were as follows:

Age Category (months)	Soil + Dust (g/day)
0 to 12	0.086
13 to 24	0.094
25 to 36	0.067
37 to 48	0.063
49 to 60	0.067
61 to 72	0.052
73 to 84	0.055

12

13 **Recommendations.** Based on the Exposure Factors Handbook ([U.S. EPA, 2017](#)), the following values
14 are recommended as default values for the parameters *IR_dust* and *IR_soil* to represent average U.S.
15 ingestion rates in children and adults. The default values for adults may not represent activities that result
16 in intensive dermal contact with surface dusts, such as construction or excavation.

Age (days)	Dust Ingestion <i>IR_dust</i> (g/day)	Soil Ingestion <i>IR_soil</i> (g/day)	Combined Dust and Soil <i>IR_sd</i> (g/day)	Soil Fraction <i>f_IR_soil</i>
0	0.022	0.018	0.040	0.45
90	0.039	0.032	0.070	0.45
365	0.050	0.041	0.090	0.45
1825	0.044	0.036	0.080	0.45
3650	0.033	0.027	0.060	0.45
5475	0.017	0.014	0.030	0.45
9125	0.017	0.014	0.030	0.45
≥18250	0.017	0.014	0.030	0.45

1

2 **WATER INTAKE RATE**3 AALM Variables *IR_water*

4 Water ingestion rate can be expected to vary with age, activity level and environmental factors
5 (e.g. temperature, humidity). [U.S. EPA \(2011\)](#) has recommended the following age-specific water
6 ingestion rates for use in EPA risk assessments of the general population:

Age	Mean Intake (mL/day)	95 th Percentile (mL/day)
Birth to <1 mo	184	839
1 to <3 mo	227	896
3 to < 6 mo	362	1056
6 to <12 mo	360	1055
1 to <2 yr	271	837
2 to <3yr	317	877
3 to <6 yr	327	959
6 to <11 yr	414	1316
11 to <16 yr	520	1821
16 to <21 yr	573	1783
18 to <21 yr	681	2368
≥21 yr	1043	2958
≥65 yr	1046	2733
All ages	869	2717

7

8 The EPA TRW estimated drinking water intakes rates in children based on and analysis of data from the e
9 1994–1996 and 1998 Continuing Survey of Food Intakes by Individuals ([CSFII; USDA, 2000](#)) as
10 reported by [Kahn and Stralka \(2009\)](#). Age category mean ventilation rates were as follows:

Age Category (months)	Water Intake (L/day)
0 to <12	0.40
12 to <24	0.43
24 to <36	0.51
36 to <48	0.54
40 to <60	0.57
60 to <72	0.60
72 to <84	0.63

1

2 **Recommendations.** Based on the above data, the following values are recommended as default values
3 for the parameter *IR_{water}* to represent average U.S. drinking water ingestion rates in children and adults:

Age (days)	Water Intake (L/day)
0	0.20
90	0.30
365	0.35
1825	0.35
3650	0.45
5475	0.55
9125	0.70
≥18250	1.04

4

5 VENTILATION RATE

6 AALM Variable: *V_{air}*

7 The AALM.FOR assigns values for regional deposition of inhaled Pb (see parameters *B1, B2, B3, B4*;
8 Appendix D and clearance in the RT (see parameter *CILIAR*; Appendix D). Values for these parameters
9 were based on experimental studies conducted adults who inhaled submicron particles from automobile
10 exhausts while they were sedentary. However, regional deposition and clearance in the RT (will depend
11 on numerous factors, including age and particle size, as well as various factors that affect ventilation rates
12 (m³/day) which vary with age and physical activity. The interrelationships between particle size,
13 clearance, regional deposition and ventilation rate should be considered in assigning values to these
14 parameters for simulating specific populations and exposure settings. these subjects are treated in depth in
15 [ICRP \(1994\)](#).

16 The [ICRP \(1994\)](#) has recommended the following age-specific activity weighted ventilation rates for use
17 in radiation dosimetry assessments of the general population:

Age	Ventilation (m ³ /day) Male	Ventilation (m ³ /day) Female	Ventilation (m ³ /day) Average
3 mo	2.86	2.86	2.86
1 yr	5.2	5.2	5.2
5 yr	8.76	8.76	8.76
10 yr	15.28	15.28	15.28
15 yr	20.1	15.72	17.91
>17 yr	22.18	17.68	19.93

From [ICRP \(1994\)](#).

Values for children are from Table B.16A

Values for >17 yr are for sedentary workers (Table B.16B)

1

2 The above ventilation rates can be matched to corresponding regional deposition rates, also provided in
3 [ICRP \(1994\)](#).

4 [U.S. EPA \(2011\)](#) has recommended the following age-specific activity weighted ventilation rates for use
5 in EPA risk assessments of the general population:

Age Category	Mean Ventilation (m ³ /day)	95 th Percentile (m ³ /day)
Birth to <1 mo	3.6	7.1
1 to <3 mo	3.5	5.8
3 to <6 mo	4.1	6.1
6 to <12 mo	5.4	8.0
Birth to <1 yr	5.4	9.2
1 to <2 yr	8.0	12.8
2 to <3yr	8.9	13.7
3 to <6 yr	10.1	13.8
6 to <11 yr	12.0	16.6
11 to <16 yr	15.2	21.9
16 to <21 yr	16.3	24.6
21 to <31 yr	15.7	21.3
31 to <41 yr	16.0	21.4
41 to 51 yr	16.0	21.2
51 to 61 yr	15.7	21.3
61 to 71 yr	14.2	18.1
71 to <81 yr	12.9	16.6
≥ 81 yr	12.2	15.7

6

7 The EPA TRW estimated ventilation rates in children based on and analysis of data on total energy
8 expenditure (estimated from doubly labeled water studies) and relationships between energy expenditure

1 and ventilation rate ([Stifelman, 2007](#); [Brochu et al., 2006](#); [IOM, 2005](#); [Layton, 1993](#)). Age category mean
2 ventilation rates were as follows:

Age Category (months)	Ventilation Rate (m ³ /day)
0 to <12	3.22
12 to <24	4.97
24 to <36	6.09
36 to <48	6.95
40 to <60	7.68
60 to <72	8.32
72 to <84	8.89

3
4 **Recommendations.** Based on the above data, the following values are recommended as default values
5 for the parameter V_{air} to represent average U.S. ventilation rates in children and adults:

Age (days)	Ventilation (m ³ /day)
0	2.9
90	2.9
365	5.2
1825	8.8
3650	15.3
5475	17.9
9125	19.9
≥18250	19.9

6
7 **RBA_{dust}.** A discussion of available data on RBA of Pb in indoor dust can be found in [U.S. EPA \(2013\)](#).
8 RBA of Pb in house dusts has not been rigorously evaluated quantitatively in humans or in experimental
9 animal models, unlike soil (see section on *RBA_{soil}*). As with soil, RBA of dust Pb can be expected to
10 vary depending on the Pb mineralogy, physical characteristics of the Pb in the dust (e.g., encapsulated or
11 exposed) and size of the Pb-bearing particles. The RBA for paint Pb mixed with soil (relative to lead
12 acetate) was reported to be approximately 0.72 (95% CI: 0.44, 0.98) in juvenile swine, suggesting that
13 paint Pb dust reaching the gastrointestinal tract maybe highly bioavailable ([Casteel et al., 2006](#)). Several
14 studies have measured in vitro bioaccessibility (IVBA) of Pb in residential indoor dust; however, with
15 few exceptions, these have not used IVBA methods for from which RBA can be reliably predicted
16 ([Juhasz et al., 2011](#); [Lu et al., 2011](#); [Smith et al., 2011](#); [Roussel et al., 2010](#); [Yu et al., 2006](#)). A study
17 conducted at two sites in EPA Region 7 compared Pb RBA predicted from IVBA using a prediction
18 method that had been validated for soil as described in [U.S. EPA \(2013\)](#). At the Herculaneum site, mean
19 RBA was 0.47 (SD 0.07, 10 samples) for indoor dust and 0.69 (SD 0.03, 12 samples) for soil. At the
20 Omaha site, mean Pb RBA was 0.73 (SD 0.10, 90 samples) for indoor dust and 0.70 (SD 0.10, 45
21 samples) for soil.

1 **RBA_{soil}**. A discussion of available data on RBA of Pb in soil can be found in [U.S. EPA \(2013\)](#). RBA of
 2 soil Pb can be expected to vary depending on the Pb mineralogy, physical characteristics of the Pb in the
 3 soil (e.g., encapsulated or exposed) and size of the Pb-bearing particles. The EPA TRW has
 4 recommended a value of 60% for RBA for ingested soil Pb based on analysis of data on soil Pb RBA
 5 estimated in bioassays of juvenile swine ([Bannon et al., 2009](#); [Smith et al., 2009](#); [Casteel et al., 2006](#);
 6 [Marschner et al., 2006](#)); and other unpublished data collected as part of site risk assessments. The soil
 7 RBA measured in the swine assay is equivalent to the ratio of the absorbed fraction of an ingested dose of
 8 soil Pb to that of water-soluble Pb acetate. Analysis of 31 soils (excluding galena-enriched soil, soils from
 9 firing ranges, and soils sieved at >250 µm) resulted in a median RBA estimate of 60% with the 5th–95th
 10 percentile range from 11–97%; the mean RBA is 54% ±32 SD. RBA estimates for soils collected from
 11 eight firing ranges were approximately 100% ([mean =108% ± 18; Bannon et al., 2009](#)). The relatively
 12 high RBA for the firing range soils may reflect the high abundance of relatively un-encapsulated lead
 13 carbonate (30-90% abundance) and lead oxide (1–60%) in these soils. Similarly, a soil sample (low Pb
 14 concentration) mixed with a National Institute of Standards and Technology paint standard (55% lead
 15 carbonate, 44% lead oxide) also had a relatively high bioavailability (72%; [Casteel et al., 2006](#)). Samples
 16 of smelter slag, or soils contaminated with slag, had relatively low RBA (14–40%, n = 3) as did a sample
 17 from a mine tailings pile (RBA = 6%), and a sample of finely ground galena mixed with soil (1%; [Casteel](#)
 18 [et al., 2006](#)). A single estimate for RBA of interior dust was 51% for a sample collected at the
 19 Herculaneum site.

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

24 **RBA_{water}**. RBA of Pb dissolved in water is assumed to be 1. This is based on evidence that dissolution
 25 of Pb from the soil/mineralogical matrix in the stomach appears to be the major process that renders soil
 26 Pb bioaccessible for absorption in the GI tract ([U.S. EPA, 2013, 2007b](#)). However, this may not apply to
 27 Pb-bearing particles suspended in surface water and this may be relevant to certain exposure settings (e.g.,
 28 incidental ingestion of suspended sediments during activities such as swimming or play near shorelines).

29 **Recommendations**. Based on the above data, the following values are recommended as default values
 30 for the parameters *RBA_{dust}*, *RBA_{soil}*, *RBA_{food}*, *RBA_{water}*:

Medium	RBA
Dust_paint ^a	1
Dust_soil ^b	0.6
Soil	0.6
Food	1
Water	1

^aIndoor dust derived from Pb-based paint

^bIndoor dust derived from soil

1 **TABLE C-1. LIST OF PARAMETERS THAT ARE ASSIGNED CONSTANTS OR ARE REPRESENTED BY AGE ARRAYS**

Variable	Units	Form	Type	Explanation	Value		Reference
Air_baseline	$\mu\text{g}/\text{m}^3$	C	F	Baseline air Pb concentration used in exposure pulse train	0.01–0.2		(U.S. EPA, 2013)
Air_i; i= 1, 2,3	$\mu\text{g}/\text{m}^3$	A	F	Air Pb concentrations for discrete exposures	User defined		
Air_pulse	$\mu\text{g}/\text{m}^3$	C	F	Air Pb concentration used in exposure pulse train	User defined		
Dust_baseline	$\mu\text{g}/\text{g}$	C	F	Baseline indoor dust Pb concentration used in exposure pulse train	Residential	175	(U.S. EPA, 2019)
Dust_i; i= 1, 2,3	$\mu\text{g}/\text{g}$	A	F	Dust Pb concentrations for discrete exposures	User defined		
Dust_pulse	$\mu\text{g}/\text{g}$	C	F	Dust Pb concentration used in exposure pulse train	User defined		
f_Air_i; i= 1,2,3	unitless	A	F	Fraction of discrete Air_i contributing to daily air Pb exposure	User defined		See Chapter 16 of U.S. EPA (2011)
f_Dust_i; i= 1,2	unitless	A	F	Fraction of discrete Dust_i contributing to daily dust Pb exposure	User defined		See Chapter 16 of U.S. EPA (2011)
f_IR_soil	unitless	C	F	Soil fraction of combined dust and soil ingestion rate	0.45		Based Table 5-1 of U.S. EPA (2017)

Variable	Units	Form	Type	Explanation	Value	Reference
f_Other_i; i= 1,2,3	unitless	A	F	Fraction of discrete Other_i contributing to daily other Pb exposure	User defined	See Chapter 16 of U.S. EPA (2013)
f_pulse_air	unitless	C	F	Fraction of air daily air exposure from pulse train	User defined	
f_pulse_dust	unitless	C	F	Fraction of daily dust exposure from pulse train	User defined	
f_pulse_other	unitless	C	F	Fraction of daily other exposure from pulse train	User defined	
f_pulse_soil	unitless	C	F	Fraction of daily soil exposure from pulse train	User defined	
f_pulse_water	unitless	C	F	Fraction of daily water exposure from pulse train	User defined	(Clayton et al., 1999)
f_Water_i; i= 1,2,3	unitless	A	F	Fraction of discrete Water_i contributing to daily water Pb exposure	User defined	See Chapter 16 of U.S. EPA (2011)
Food_baseline	µg/day	C	F	Baseline food Pb intake used in exposure pulse train	10 µg/kg bw/day	(Clayton et al., 1999)
Food_i; i= 1, 2,3	µg/day	A	F	Food Pb intakes for discrete exposures	User defined	See Chapter 16 of U.S. EPA (2011)
Food_pulse	µg/day	C	F	Food Pb intake used in exposure pulse train	User defined	

Variable	Units	Form	Type	Explanation	Value		Reference
IR_sd	µg/day	A	F	Combined dust and soil ingestion rate	Age-day	Value	Based Table 5-1 of U.S. EPA (2017)
					0	0.040	
					90	0.070	
					365	0.090	
					1825	0.080	
					3650	0.060	
					5475	0.030	
					9125	0.030	
					18250	0.030	
					25550	0.030	
					32850	0.030	
IR_water	L/day	C	F	Water ingestion rate for water Pb exposures	Age-day	Value	Based on U.S. EPA (2011) , Table 3-1, per capita; values are interpolated between ages
					0	0.20	
					90	0.30	
					365	0.35	
					1825	0.35	
					3650	0.45	
					5475	0.55	
					9125	0.70	
					18250	1.04	
					25550	1.04	
					32850	1.04	
Other_baseline	µg/day	C	F	Baseline other Pb intake used in exposure pulse train	User defined		

Variable	Units	Form	Type	Explanation	Value	Reference
Other_i; i= 1, 2,3	µg/day	A	F	Food Pb intakes for discrete exposures	User defined	
Other_pulse	µg/day	C	F	Other Pb intake used in exposure pulse train	User defined	
Pulse_i_period_air; i=1,2	day	C	F	Period for pulse train exposure to air	User defined	
Pulse_i_period_dust; i=1,2	day	C	F	Period for pulse train exposure to dust	User defined	
Pulse_i_period_food; i=1,2	day	C	F	Period for pulse train exposure to food	User defined	
Pulse_i_period_other; i=1,2	day	C	F	Period for pulse train exposure to other	User defined	
Pulse_i_period_soil; i=1,2	day	C	F	Period for pulse train exposure to soil	User defined	
Pulse_i_period_water; i=1,2	day	C	F	Period for pulse train exposure to water	User defined	
Pulse_i_width_air; i=1,2	day	C	F	Width for pulse train exposure to air	User defined	
Pulse_i_width_dust; i=1,2	day	C	F	Width for pulse train exposure to dust	User defined	
Pulse_i_width_food; i=1,2	day	C	F	Width for pulse train exposure to food	User defined	
Pulse_i_width_other; i=1,2	day	C	F	Width for pulse train exposure to other	User defined	
Pulse_i_width_soil; i=1,2	day	C	F	Width for pulse train exposure to soil	User defined	
Pulse_i_width_water; i=1,2	day	C	F	Width for pulse train exposure to water	User defined	

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Variable	Units	Form	Type	Explanation	Value	Reference
Pulse_start_air	day	C	F	Start age for pulse train exposure to air	User defined	
Pulse_start_dust	day	C	F	Start age for pulse train exposure to dust	User defined	
Pulse_start_food	day	C	F	Start age for pulse train exposure to food	User defined	
Pulse_start_other	day	C	F	Start age for pulse train exposure to other	User defined	
Pulse_start_soil	day	C	F	Start age for pulse train exposure to soil	User defined	
Pulse_start_water	day	C	F	Start age for pulse train exposure to water	User defined	
Pulse_stop_air	day	C	F	Stop age for pulse train exposure to air	User defined	
Pulse_stop_dust	day	C	F	Stop age for pulse train exposure to dust	User defined	
Pulse_stop_food	day	C	F	Stop age for pulse train exposure to food	User defined	
Pulse_stop_other	day	C	F	Stop age for pulse train exposure to other	User defined	
Pulse_stop_soil	day	C	F	Stop age for pulse train exposure to soil	User defined	
Pulse_stop_water	day	C	F	Stop age for pulse train exposure to water	User defined	

Variable	Units	Form	Type	Explanation	Value	Reference	
RBA_dust	unitless	C	F	Relative bioavailability of dust Pb	0.6	(U.S. EPA, 1994)	
RBA_food	unitless	C	F	Relative bioavailability of food Pb	1	Assumed to be water soluble (U.S. EPA, 1994)	
RBA_other	unitless	C	F	Relative bioavailability of other Pb	User defined		
RBA_soil	unitless	C	F	Relative bioavailability of soil Pb	0.6	(U.S. EPA, 1994)	
RBA_water	unitless	C	F	Relative bioavailability of water Pb	1	Assumed to be water soluble (U.S. EPA, 1994)	
Soil_baseline	µg/g	C	F	Baseline indoor Soil Pb concentration used in exposure pulse train	Background	25	(U.S. EPA, 2019 ; Smith et al., 2013)
					Residential (>1940)	50	
					Residential (<1940)	250	
Soil_i; i= 1, 2,3	µg/g	A	F	Soil Pb concentrations for discrete exposures	User defined		
Soil_pulse	µg/g	C	F	Soil Pb concentration used in exposure pulse train	User defined		
Water_baseline	µg/L	C	F	Baseline water Pb concentration used in exposure pulse train	0.9	(U.S. EPA, 2019 ; Zartarian et al., 2017)	

Variable	Units	Form	Type	Explanation	Value		Reference
Water _i ; i= 1, 2,3	µg/L	A	F	Water Pb concentrations for discrete exposures	User defined		See Chapter 16 of U.S. EPA (2011)
Water_pulse	µg/L	C	F	Water Pb concentration used in exposure pulse train	User defined		
V _{air}	m ³ /day	A	F	Ventilation rate for air Pb exposures	Age-day	Value	Based on ICRP (1994) ; also see Chapter 6 of U.S. EPA (2011)
					0	2.9	
					90	2.9	
					365	5.2	
					1825	8.8	
					3650	15.3	
					5475	17.9	
					9125	19.9	
					18250	19.9	
					25550	19.9	
32850	19.9						

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1 APPENDIX D – ALL AGES LEAD MODEL (AALM.FOR) BIOKINETICS

2 PARAMETER VALUES

3 AALM biokinetics parameters and values are listed in Table D-1. The bases for values assigned to each
4 parameter are summarized below. Parameters are presented in alphabetical order, according to the
5 parameter name.

6 **AFC1, AFC2:** Parameters used calculating age-specific absorption fraction of Pb from small intestine
7 (see variable *FI* in Biokinetics GI Tract, Appendix A). The absorption fraction is calculated based on an
8 expression from [O'Flaherty \(1995, 1993\)](#). AF_{C1} and AF_{C2} were assigned values of 0.40 and 0.28,
9 respectively, based on fitting simulations to data on blood Pb concentration in children ([Sherlock and](#)
10 [Quinn, 1986](#); [Ryu et al., 1983](#)) and adults ([Rabinowitz et al., 1976](#)) as described in Chapter 4. The values
11 for AF_{C1} and AF_{C2} of 0.40 and 0.28, respectively, produce absorption fractions of 30-40% in infants and
12 during early childhood ([Ziegler et al., 1978](#); [Alexander et al., 1974](#)) and 12% in adults ([Maddaloni et al.,](#)
13 [2005](#); [U.S. EPA, 2003](#)).

14 **AGSCAL:** Age-scaling factor for gastrointestinal transfer rates. Age-dependent values assigned to
15 *AGSCAL* are the same as those in [Leggett \(1993\)](#). The value of 1 is assigned to adults and higher values
16 for infants and children. This results in a slower removal kinetics in children compared to adults
17 ([Corazziari et al., 1985](#)).

18 **ARBLAD:** Rate coefficient for Pb transfer from urinary bladder to urine. The value assigned to
19 *ARBLAD* is from [Leggett \(1993\)](#). The value of 5 d^{-1} for adults is based on a removal $t_{1/2}$ of 0.1 days for Pb
20 being voided from the bladder ([ICRP, 1975](#)), which approximates a transfer rate of $0.693/0.1 \text{ d} = 7 \text{ d}^{-1}$.
21 The rate coefficients for children are 7, 8, 11, 15, 12, and 12 d^{-1} for 15, 10, 5, and 1 year old, 3 months
22 old, and birth, respectively.

23 **ARBRAN:** Rate coefficient for Pb transfer from brain to diffusible plasma. The value assigned to
24 *ARBRAN* is from [Leggett \(1993\)](#). The value of 0.00095 d^{-1} derives from a removal $t_{1/2}$ of 2 years ($0.693/2$
25 $\text{yrs} = 9.5 \times 10^{-4} \text{ d}^{-1}$). The values for *ARBRAN* and *TOBRAN* (deposition of 0.015% of Pb from diffusible
26 plasma), are based on comparison of predicted and observed brain Pb in dogs and baboons ([Lloyd et al.,](#)
27 [1975](#); [Cohen et al., 1970](#)) and human autopsy observations ([Grandjean, 1978](#); [Niyogi, 1974](#)).

28 **ARCORT:** Rate coefficient for Pb transfer from non-exchangeable cortical bone to diffusible plasma.
29 [Leggett \(1993\)](#) assigned a value of 0.000082 d^{-1} for *ACORT* in adults based on the assumption that
30 removal of Pb from the non-exchangeable bone volume is occurs at same rate as bone resorption.
31 Childhood and adult rates were adopted from [ICRP \(1990\)](#) for bone-seeking radionuclides, based on
32 histomorphometric measurements taken of human ribs, iliac crest, and various long bones. By adulthood,
33 trabecular bone resorption is about 6-fold higher than in cortical bone. As discussed in Chapter 4, values
34 for children and adults were increased by a factor of 2, based on calibration of simulations of bone Pb
35 elimination kinetics in retired Pb workers ([Nilsson et al., 1991](#)).

36 **ARCS2B:** Rate coefficient for Pb transfer from cortical bone surface to diffusible plasma. The value
37 assigned to *ARCS2B* is from [Leggett \(1993\)](#). The value of 0.5 d^{-1} for adults was based on model fit of
38 skeletal Pb data for humans ([Heard and Chamberlain, 1984](#)), baboons ([Cohen et al., 1970](#)), and dogs
39 ([Lloyd et al., 1975](#)), assuming a transfer rate of 1 d^{-1} from bone surface and 0.5 d^{-1} each to plasma or
40 exchangeable bone volume. For children, the rate coefficient 0.65 d^{-1} was assigned to *ARCS2B* based on
41 the assumption that, in children, a larger fraction of Pb leaving bone surfaces goes to plasma. By analogy

1 to strontium, approximately 1.25-fold more Pb transfers from bone surface to plasma in children,
2 compared to adults ($1.25 \times 0.5 \text{ d}^{-1} = 0.65 \text{ d}^{-1}$).

3 **ARCS2DF**: Rate coefficient for Pb transfer from cortical bone surface to exchangeable cortical bone
4 volume. The value assigned to *ARCS2DF* is from [Leggett \(1993\)](#). The value of 0.5 d^{-1} in adults was based
5 on model fits to skeletal Pb data for humans ([Heard and Chamberlain, 1984](#)), baboons ([Cohen et al.,](#)
6 [1970](#)), and dogs ([Lloyd et al., 1975](#)) assuming transfer rate of 1 d^{-1} from bone surface and 0.5 d^{-1} each to
7 plasma or exchangeable bone volume. For children to age 15, the rate coefficient is 0.35 d^{-1} . By analogy
8 to strontium, approximately 1.25-fold more Pb transfers from bone surface to plasma in children,
9 compared to adults ($1.25 \times 0.5 \text{ d}^{-1} = 0.65 \text{ d}^{-1}$). The remaining Pb transfers to exchangeable bone volume at
10 a rate of 0.35 d^{-1} .

11 **ARKDN2**: Rate coefficient for transfer from kidney compartment 2 to diffusible plasma. [Leggett \(1993\)](#)
12 assigned a value of 0.0019 d^{-1} for adults. After parameter values for *TOKDNI* and *RKDNI* were set,
13 0.02% deposition from diffusible plasma and a removal $t_{1/2}$ of 1 year (rate coefficient: $0.693/1 \text{ yrs} =$
14 0.0019 d^{-1}) replicated and overestimated slow renal Pb loss in humans ([Heard and Chamberlain, 1984](#))
15 and animals ([Lloyd et al., 1975](#); [Cohen et al., 1970](#)), respectively. Rate coefficients for children ages 10-
16 15 years were assigned the adult value, while 0.00693 d^{-1} was used to represent birth to 5 years of age,
17 assuming a removal $t_{1/2}$ of 100 days. This assumption was needed to keep predicted Pb levels from overly
18 accumulating in long-term kidney compartments. These values were revised downward in the
19 AALM.FOR based on calibration of simulations (see Chapter 4) of post-mortem soft tissue-bone Pb
20 concentrations in children and adults reported by [Barry \(1975\)](#). The adjustments were a factor of $\times 0.1$ for
21 ages ≤ 25 years, increasing to 0.5 at age 30 years and 1 by age 40 years.

22 **ARLVR2**: Rate coefficient for Pb transfer from the slow liver compartment 2 to diffusible plasma.
23 [Leggett \(1993\)](#) assigned a value of 0.0019 d^{-1} for adults and children ≥ 10 years of age to reproduce
24 observations of 2% fraction of body Pb in liver of chronically exposed humans. For children ages 10–15
25 years, the rate coefficient was the same as adults, while 0.00693 d^{-1} was used for birth to 5 years of age,
26 assuming a removal $t_{1/2}$ of 100 days. This assumption was made to keep predicted Pb levels from overly
27 accumulating in long-term compartments. Values for children and adults were revised downward in the
28 AALM.FOR based on calibration of simulations (see Chapter 4) of post-mortem soft tissue-bone Pb
29 concentration ratios in children and adults reported by [Barry \(1975\)](#). The adjustments were a factor of 0.1
30 for ages ≤ 1 year, increasing progressively to 0.3 at age 10 years, 0.75 at age 30 years, 1.6 at age 40 years,
31 and 1.8 at 60 years.

32 **ARRBC**: Rate coefficient for Pb transfer from RBC to diffusible plasma. [Leggett \(1993\)](#) assigned a
33 value of 0.0019 for adults and children ≥ 10 years of age, based on a removal $t_{1/2}$ from RBCs to plasma of
34 5 days [$0.693/5 \text{ days} = 0.0019 \text{ d}^{-1}$; ([Chamberlain et al., 1978](#))]. For children from birth to 5 years of age,
35 0.00693 d^{-1} was assigned to provide reasonable agreement with the reference distributions of RBC levels
36 derived by [Leggett \(1993\)](#). Values for ages 1–10 years were revised upward in the AALM.FOR to
37 achieve alignment of Pb uptake-blood Pb concentration relationships in children predicted by the AALM
38 and IEUBK model (Chapter 4). The adjustments were a factor of $\times 1.7$ at age 1 year, $\times 1.4$ at age 5 years
39 and $\times 1.4$ at age 10 years.

40 **ARTRAB**: Rate coefficient for Pb transfer from non-exchangeable trabecular bone volume to diffusible
41 plasma. [Leggett](#) assigned a value of 0.000493 d^{-1} to adults (assuming that removal of Pb from the non-
42 exchangeable bone volume occurs at same rate as bone resorption). Childhood and adult rates were

1 adopted from [ICRP \(1990\)](#) for bone-seeking radionuclides, based on histomorphometric measurements
2 taken of human ribs, iliac crest, and various long bones. By adulthood, trabecular bone resorption is
3 about 6-fold higher than in cortical bone. Values for children and adults were increased by a factor of $\times 3$,
4 based on calibration of simulations (see Chapter 4) of bone Pb elimination kinetics in retired Pb workers
5 ([Nilsson et al., 1991](#)).

6 **ARTS2B**: Rate coefficient for Pb transfer from trabecular bone surface to diffusible plasma. Values for
7 *ARTS2B* are from [Leggett \(1993\)](#). For adults, the value 0.5 d^{-1} was based on model fit to skeletal Pb data
8 for humans ([Heard and Chamberlain, 1984](#)), baboons ([Cohen et al., 1970](#)), and dogs ([Lloyd et al., 1975](#)).
9 Assuming a total transfer rate of 1 d^{-1} from bone surface, a rate of 0.5 d^{-1} each transfers Pb to plasma or
10 exchangeable bone volume. The rate coefficient for children (≤ 15 years) is 0.65 d^{-1} , based on the
11 assumption that, in children, a larger fraction of Pb leaves bone surfaces and goes to plasma. By analogy
12 to strontium, approximately 1.25-fold more Pb transfers from bone surface to plasma in children,
13 compared to adults ($1.25 \times 0.5 \text{ d}^{-1} = 0.65 \text{ d}^{-1}$).

14 **ARTS2DF**: Rate coefficient for Pb transfer from surface trabecular bone to exchangeable trabecular
15 bone volume. Values for *ARTS2DF* are from [Leggett \(1993\)](#). For adults, the value 0.5 d^{-1} was based on
16 model fit to skeletal Pb data for humans ([Heard and Chamberlain, 1984](#)), baboons ([Cohen et al., 1970](#)),
17 and dogs ([Lloyd et al., 1975](#)). Assuming a total transfer rate of 1 d^{-1} from bone surface, a rate of 0.5 d^{-1}
18 each transfers Pb to plasma or exchangeable bone volume. the rate coefficient for children ≤ 15 years is
19 0.35 d^{-1} . By analogy to strontium, approximately 1.25-fold more Pb transfers from bone surface to
20 plasma in children, compared to adults ($1.25 \times 0.5 \text{ d}^{-1} = 0.65 \text{ d}^{-1}$). The remaining Pb transfers to
21 exchangeable bone volume at a rate of 0.35 d^{-1} .

22 **ATBONE**: Deposition fraction for Pb from diffusible plasma to surface bone. The value of 8% for
23 adults reproduces observations of Pb deposition to total bone of humans ([Heard and Chamberlain, 1984](#)),
24 baboons ([Cohen et al., 1970](#)), and dogs ([Lloyd et al., 1975](#)). For children, the following deposition
25 fractions were used: 23.7% at 15 years, 17.9% at 10 years, 12.8% at 5 years, 14.4% at year, and 24% at
26 birth and 3 months. These values arise from the assumption that Pb deposits to bone surfaces
27 proportional to the rate of calcium addition, as described by [Leggett \(1992\)](#).

28 **ATBRAN**: Deposition fraction for Pb from diffusible plasma to brain. Values for *ATBRAN* are from
29 [Leggett \(1993\)](#). For children ≥ 5 years old and adults, the value of 0.015%, combined with a removal $t_{1/2}$
30 of 2 years ($0.693/2 \text{ yrs} = 9.49 \times 10^{-4} \text{ d}^{-1}$) were assigned based on model fit to observations of brain Pb
31 levels in dogs ([Lloyd et al., 1975](#)) and baboons ([Cohen et al., 1970](#)) and human autopsy observations
32 ([Grandjean, 1978](#); [Niyogi, 1974](#)). For children from birth to 1 year, the a 3-fold higher value of 0.045%
33 was assigned to account for the relatively larger brain mass:body weight ratio in this age range.

34 **ATFRAC**: Fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone. Values
35 for *ATFRAC* are from [Leggett \(1993\)](#). For adults, the value of 55.6% was assigned based on an
36 approximate 4-fold larger trabecular bone mass than cortical bone in humans ([ICRP, 1975](#)), and that
37 calcium deposits in trabecular bone are 5- to 6-fold greater than in cortical bone in humans ([Leggett,](#)
38 [1992](#); [Leggett et al., 1982](#)). The fraction transferring from diffusible plasma to cortical bone is $1 - \text{ATFRAC}$,
39 or 0.444. For children, the following values were assigned: 27.95% for 15 years, 25% for 10 years,
40 22.2% for 5 years, or 20% for birth to 3 months.

- 1 **ATOSOF0:** Deposition fraction for Pb from diffusible plasma to the fast soft tissue compartment 0.
2 Values for *ATOSOF0* are from [Leggett \(1993\)](#). For adults, the value of 8.88%, and a removal $t_{1/2}$ of 8
3 hours (RSOF0) was assumed in order to replicate Pb reappearance in blood from extravascular fluid after
4 the first day following Pb injections in animals ([Gregus and Klaassen, 1986](#); [Victery et al., 1979](#); [Lloyd et](#)
5 [al., 1975](#); [Potter et al., 1971](#); [Cohen et al., 1970](#); [Lloyd et al., 1970](#)). For children, values of 8.38 and
6 8.35% were assigned to ages 5 to 15 years and birth to 1 year, respectively.
- 7 **ATOSOF1:** Deposition fraction for Pb from diffusible plasma to the intermediate soft tissue
8 compartment 1. Values for *ATOSOF1* are from [Leggett \(1993\)](#). For adults, the value of 0.5% produced
9 an intermediate-rate loss of Pb from soft tissues and that aligned with blood Pb and excretion kinetics
10 (hair, nails, and skin) in humans ([Rabinowitz et al., 1976](#)). A value of 1% was assigned children up to 15
11 years of age ([Leggett, 1993](#)).
- 12 **ATOSOF2:** Deposition fraction for Pb from diffusible plasma to the slow soft tissue compartment 2.
13 Values for *ATOSOF2* are from [Leggett \(1993\)](#). The value of 0.1% for adults and children, along with a
14 retention time of at ≥ 5 years was based on comparisons of predicted and observed post-mortem soft tissue
15 Pb levels in chronically exposed humans ([Grandjean, 1978](#); [Niyogi, 1974](#)).
- 16 **BLDMOT:** Maternal blood Pb concentration. The value 0.6 $\mu\text{g/dL}$ is based on an analysis of blood Pb
17 concentration data for U.S. females age 17–45 years reported in the NHANES 2009–2014 and assessed
18 by [U.S. EPA \(2017\)](#).
- 19 **BR1:** Rate coefficient for Pb transfer from RT compartment 1 to the gastrointestinal tract (*CILIAR*) or
20 diffusible plasma (1-*CILIAR*). The value assigned to *BR1* is from [Leggett \(1993\)](#). The value of 16.6 is
21 based on observations of clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols in humans
22 ([Chamberlain et al., 1978](#)), in which 22% of deposited Pb was cleared from lungs with a $t_{1/2}$ of 0.8 hours.
23 The rate of clearance is calculated as $0.693/0.04167 \text{ days} = 16.6 \text{ d}^{-1}$.
- 24 **BR2:** Rate coefficient for Pb transfer from RT compartment 2 to the gastrointestinal tract (*CILIAR*) or
25 diffusible plasma (1-*CILIAR*). The value assigned to *BR2* is from [Leggett \(1993\)](#). The value of 5.54 is
26 based on observations of clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols in humans
27 ([Chamberlain et al., 1978](#)), in which 34% of deposited Pb was cleared from lungs with a $t_{1/2}$ of 2.5 hours.
28 The rate of clearance is calculated as $0.693/0.125 \text{ days} = 5.54 \text{ d}^{-1}$.
- 29 **BR3:** Rate coefficient for Pb transfer from RT compartment 3 to the gastrointestinal tract (*CILIAR*) or
30 diffusible plasma (1-*CILIAR*). The value assigned to *BR3* is from [Leggett \(1993\)](#). The value of 1.66 d^{-1}
31 was chosen based on observations of clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols
32 in humans ([Chamberlain et al., 1978](#)), in which 33% of deposited Pb was cleared from lungs with a $t_{1/2}$ of
33 9 hours. The rate of clearance is calculated as $0.693/0.375 \text{ days} = 1.66 \text{ d}^{-1}$.
- 34 **BR4:** Rate coefficient for Pb transfer from RT compartment 4 to the gastrointestinal tract (*CILIAR*) or
35 diffusible plasma (1-*CILIAR*). The value assigned to *BR4* is from [Leggett \(1993\)](#). The value of 0.347 d^{-1}
36 is based on observations of clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols in humans
37 ([Chamberlain et al., 1978](#)), in which 12% of deposited Pb was cleared from lungs with a $t_{1/2}$ of 44 hours.
38 The rate coefficient is calculated as $0.693/2 \text{ days} = 0.347 \text{ d}^{-1}$.
- 39 **BRATIO:** Child (at birth):maternal blood Pb concentration ratio. The value assigned to BRATIO is from
40 [Leggett \(1993\)](#). The value of 0.85 is based on studies that have compared maternal and fetal cord blood

1 Pb concentrations which have observed cord-maternal ratios ranging from 0.7 to 1 ([Baranowska-Bosiacka](#)
2 [et al., 2016](#); [Gulson et al., 2016](#); [Kayaalti et al., 2015](#); [Kim et al., 2015](#); [Baeyens et al., 2014](#); [Chen et al.,](#)
3 [2014](#); [Kazi et al., 2014](#); [Reddy et al., 2014](#); [Amaral et al., 2010](#); [Kordas et al., 2009](#); [Patel and Prabhu,](#)
4 [2009](#); [Carbone et al., 1998](#); [Goyer, 1990](#); [Graziano et al., 1990](#)).

5 **BRETH:** Pb deposition in RT ($\mu\text{g}/\text{day}$). Values are assigned by the user in AALM Fortran.xlsm (see
6 parameters *IN_air_total*, Appendix B).

7 **CHAGE:** Age years for parameters that are assigned values at specific ages. Values assigned to *CHAGE*
8 are from [Leggett \(1993\)](#).

9 **CHR:** Pb intake to blood ($\mu\text{g}/\text{day}$), for simulating injection. This parameter is in the Fortran code;
10 however, injection intakes are not simulated in the AALM.FOR.

11 **CILIAR:** Fraction of inhaled Pb transferred to gastrointestinal tract. A value of 4% was assigned by
12 [Leggett \(1993\)](#) to the fraction of total deposited Pb deposited cleared from the lung via mucociliary
13 escalation. This value is based observations that in adults approximately 95% of Pb deposited in the RT
14 was absorbed directly to blood ([Wells et al., 1977](#); [Hursh et al., 1969](#)). Assuming a total deposition of
15 40% of inhaled Pb, the value for *CILIAR* is 1.6% ($0.016 = 0.04 \times 0.40$).

16 **DELTO:** Starting value for numerical integration time step. The default value is 0.1 day is intended to
17 limit integration error in the calculation of blood Pb concentration to less than 5%

18 **DELTi:** Array of numerical integration time steps if the time step varies in the simulation. The default
19 for the AALM.FOR is to use a single time step for the simulation (0.1 day).

20 **EAT:** Pb ingestion ($\mu\text{g}/\text{day}$) for each exposure time step (*NCHRON*). Values are assigned by the user in
21 AALM Fortran.xlsm (see parameters *IN_ingestion_total*, Appendix B).

22 **ENDAY:** Ending day of simulation. For example, for a simulation from birth to age 60 years,
23 $ENDAY=60 * 365=21900$.

24 **EXPAGE:** Age at start of the simulation. The default value for *EXPAGE* is zero in the AALM.FOR
25 which simulates Pb biokinetics beginning at birth, with a pre-existing body Pb burden based on maternal
26 blood Pb (*BLODMOT*).

27 **FLONG:** Fraction of total Pb transfer from the exchangeable bone volume to non-exchangeable bone
28 volume. The fraction of total Pb transfer from the exchangeable bone volume to bone surface (cortical or
29 trabecular) is $1.0 - FLONG$. The value of 20% from [Leggett \(1993\)](#) was revised to 0.6, based on
30 calibration of simulations (see Chapter 4) of bone Pb elimination kinetics in retired Pb workers ([Nilsson](#)
31 [et al., 1991](#)).

32 **HITOBL:** Fraction of Pb transfer from liver compartment 1 to diffusible plasma. The value assigned to
33 *HITOBL* is from [Leggett \(1993\)](#). Transfer out of liver compartment 1 includes 45% to diffusible plasma
34 (*HITOBL*), 45% to small intestine (*HITOSI*) and 10% to liver compartment 2 (*HITOH2*). These
35 assumptions based on estimates of hepatic uptake and retention in humans and animals, and biliary
36 secretion in humans ([Heard and Chamberlain, 1984](#); [Lloyd et al., 1975](#); [Cohen et al., 1970](#)).

37 **HITOH2:** Fraction of Pb transfer from liver compartment 1 to liver compartment 2. The value assigned
38 to *HITOH2* is from [Leggett \(1993\)](#). Transfer out of liver compartment 1 includes 45% to diffusible
39 plasma (*HITOBL*), 45% to small intestine (*HITOSI*) and 10% to liver compartment 2 (*HITOH2*). These

- 1 assumptions based on estimates of hepatic uptake and retention in humans and animals, and biliary
2 secretion in humans ([Heard and Chamberlain, 1984](#); [Lloyd et al., 1975](#); [Cohen et al., 1970](#)).
- 3 **HITOSI:** Fraction of Pb transfer from liver compartment 1 to the small intestine. The value assigned to
4 *HITOSI* is from [Leggett \(1993\)](#). Transfer out of liver compartment 1 includes 45% to diffusible plasma
5 (*HITOBL*), 45% to small intestine (*HITOSI*) and 10% to liver compartment 2 (*HITOH2*). These
6 assumptions based on estimates of hepatic uptake and retention in humans and animals, and biliary
7 secretion in humans ([Heard and Chamberlain, 1984](#); [Lloyd et al., 1975](#); [Cohen et al., 1970](#)).
- 8 **HALF:** Age at which body weight is half of *WCHILD*. This parameter is used in body weight and tissue
9 volume growth equations (see variables *WBODY*, *VK*, *VL*, Appendix A). The value assigned to *WCHILD*
10 is from [O'Flaherty \(1995, 1993\)](#).
- 11 **HCTA:** Adult hematocrit. Sex-specific values assigned to *HCTA* are from [O'Flaherty \(1995, 1993\)](#).
- 12 **IACUTE:** Switch for acute (1) or chronic array (2) uptakes. The default value is 2 in the AALM.FOR
13 which simulates chronic (i.e., repeated) daily exposures. Acute (e.g. single day exposures) can be
14 simulated with discrete exposure inputs or pulse train inputs (see Exposure Model Parameters, Appendix
15 C).
- 16 **ICHEL:** Switch for chelation simulation off (0) or on (1). The default value is 0 (no chelation). The
17 AALM Fortran.xlsm user interface does not support the chelation option.
- 18 **IFETAL:** Switch for fetal simulation on (1) or off (0). The default value is 1 which turns on calculations
19 of Pb body burden at birth based on maternal blood Pb (*BLDMOT*, see variables for Pb Masses at Birth,
20 Appendix A).
- 21 **INMODE:** Switch for injection (0), inhalation (1), ingestion (2), or combination (3). The default value is
22 3 which allows combined ingestion and inhalation exposures. Injection intakes are not supported in the
23 AALM.FOR.
- 24 **IRBC:** Switch for linear (0) or non-linear (1) RBC uptake. The default value is 1 which implements a
25 threshold-specified RBC uptake of Pb from plasma.
- 26 **KAPPA:** Logistic parameter for calculation of body weight (see variable *WBODY* in Appendix A). The
27 parameters *KAPPA* and *LAMBDA* determine the pre-adult rate of increase of body weight. The default
28 value for *KAPPA* is 600 ([O'Flaherty, 1995, 1993](#)).
- 29 **LAMBDA:** Logistic parameter in calculation of body weight (see variable *WBODY* in Appendix A). The
30 parameters *KAPPA* and *LAMBDA* determine the pre-adult rate of increase of body weight during. The
31 default value for *LAMBDA* is 0.017 for females and 0.0095 for males ([O'Flaherty, 1995, 1993](#)).
- 32 **NCHRON:** Number of exposure time steps, where the exposure time step is an age-day range within
33 which ingestion intake (*EAT*) or inhalation intake (*BRETH*) remains constant.
- 34 **NCYCLE:** Number of numerical integration steps for the simulation. If the numerical integration step
35 size is 0.1 day, *NCYCLE* is the day length of the simulation (*ENDDAY*)/0.1 day.
- 36 **NDELT:** Number of times the numerical integration time step changes during the simulation. The default
37 is 1 which applies the same time step throughout the simulation
- 38 **NUMAGE:** Number of ages (*CHAGE*) at which age-dependent parameters are assigned specific values.

- 1 **OUTPUTS:** Variable identity numbers selected for output. This parameter is in the Fortran code;
2 however, is it not used in the implementation of AALM.FOR, which specifies output variables in the
3 AALM Fortran.xlsm file.
- 4 **POWER:** Exponent factor for non-linear expression for RBC deposition. The value assigned to *POWER*
5 is from [Leggett \(1993\)](#). The value of 1.5 was empirically derived based on data on Pb in human urine,
6 plasma, and blood ([Minoia et al., 1990](#); [Iyengar and Woittiez, 1988](#); [Somerville et al., 1988](#); [Skerfving et](#)
7 [al., 1985](#); [Manton and Cook, 1984](#); [DeSilva, 1981](#); [Chamberlain et al., 1978](#); [Schütz and Skerfving, 1976](#);
8 [Cooper et al., 1973](#)).
- 9 **R1:** Fraction of inhaled Pb deposited in the RT compartment 1. [Leggett \(1993\)](#) assigned values for the
10 regional distribution of deposited Pb based on observations of clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -
11 labeled exhaust aerosols in humans ([Chamberlain et al., 1978](#)), with 22% of deposited Pb cleared from
12 lungs. [Leggett \(1993\)](#) equated cleared Pb with deposited dose and rounded up to 25% for the regional
13 distribution to compartment 1. Assuming a total deposition of 40% of inhaled Pb ([Leggett, 1993](#)), the
14 value for R1 is 10% ($0.08 = 0.20 \times 0.40$).
- 15 **R2:** Fraction of inhaled Pb deposited in the RT compartment 1, representing the tracheobronchial region.
16 [Leggett \(1993\)](#) assigned values for the regional distribution of deposited Pb based on observations of
17 clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols in humans ([Chamberlain et al., 1978](#)),
18 with 34% of deposited Pb cleared from lungs. [Leggett \(1993\)](#) equated cleared Pb with deposited dose and
19 rounded up to 35% for the regional distribution to compartment 2. Assuming a total deposition of 40% of
20 inhaled Pb, the value for R2 is 14% ($0.14 = 0.35 \times 0.40$).
- 21 **R3:** Fraction of inhaled Pb deposited in the RT compartment 1, representing the tracheobronchial region.
22 [Leggett \(1993\)](#) assigned values for the regional distribution of deposited Pb based on observations of
23 clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols in humans ([Chamberlain et al., 1978](#)),
24 with 33% of deposited Pb was cleared from lungs. [Leggett \(1993\)](#) equated cleared Pb with deposited
25 dose and rounded down to 30% for the regional distribution to compartment 3. Assuming a total
26 deposition of 40% of inhaled Pb, the value for R3 is 12% ($0.14 = 0.35 \times 0.40$).
- 27 **R4:** Fraction of inhaled Pb deposited in the RT compartment 1, representing the tracheobronchial region.
28 [Leggett \(1993\)](#) assigned values for the regional distribution of deposited Pb based on observations of
29 clearance of ^{203}PbO , $^{203}\text{Pb}(\text{NO}_3)_2$, or ^{203}Pb -labeled exhaust aerosols in humans ([Chamberlain et al., 1978](#)),
30 with 12% of deposited Pb was cleared from lungs. [Leggett \(1993\)](#) equated cleared Pb with deposited
31 dose and rounded down to 10% for the regional distribution to compartment 4. Assuming a total
32 deposition of 40% of inhaled Pb, the value for R4 is 4% ($0.04 = 0.10 \times 0.40$).
- 33 **RBCNL:** Threshold Pb concentration in RBCs at which non-linear deposition of Pb from diffusible
34 plasma to RBC occurs. [Leggett \(1993\)](#) assigned a value of $60 \mu\text{g dL}^{-1}$ based on an observed RBC Pb
35 concentration threshold above which non-linear kinetics of Pb in the body were observed ([Chamberlain,](#)
36 [1985](#)). The value was revised to $20 \mu\text{g/dL}$ based on calibration to data on plasma-whole blood Pb
37 concentrations measured in adults ([Smith et al., 2002](#); [Manton et al., 2001](#); [Bergdahl et al., 1999](#);
38 [Bergdahl et al., 1998](#); [Hernandez-Avila et al., 1998](#); [Bergdahl et al., 1997](#); [Schutz et al., 1996](#)).
- 39 **RDECAY:** Rate coefficient for radioactive decay of unstable Pb isotope. This parameter is set to 0 by
40 default in the AALM.FOR which simulates biokinetics of stable isotopes of Pb.

- 1 **RDIFF**: Rate coefficient for Pb transfer from exchangeable bone (cortical or trabecular) volume to
 2 surface or non-exchangeable bone volume (see FLONG for fraction to non-exchangeable). The value
 3 assigned to *RDIFF* is from [Leggett \(1993\)](#). The value of 0.0231 d^{-1} was based on observed rates of
 4 removal of Pb from bone of dogs, baboons, and chronically exposed humans appears, which were similar
 5 to removal of radium, which has a removal $t_{1/2}$ of 30 days ([Leggett, 1992](#)), resulting in a rate coefficient of
 6 $0.693/30 \text{ days} = 0.0231 \text{ d}^{-1}$.
- 7 **RKDN1**: Rate coefficient for transfer from kidney compartment 1 to urinary pathway. The value
 8 assigned to *RKDN1* is from [Leggett \(1993\)](#). The value of 0.139 d^{-1} was chosen based on a removal $t_{1/2}$ of
 9 5 days (transfer rate of $0.693/5 \text{ days} = 0.139 \text{ d}^{-1}$) and a deposition fraction of 2%, which predicts kidney
 10 levels in rats and baboons ([Cohen et al., 1970](#)) and is also consistent with human excretion data
 11 ([Campbell et al., 1984](#); [Chamberlain et al., 1978](#); [Hursh and Mercer, 1970](#); [Booker et al., 1969](#); [Hursh and](#)
 12 [Suomela, 1968](#)).
- 13 **RLLI**: Rate coefficient for Pb transfer from lower large intestine to feces. The value assigned to *RLLI* is
 14 from [Leggett \(1993\)](#). The value of 1 d^{-1} is from the [ICRP \(1979\)](#) gastrointestinal tract model.
- 15 **RLVR1**: Rate coefficient for Pb transfer from liver compartment 1 to small intestine or diffusible
 16 plasma. The value assigned to *RLVR1* (0.693 d^{-1}) is from [Leggett \(1993\)](#). The removal $t_{1/2}$ for liver
 17 compartment 1 is assumed to be 10 days, resulting in a rate coefficient of $0.693/10 \text{ days} = 0.693 \text{ d}^{-1}$. A
 18 relatively short $t_{1/2}$ is needed to reproduce hepatic uptake and loss in humans ([Chamberlain et al., 1978](#)),
 19 baboons ([Cohen et al., 1970](#)), and dogs ([Lloyd et al., 1975](#)) for the first weeks following intravenous Pb
 20 injection.
- 21 **RPLAS**: Rate coefficient for Pb transfer from diffusible plasma to all compartments, scaled to bone
 22 surface deposition. The value assigned to *RPLAS* is from [Leggett \(1993\)](#). The value of 2000 d^{-1} reflects
 23 the removal of radio-Pb from plasma at about 1 minute ([Campbell et al., 1984](#); [Wells et al., 1977](#); [Booker](#)
 24 [et al., 1969](#)). Adjusting for rapid uptake in to RBCs and EVF, the rate becomes $1.3\text{--}1.4 \text{ min}^{-1}$, rounded to
 25 2000 d^{-1} .
- 26 **RPROT**: Rate coefficient for Pb transfer from bound plasma to diffusible plasma. The value assigned to
 27 *RPROT* is from [Leggett \(1993\)](#). The value of 0.139 d^{-1} ($0.693/5 \text{ days} = 0.139 \text{ d}^{-1}$) is based on a removal
 28 $t_{1/2}$ of approximately 5 days, the same as observed for plasma proteins ([Orten and Neuhaus, 1982](#)).
- 29 **RSIC**: Rate coefficient for Pb transfer from small intestine to upper large intestine. The value assigned
 30 to *RSIC* is from [Leggett \(1993\)](#). The value of 6 d^{-1} is from the first-order transfer rate in the [ICRP \(1979\)](#)
 31 gastrointestinal tract model.
- 32 **RSOF0**: Rate coefficient for Pb transfer from soft tissues with fast Pb clearance to diffusible plasma.
 33 The value assigned to *RSOF0* is from [Leggett \(1993\)](#). The value of 2.079 d^{-1} , based on a removal $t_{1/2}$ of 8
 34 hours ($0.693/8 \text{ hours} = 2.079 \text{ d}^{-1}$) and a deposition fraction of 8.875% from diffusible plasma, reproduces
 35 Pb reappearance in blood from EVF after the first day following Pb injections in animals ([Gregus and](#)
 36 [Klaassen, 1986](#); [Victory et al., 1979](#); [Lloyd et al., 1975](#); [Potter et al., 1971](#); [Cohen et al., 1970](#); [Lloyd et](#)
 37 [al., 1970](#)).
- 38 **RSOF1**: Rate coefficient for Pb transfer from soft tissues with medium Pb clearance to diffusible plasma.
 39 The value assigned to *RSOF1* is from [Leggett \(1993\)](#). The value of 0.00693 d^{-1} , based on an removal $t_{1/2}$
 40 of 100 days ($0.693/100 \text{ days} = 0.00693 \text{ d}^{-1}$) and a deposition fraction of 0.5% from diffusible plasma,
 41 reproduces Pb reappearance in blood from EVF after the first day following Pb injections in animals

- 1 ([Gregus and Klaassen, 1986](#); [Victery et al., 1979](#); [Lloyd et al., 1975](#); [Potter et al., 1971](#); [Cohen et al.,](#)
2 [1970](#); [Lloyd et al., 1970](#)).
- 3 **RSOF2**: Rate coefficient for Pb transfer from soft tissues with slow Pb clearance to diffusible plasma.
4 The value assigned to *RSOF2* (0.00038 d^{-1}) is from [Leggett \(1993\)](#). Assuming no more than 0.1% of
5 diffusible plasma Pb is deposited into soft tissue having tenacious Pb retention, and the retention time is
6 at least 5 years, consistent with autopsy data for chronically exposed humans ([Grandjean, 1978](#); [Niyogi,](#)
7 [1974](#)).
- 8 **RSTMC**: Rate coefficient for Pb transfer from stomach to small intestine. The value assigned to *RSTMC*
9 is from [Leggett \(1993\)](#). The value of 24 d^{-1} is from the [ICRP \(1979\)](#) gastrointestinal tract model.
- 10 **RULI**: Rate coefficient for Pb transfer from upper large intestine to lower large intestine. The value
11 assigned to *RULI* is from [Leggett \(1993\)](#). The value of 1.85 d^{-1} is from the [ICRP \(1979\)](#) gastrointestinal
12 tract model.
- 13 **S2HAIR**: Fraction of Pb transfer from intermediate soft tissue (*SOF2*) to hair, nails, and desquamated
14 skin. The value assigned to *S2HAIR* is from [Leggett \(1993\)](#). The value of 40% is based on observations of
15 3% of the Pb body burden in soft tissues and the remainder in pelt of animals at 28 days after injection
16 ([Lloyd et al., 1975, 1970](#)). The remaining fraction leaving *SOF2* ($1 - S2HAIR = 60\%$) returns to diffusible
17 plasma.
- 18 **SATRAT**: Maximum (saturating) concentration of Pb in RBCs. The value assigned to *SATRAT* is from
19 [Leggett \(1993\)](#). The concentration of $350 \mu\text{g dL}^{-1}$ was assigned based on the observed upward inflection
20 of ratios of urinary:blood Pb and plasma:blood Pb at RBC concentrations above this level ([Minoia et al.,](#)
21 [1990](#); [Iyengar and Woittiez, 1988](#); [Somerville et al., 1988](#); [Skerfving et al., 1985](#); [Manton and Cook,](#)
22 [1984](#); [DeSilva, 1981](#); [Chamberlain et al., 1978](#); [Schütz and Skerfving, 1976](#); [Cooper et al., 1973](#)).
- 23 **SIZEVF**: Relative volume of the EVF compartment compared to plasma (EVF/Plasma). The value
24 assigned to *SIZEVF* is from [Leggett \(1993\)](#). The value of 3-fold was chosen because plasma Pb is about
25 three times that of EVF at equilibrium.
- 26 **TOEVF**: Deposition fraction for Pb from diffusible plasma to extravascular fluid. The value assigned to
27 *STOEVF* is from [Leggett \(1993\)](#). The value of 50% was based on observations of rapid return of Pb to
28 blood from extravascular spaces ([Heard and Chamberlain, 1984](#); [Booker et al., 1969](#); [Hursh and Suomela,](#)
29 [1968](#); [Stover, 1959](#)).
- 30 **TOFECE**: Deposition fraction for Pb from diffusible plasma directly to the small intestine (not including
31 the transfer from biliary secretion, specified by *RLVRI*). The value assigned to *TOFECE* is from [Leggett](#)
32 [\(1993\)](#). The value of 0.6%, as well as Pb entering from biliary excretion (*HITOSI*) was based on
33 observations of fecal excretion and the feces-to-urine Pb ratios in adults ([Heard and Chamberlain, 1984](#);
34 [Chamberlain et al., 1978](#); [Wells et al., 1977](#)).
- 35 **TOKDNI**: Deposition fraction for Pb from diffusible plasma to kidney compartment 1. [Leggett \(1993\)](#)
36 assigned a value of 2% and a removal $t_{1/2}$ of 5 days (*RKDNI*) based on observed kidney levels in rats and
37 baboons ([Cohen et al., 1970](#)) that were also consistent with human excretion data ([Campbell et al., 1984](#);
38 [Chamberlain et al., 1978](#); [Hursh and Mercer, 1970](#); [Booker et al., 1969](#); [Hursh and Suomela, 1968](#)).
39 Values for children and adults were revised upward in the AALM.FOR by a factor of $\times 1.25$ based on

- 1 calibration of simulations of plasma-to-urine clearance estimated for adults from data reported in ([Araki](#)
2 [et al., 1986](#); [Manton and Cook, 1984](#); [Manton and Malloy, 1983](#); [Chamberlain et al., 1978](#)).
- 3 **TOKDN2:** Deposition fraction for Pb from diffusible plasma to kidney compartment. The value of
4 0.02% was chosen. [Leggett \(1993\)](#) assigned a value of 0.02% and a removal $t_{1/2}$ of 1 year (*RKDN2*), after
5 values for *TOKDNI* and *RKNDI* were set, based on observations of a slow component for loss of Pb from
6 kidney in humans ([Heard and Chamberlain, 1984](#)) and animals ([Lloyd et al., 1975](#); [Cohen et al., 1970](#)),
7 respectively. Values for children and adults were revised upward in the AALM.FOR by a factor of $\times 2$
8 based on calibration of simulations (see Chapter 4) of post-mortem soft tissue-bone Pb concentrations in
9 children and adults reported by [Barry \(1975\)](#).
- 10 **TOLVRI:** Deposition fraction for Pb from diffusible plasma to liver compartment 2. The value assigned
11 to *TOLVRI* is from [Leggett \(1993\)](#). The value of 4% was assigned based on observed uptake and
12 retention of Pb in liver in humans and animals, and biliary secretion in humans ([Heard and Chamberlain,](#)
13 [1984](#); [Lloyd et al., 1975](#); [Cohen et al., 1970](#)).
- 14 **TOPROT:** Deposition fraction for Pb from diffusible plasma to protein-bound plasma. The value
15 assigned to *TOPROT* is from [Leggett \(1993\)](#). The value of 0.04% was selected to achieve (1) early
16 bifurcation of tracer Pb between plasma and RBCs, (2) observed urinary clearance of plasma Pb, (3)
17 plasma containing 0.2% of blood Pb at equilibrium, and (4) 15% ultrafilterable plasma Pb at equilibrium.
- 18 **TORBC:** Deposition fraction from diffusible plasma to RBCs. The value assigned to *TORBC* is from
19 [Leggett \(1993\)](#). The value of 24% was based on the observation that approximately one quarter of Pb
20 depositing to RBCs provides good fits to data of [Hursh et al. \(1969\)](#).
- 21 **TOSWET:** Deposition fraction for Pb from diffusible plasma to sweat. The value assigned to *TOSWET*
22 is from [Leggett \(1993\)](#). The value of 0.35% was assigned based on observations of Pb excretion in sweat
23 and which was approximately 10% of urinary excretion for chronic exposure ([Rabinowitz et al., 1976](#)).
- 24 **TOURIN:** Deposition fraction for Pb from diffusible plasma to urine. [Leggett \(1993\)](#) assigned a value
25 of 1.5% for *TOURIN*, in addition to 2% being removed from urinary path to bladder (*TOKDNI*), based on
26 observations of human urinary clearance ([Minoia et al., 1990](#); [Iyengar and Woittiez, 1988](#); [Somerville et](#)
27 [al., 1988](#); [Skerfving et al., 1985](#); [Chamberlain et al., 1978](#); [Schütz and Skerfving, 1976](#); [Cooper et al.,](#)
28 [1973](#)). This parameter was set to zero in the AALM.FOR after calibration of parameter *TOKDNI* to data
29 on plasma-to-urine clearance adults ([Araki et al., 1986](#); [Manton and Cook, 1984](#); [Manton and Malloy,](#)
30 [1983](#); [Chamberlain et al., 1978](#)).
- 31 **VBLC:** Blood volume fraction of body weight. The value assigned to *VBLC* is from [O'Flaherty \(1995,](#)
32 [1993\)](#).
- 33 **VKC:** Blood volume fraction of body weight. The value assigned to *VKC* is from [O'Flaherty \(1995,](#)
34 [1993\)](#).
- 35 **VLC:** Liver volume fraction of body weight. The value assigned to *VLC* is from [O'Flaherty \(1995, 1993\)](#).
- 36 **VLUC:** Lung volume fraction of body weight. The value assigned to *VLC* is from [O'Flaherty \(1995,](#)
37 [1993\)](#).
- 38 **WADULT:** Adult maximum weight used in calculation of body weight growth (see variable *WBODY* in
39 Appendix A). The value assigned to *WADULT* is from [O'Flaherty \(1995, 1993\)](#).

1 **WBIRTH:** Weight at birth used in calculation of body weight growth (see variable *WBODY* in Appendix
2 A). The value assigned to *WBIRTH* is from [O'Flaherty \(1995, 1993\)](#).

3 **WCHILD:** Maximum body weight achieved during early hyperbolic growth phase, used in calculation of
4 body weight growth (see variable *WBODY* in Appendix A). The value assigned to *WCHILD* is from
5 [O'Flaherty \(1995, 1993\)](#).

6 **TABLE D-1. AALM BIOKINETICS PARAMETERS AND VALUES**

Parameter	Unit	Form	Type	Description	Value		Source
AFC1	unitless	C	F	Parameter used in calculating age-specific absorption fraction (<i>F1</i>)	0.40		(Ziegler et al., 1978; Alexander et al., 1974)
AFC2	unitless	C	F	Parameter used in calculating age-specific absorption fraction (<i>F1</i>)	0.28		(Maddaloni et al., 2005)
AGSCAL	unitless	A	F	Age scaling factor for gastrointestinal transfer rates	Age	Value	(Leggett, 1993)
					≥25 yr	1	
					15 yr	1.33	
					10 yr	1.67	
					5 yr	1.67	
					1 yr	1.67	
					0.274 yr	1.67	
Birth	1.67						
ARBRAN	d ⁻¹	A	F	Rate coefficient for Pb transfer from brain to diffusible plasma	9.5E04		(Leggett, 1993)
ARCORT	d ⁻¹	A	F	Rate coefficient for Pb transfer from non-exchangeable cortical bone to diffusible plasma	Age	Value	(Leggett, 1993; Nilsson et al., 1991) Also see Chapter 4
					≥25 yr	1.644 E-04	
					15 yr	1.024 E-03	
					10 yr	1.780 E-03	
					5 yr	3.080 E-03	
					1 yr	5.760 E-03	
					0.274 yr	1.644 E-02	

Parameter	Unit	Form	Type	Description	Value		Source
					Birth	2.040 E-02	
ARCS2B	d ⁻¹	A	F	Rate coefficient for Pb transfer from cortical bone surface to diffusible plasma.	Age	Value	(Leggett, 1993)
					≥25 yr	0.50	
					15 yr	0.35	
					10 yr	0.35	
					5 yr	0.35	
					1 yr	0.35	
					0.274 yr	0.35	
					Birth	0.35	
ARCS2DF	d ⁻¹	A	F	Rate coefficient for Pb transfer from cortical bone surface to exchangeable cortical bone volume	Age	Value	(Leggett, 1993)
					≥25 yr	0.50	
					15 yr	0.65	
					10 yr	0.65	
					5 yr	0.65	
					1 yr	0.65	
					0.274 yr	0.65	
					Birth	0.65	
ARKDN2	d ⁻¹	A	F	Rate coefficient for transfer from kidney compartment 2 to diffusible plasma	Age	Value	(Leggett, 1993; Barry, 1975) Also see Chapter 4
					≥40 yr	1.90E-03	
					30 yr	9.50E-04	
					25 yr	1.90E-04	
					15 yr	1.90E-04	
					10 yr	1.90E-04	
					5 yr	6.93E-04	
					1 yr	6.93E-04	
					0.274 yr	6.93E-04	
					Birth	6.93E-04	

Parameter	Unit	Form	Type	Description	Value		Source
ARLVR2	d ⁻¹	A	F	Rate coefficient for Pb transfer from the slow liver compartment 2 to diffusible plasma	Age	Value	
					90 yr	3.800 E-03	
					60 yr	3.420 E-03	
					40 yr	3.040 E-03	
					30 yr	1.425 E-03	
					25 yr	5.700 E-04	
					15 yr	5.700 E-04	
					10 yr	5.700 E-04	
					5 yr	1.386 E-03	
					1 yr	6.930 E-04	
					0.274 yr	6.930 E-04	
Birth	6.930 E-04						
ARRBC	d ⁻¹	A	F	Rate coefficient for Pb transfer from RBC to diffusible plasma	Age	Value	(Leggett, 1993) Also see Chapter 4
					≥15 yr	1.390 E-01	
					10 yr	1.946 E-01	
					5 yr	4.986 E-01	
					1 yr	7.854 E-01	
					0.274 yr	4.620 E-01	
					Birth	4.620 E-01	
ARTRAB	d ⁻¹	A	F	Rate coefficient for Pb transfer from non-exchangeable trabecular bone volume to diffusible plasma	Age	Value	(Leggett, 1993; Nilsson et al., 1991)
					≥25 yr	9.860 E-04	
					15 yr	1.912 E-03	

Parameter	Unit	Form	Type	Description	Value		Source
					10 yr	2.640 E-03	Also see Chapter 4
					5 yr	3.620 E-03	
					1 yr	5.760 E-03	
					0.274 yr	1.644 E-02	
					≥25 yr	2.040 E-02	
ARTS2B	d ⁻¹	A	F	Rate coefficient for Pb transfer from trabecular bone surface to diffusible plasma	Age	Value	(Leggett, 1993)
					≥25 yr	0.50	
					15 yr	0.35	
					10 yr	0.35	
					5 yr	0.35	
					1 yr	0.35	
					0.274 yr	0.35	
					Birth	0.35	
ARTS2DF	d ⁻¹	A	F	Rate coefficient for Pb transfer from surface trabecular bone to exchangeable trabecular bone volume	Age	Value	(Leggett, 1993)
					≥25 yr	0.50	
					15 yr	0.65	
					10 yr	0.65	
					5 yr	0.65	
					1 yr	0.65	
					0.274 yr	0.65	
					Birth	0.65	
ATBONE	unitless	A	F	Deposition fraction for Pb from diffusible plasma to surface bone	Age	Value	(Leggett, 1993)
					≥25 yr	8.00E-02	
					15 yr	2.37E-01	
					10 yr	1.79E-01	
					5 yr	1.28E-01	
					1 yr	1.44E-01	

Parameter	Unit	Form	Type	Description	Value		Source
					0.274 yr	2.40E-01	
					Birth	2.40E-01	
ATBRAN	unitless	A	F	Deposition fraction for Pb from diffusible plasma to brain	Age	Value	(Leggett, 1993)
					≥5 yr	1.5E094	
					1 yr	4.5E-04	
					0.274 yr	4.5E-04	
					Birth	4.5E-04	
ATFRAC	unitless	A	F	Fraction of diffusible plasma-to-bone deposition that goes to trabecular surface bone	Age	Value	(Leggett, 1993)
					≥25 yr	0.556	
					15 yr	0.279	
					10 yr	0.250	
					5 yr	0.222	
					1 yr	0.200	
					0.274 yr	0.200	
					Birth	0.200	
ATOSOF0	unitless	A	F	Deposition fraction for Pb from diffusible plasma to the fast soft tissue compartment 0	Age	Value	(Leggett, 1993)
					≥25 yr	8.875 E-02	
					15 yr	8.375 E-02	
					10 yr	8.375 E-02	
					5 yr	8.375 E-02	
					1 yr	8.345 E-02	
					0.274 yr	8.345 E-02	
					Birth	8.345 E-02	
ATOSOF1	unitless	A	F	Deposition fraction for Pb from diffusible plasma to the	Age	Value	(Leggett, 1993)
					≥25 yr	0.005	
					15 yr	0.010	

Parameter	Unit	Form	Type	Description	Value	Source
				intermediate soft tissue compartment 1	10 yr 5 yr 1 yr 0.274 yr Birth	0.010 0.010 0.010 0.010 0.010
ATOSOF2	unitless	A	F	Deposition fraction for Pb from diffusible plasma to the slow soft tissue compartment 2	0.001	(Leggett, 1993)
BLODMOT	µg/dL	C	F	Maternal blood Pb concentration	0.6	NHANES 2009–2014; (U.S. EPA, 2017)
BR1	d ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 1 to the gastrointestinal tract (CILIAR) or diffusible plasma (1-CILIAR)	16.6	(Leggett, 1993)
BR2	d ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 2 to the gastrointestinal tract (CILIAR) or diffusible plasma (1-CILIAR)	5.54	(Leggett, 1993)
BR3	d ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 3 to the gastrointestinal tract (CILIAR) or diffusible plasma (1-CILIAR)	1.66	(Leggett, 1993)
BR4	d ⁻¹	C	F	Rate coefficient for Pb transfer from RT compartment 4 to the gastrointestinal tract (CILIAR) or diffusible plasma (1-CILIAR)	0.347	(Leggett, 1993)
BRATIO	unitless	C	F	Child (at birth):maternal blood Pb concentration ratio	0.85	Multiple references, see summary for BRATIO in this Appendix

Parameter	Unit	Form	Type	Description	Value	Source
BRETH	µg/day	A	F	Pb deposition to respiratory tract	User defined in exposure model	NA
CHAGE	day	A	F	Age years for parameters that are assigned values at specific ages	0 100 365 1825 3650 5475 9125 10950 14600 21900 32850	(Leggett, 1993) Also see Chapter 4
CHR	µg/day	A	F	Pb intake to blood from injection	Not supported in AALM.FOR	NA
CILIAR	unitless	C	F	Fraction of inhaled Pb transferred to gastrointestinal tract	0.04	(Leggett, 1993 ; Wells et al., 1977 ; Hursh et al., 1969)
DELTO	day	C	F	Starting value for numerical integration time step	0.25	Chapter 3
DELTi	day	A	F	Array of numerical integration time steps if the time step varies in the simulation	0.25	Chapter 3
EAT	µg/day	A	F	Pb ingestion (µg/day) for each exposure time step (<i>NCHRON</i>)	User defined in exposure model	NA
EXPAGE	day	C	F	Age at start of the simulation	0 (birth)	Chapter 3
FLONG	unitless	A	F	Fraction of total Pb transfer from the exchangeable bone volume to non-exchangeable bone volume; the fraction of total Pb transfer from the exchangeable bone volume to bone surface (cortical or trabecular) is 1.0-FLONG	0.6	(Leggett, 1993, 1992 ; Nilsson et al., 1991 ; Leggett et al., 1982) Also see Chapter 4

Parameter	Unit	Form	Type	Description	Value	Source
H1TOBL	unitless	C	F	Fraction of Pb transfer out of liver compartment 1 that goes to diffusible plasma	0.45	(Leggett, 1993)
H1TOH2	unitless	C	F	Fraction of Pb transfer out of liver compartment 1 that goes to liver compartment 2	0.1	(Leggett, 1993)
H1TOSI	unitless	C	F	Fraction of Pb transfer out of liver compartment 1 that goes to the small intestine	0.45	(Leggett, 1993)
HALF	year	C	F	Age at which body weight is half of <i>WCHILD</i>	3	(O'Flaherty, 1995, 1993)
HCTA	unitless	C	F	Adult hematocrit	0.41 (female) 0.46 (male)	(O'Flaherty, 1995, 1993)
IACUTE	unitless	C	I	Switch for acute (1) or chronic array (2) uptakes1	2	NA
ICHEL	unitless	C	I	Switch for chelation simulation off (0) or on (1)	0 chelation option not supported in AALM.FOR	NA
IFETAL	unitless	C	I	Switch for fetal simulation on (1) or off (0)	1	NA
INMODE	unitless	C	I	Switch for injection (0), inhalation (1), ingestion (2), or combination (3)	3	NA
IRBC	unitless	C	I	Switch for linear (0) or non-linear (1) RBC uptake	1	NA
KAPPA	unitless	C	F	Logistic parameter for calculation of body weight (see variable <i>WBODY</i>)	600	(O'Flaherty, 1995, 1993)
LAMBDA	unitless	C	F	Logistic parameter for calculation of body weight (see variable <i>WBODY</i>)	0.017 (female) 0.0095 (male)	(O'Flaherty, 1995, 1993)

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Parameter	Unit	Form	Type	Description	Value	Source
NCHRON	unitless	C	I	Number of exposure time steps	Specified by user in exposure model	NA
NCYCLE	unitless	C	I	Number of numerical integration steps for the simulation	Specified by user based on length of simulation and step size	NA
NDELT	unitless	C	I	Number of times the numerical integration time step changes during the simulation	1	NA
NUMAGE	untless	C	I	Number of ages (CHAGE) at which age-dependent parameters are assigned specific values.	1	NA
OUTPUTS	unitless	C	I	Variable identity numbers selected for output.-	Not supported in AALM.FOR	NA
POWER	unitless	C	F	Exponent factor for non-linear expression for RBC deposition.	1.5	(Leggett, 1993)
R1	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 1	0.08	(Leggett, 1993)
R2	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 2	0.14	(Leggett, 1993)
R3	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 3	0.14	(Leggett, 1993)
R4	unitless	C	F	Fraction of inhaled Pb deposited in RT compartment 4	0.04	(Leggett, 1993)
RBCNL	µg/dL	C	F	Threshold Pb concentration in RBC for non-linear deposition of Pb from diffusible plasma to RBC	20	(Leggett, 1993) Also see Chapter 4
RDECAY	d ⁻¹	C	F	Rate coefficient for radioactive decay of unstable Pb isotope	Not supported in AALM.FOR	NA

Parameter	Unit	Form	Type	Description	Value	Source
RDIFF	d ⁻¹	C	F	Rate coefficient for Pb transfer from exchangeable bone (cortical or trabecular) volume to surface or non-exchangeable bone volume (see FLONG for fraction to non-exchangeable)	0.0231	(Leggett, 1993)
RKDN1	d ⁻¹	C	F	Rate coefficient for transfer from kidney compartment 1 to urinary pathway	0.139	(Leggett, 1993)
RLLI	d ⁻¹	C	F	Rate coefficient for Pb transfer from lower large intestine to feces	1	(Leggett, 1993)
RLVR1	d ⁻¹	C	F	Rate coefficient for Pb transfer from liver compartment 1 to small intestine or diffusible plasma	0.0693	(Leggett, 1993)
RPLAS	d ⁻¹	C	F	Rate coefficient for Pb transfer from diffusible plasma to all compartments, scaled to bone surface deposition	2000	(Leggett, 1993)
RPROT	d ⁻¹	C	F	Rate coefficient for Pb transfer from bound plasma to diffusible plasma	0.139	(Leggett, 1993)
RSIC	d ⁻¹	C	F	Rate coefficient for Pb transfer from small intestine to upper large intestine	6	(Leggett, 1993)
RSOF0	d ⁻¹	C	F	Rate coefficient for Pb transfer from soft tissues with fast Pb clearance to diffusible plasma	2.079	(Leggett, 1993)
RSOF1	d ⁻¹	C	F	Rate coefficient for Pb transfer from soft tissues with medium Pb clearance to diffusible plasma	0.00693	(Leggett, 1993)

Parameter	Unit	Form	Type	Description	Value	Source
RSOF2	d ⁻¹	C	F	Rate coefficient for Pb transfer from soft tissues with slow Pb clearance to diffusible plasma	0.00038	(Leggett, 1993)
RSTMC	d ⁻¹	C	F	Rate coefficient for Pb transfer from stomach to small intestine	24	(Leggett, 1993)
RULI	d ⁻¹	C	F	Rate coefficient for Pb transfer from upper large intestine to lower large intestine	1.85	(Leggett, 1993)
S2HAIR	unitless	C	F	Fraction of Pb transfer from intermediate soft tissue to hair, nails, and desquamated skin	0.4	(Leggett, 1993)
SATRAT	µg dL ⁻¹	C	F	Maximum (saturating) concentration of Pb in RBC	350	(Leggett, 1993)
SIZEVF	unitless	C	F	Relative volume of the EVF compartment compared to plasma (EVF/Plasma)	3	(Leggett, 1993)
TOEVF	unitless	C	F	Deposition fraction for Pb from diffusible plasma to extravascular fluid	0.5	(Leggett, 1993)
TOFECE	unitless	C	F	Deposition fraction for Pb from diffusible plasma directly to the small intestine (not including the transfer from biliary secretion, specified by <i>RLVRI</i>) not scaled to bone surface deposition	0.006	(Leggett, 1993)
TOKDN1	unitless	C	F	Deposition fraction for Pb from diffusible plasma to kidney compartment 1, not scaled to bone surface deposition	0.02	(Leggett, 1993)

Parameter	Unit	Form	Type	Description	Value	Source
TOKDN2	unitless	C	F	Deposition fraction for Pb from diffusible plasma to kidney compartment 2, not scaled to bone surface deposition	0.0002	(Leggett, 1993)
TOLVR1	unitless	C	F	Deposition fraction for Pb from diffusible plasma to liver compartment 2, not scaled to bone surface deposition	0.04	(Leggett, 1993)
TOPROT	unitless	C	F	Deposition fraction for Pb from diffusible plasma to protein-bound plasma, not scaled to bone surface deposition	0.0004	(Leggett, 1993)
TORBC	unitless	C	F	Deposition fraction from diffusible plasma to RBC, not scaled to bone surface deposition	0.24	(Leggett, 1993)
TOSWET	–	C	F	Deposition fraction for Pb from diffusible plasma to sweat not scaled to bone surface deposition, not scaled to bone surface deposition	0.0035	(Leggett, 1993)
TOURIN	–	C	F	Deposition fraction for Pb from diffusible plasma to urine, not scaled to bone surface deposition	0.015	(Leggett, 1993) Also see Chapter 4
VBLC	unitless	C	F	Blood volume fraction of body weight.	0.067	(O'Flaherty, 1995, 1993)
VKC	unitless	C	F	Kidney volume fraction of body weight.	0.0085	(O'Flaherty, 1995, 1993)
VLC	unitless	C	F	Liver volume fraction of body weight.	0.025	(O'Flaherty, 1995, 1993)
VLUC	unitless	C	F	Lung volume fraction of body weight.	0.015	(O'Flaherty, 1995, 1993)

Parameter	Unit	Form	Type	Description	Value	Source
WADULT	kg	C	F	Adult maximum weight used in calculation of body weight growth (see variable WBODY)	34 (female) 50 (male)	(O'Flaherty, 1995, 1993)
WBIRTH	kg	C	F	Weight at birth used in calculation of body weight growth (see variable WBODY)	3.5	(O'Flaherty, 1995, 1993)
WCHILD	kg	C	F	Maximum body weight achieved during early hyperbolic growth phase, used in calculation of body weight growth (see variable WBODY)	22 (female) 23 (male)	(O'Flaherty, 1995, 1993)

1 A, array; C, constant; F, floating point, I, integer, NA, not applicable.

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