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BACKGROUND INFORMATION ON MECHANISTIC MODELS OF HUMAN EXPOSURE/BIOKINETICS THAT PREDICT TISSUE DISTRIBUTION OF LEAD

1.0 INTRODUCTION

Models are essential for quantifying human health risks that derive from exposures to lead. Dose-response relationships for nearly all of the major health effects of lead in humans are expressed in terms of internal dose (e.g., blood or bone lead concentrations). Application of the internal dose-response information to assessment of risks from environmental lead exposures requires a way of relating internal dose to levels of lead in environmental media (e.g., air, water, surface dust) to which humans come in contact. Models provide the only means for accomplishing this objective; and they come in various forms. Multivariate regression models, commonly used in epidemiology, provide estimates of the contribution of various determinants or control variables (e.g., surface dust lead concentration, air lead concentration) to variance in internal dose metrics. Structural equation modeling links several regression models together to estimate the influence of control variables on a given internal dose metric. Regression models can provide estimates of the rate of change of blood or bone lead concentration in response to an incremental change in exposure level (i.e., slope factor). The strength of regression models is that they have relatively few parameters, which allows a rigorous quantitative assessment of uncertainty in the slope factor. However, the simplicity of regression models also omits from the models numerous parameters that are known to influence human lead exposures and relationships between human exposure and tissue lead levels, including parameters expected to vary spatially and temporally. Thus, extrapolation of regression models to other spatial or temporal contexts, which is often necessary for regulatory applications of the models, can be problematic.

An alternative to regression models are mechanistic models, which attempt to specify all important parameters needed to describe the mechanisms (or processes of) transfer of lead from the environment to human tissues. Such mechanistic models are more complex than regression models, which poses challenges in terms of their mathematical solution. However, by incorporating parameters that can be expected to vary spatially or temporally, or across

individuals or populations, mechanistic models can be extrapolated to a wide range of exposure and receptor contexts. Exposure-biokinetic models are examples of mechanistic models. Exposure models are highly simplified mathematical representations of relationships between levels of lead in environmental media and human lead intakes (e.g., µg lead ingested per day). Such models include parameters that represent processes of transfer of lead between environmental media (e.g., air to surface dust) and from environmental media to humans, including rates of human contact with the media and intakes of the media (e.g., g soil ingested per day). Biokinetic models provide analogous mathematical representations of relationships between lead intakes and levels of lead in body tissues (e.g., blood lead concentration); and they include parameters that represent processes of transfer of lead (a) from portals of entry of lead into the body and (b) from blood to tissues and excreta. When linked together, exposure and biokinetic models provide a means for predicting blood lead concentrations (or lead concentrations in other tissues) that correspond to a specified exposure (medium, level, and duration). Such models can provide these predictions in the absence of complete information on the exposure history and blood lead concentrations for an individual (or population) of interest. Such detailed information on exposure and internal dose can be obtained from controlled experiments, but almost never from epidemiological observations or from public health monitoring programs. Therefore, exposure-biokinetic models are critical to applying epidemiologically-based information on blood lead-response relationships to the quantification and characterization of human health risk. They are also critical for assessing the potential impacts of public health programs directed at mitigation of lead exposure or of remediation of contaminated sites.

Mechanistic models also have several other important features that are useful for risk assessment and for improving our basic understanding of lead exposures and biokinetics. Mechanistic models integrate complex information on lead exposure and biokinetics into a form that provides predictions, rather than just an organized grouping of observations. By analyzing the relationships between model assumptions and predictions (i.e., sensitivity analysis), and by comparing predictions to observations (i.e., model evaluation), models can contribute to the identification of important gaps in our understanding of lead exposure, biokinetics, and risk. Thus, models provide a consistent approach for making, evaluating and improving predictions that support risk assessment and risk management decisions.

Modeling of human lead exposures and biokinetics has advanced considerably during the past several decades. Among the most important new advances are development, evaluation, and extensive application of the Integrated Exposure Uptake Biokinetics (IEUBK) Model for Lead in Children (U.S. Environmental Protection Agency 1994) and the development of models that simulate lead biokinetics in humans from birth through adulthood (Leggett, 1993; O'Flaherty 1993, 1995). While these developments represent important conceptual advances, important challenges remain for further advancements in modeling and applications to risk assessment. The greatest challenge derives from the complexity of the models. Human exposure-biokinetic models include large numbers of parameters, which are required to describe the many processes that contribute to lead intake, absorption, distribution, and excretion. The large number of parameters complicates the assessment of confidence in parameter values, many of which cannot be directly and individually measured. Statistical procedures can be used to evaluate the degree to which model outputs conform to "real-world" observations, and values of influential parameters can be statistically estimated to achieve good agreement with observations. Still, large uncertainty can be expected to remain about many, or even most, parameters in complex exposure-biokinetics models such as those described below.

Given the difficulties in quantitatively assessing certainty for values specified for all the individual parameters in an exposure-biokinetics model, complete validation that the model accurately represents the real world in all aspects represented in the model is virtually impossible. As a consequence of this, Oreskes (1998) noted: *"…the goals of scientists working in a regulatory context should be not validation but evaluation, and where necessary, modification and even rejection. Evaluation implies an assessment in which both positive and negative results are possible, and where the grounds on which a model is declared good enough are clearly articulated."* From this perspective, evaluation of confidence associated with a given exposure-biokinetics model rests largely on assessment of the degree to which model predictions, made within a given context of certainty in model inputs, conform to observations and/or expectations and, most importantly, the degree to which this conformity does or does not satisfy requirements for use of the model in a specific context. Thus, because of limitations in observations of predicted outcomes, it may be possible to evaluate confidence in some uses of a model, but not others. Similarly, it is possible for confidence in a model to be judged acceptable

for a given use, but not for other uses. The concept of *validation* of highly complex mechanistic models, outside of the context of a specific use of the model, has little meaning.

In the discussion below of specific models, reported efforts to evaluate each model are noted. However, the relevance of these evaluations to the assessment of confidence in a specific use of that model (e.g. predicting average blood lead concentrations in children who live in areas that have certain cross-sectionally measured environmental lead levels), in most cases, cannot be ascertained from the reported literature. Nevertheless, as framework for qualitatively comparing the various evaluative procedures that have been applied to the models, the following general classification of model evaluations has been adopted:

- Sensitivity analysis has been conducted and most influential parameters identified and uncertainty characterized.
- Model predictions have been compared qualitatively to observations.
- Predictions have been compared quantitatively to observations (i.e., a statistical model has been applied for estimation of "goodness of fit" and uncertainty).
- Confidence in model predictions for specific uses has been quantitatively evaluated.
- Accuracy of model implementation code has been verified.

In the sections that follow, an overview is provided with regard to the evolution of important lead biokinetic modeling aspects that constitute major modeling advances during the past 25 years or so leading to development of EPA's All Ages Lead Model (AALM). Descriptions of individual models are intended to provide only brief snapshops of key features of each model, with particular attention to conceptual features that are unique to each. Key references are cited for where more complete specification of all model parameters can be found for each model.

2.0 HISTORIC OVERVIEW OF LEAD MODELS

2.1 RABINOWTIZ MODEL

Early lead modeling applications presented lead biokinetics in classical pharmacokinetics terms. Compartments represented kinetically homogeneous pools of lead which might be associated with individual organs or groups of organs. Among the first such models was one proposed by Rabinowitz et al. (1976) based on a study of the kinetics of ingested stable lead isotope tracers and lead balance data in five healthy adult males. The Rabinowitz model includes

three compartments: (1) a central compartment representing blood and other tissues and spaces in rapid equilibrium with blood (e.g., interstitial fluid); (2) a shallow tissue compartment, representing soft tissues and rapidly exchanging pools within the skeleton; and (3) a deep tissue compartment, representing, primarily, slowly exchanging pools of lead within bone. Excretion pathways represented in the model included urinary (from the central compartment) and bile, sweat, hair, and nails (from the shallow tissue compartment). A diagram of the model is shown in Figure 1. The model predicts pseudo-first order half-times for lead of approximately 25, 28, and 10^4 days in the central, shallow tissue, and deep compartments, respectively (these values were calculated based on reported residence times, the reciprocal of the sum of the individual elimination rate constants). The slow kinetics of the deep tissue compartment leads to the prediction that it would contain most of the lead burden after lengthy exposures (e.g., years), consistent with lead measurements made in human autopsy samples (Barry, 1975; Gross et al., 1975; Schroeder and Tipton, 1968). Note that this model did not simulate the distribution of lead within blood, nor did it simulate subcompartments within bone or physiological processes of bone turnover that might affect kinetics of the deep tissue compartment.

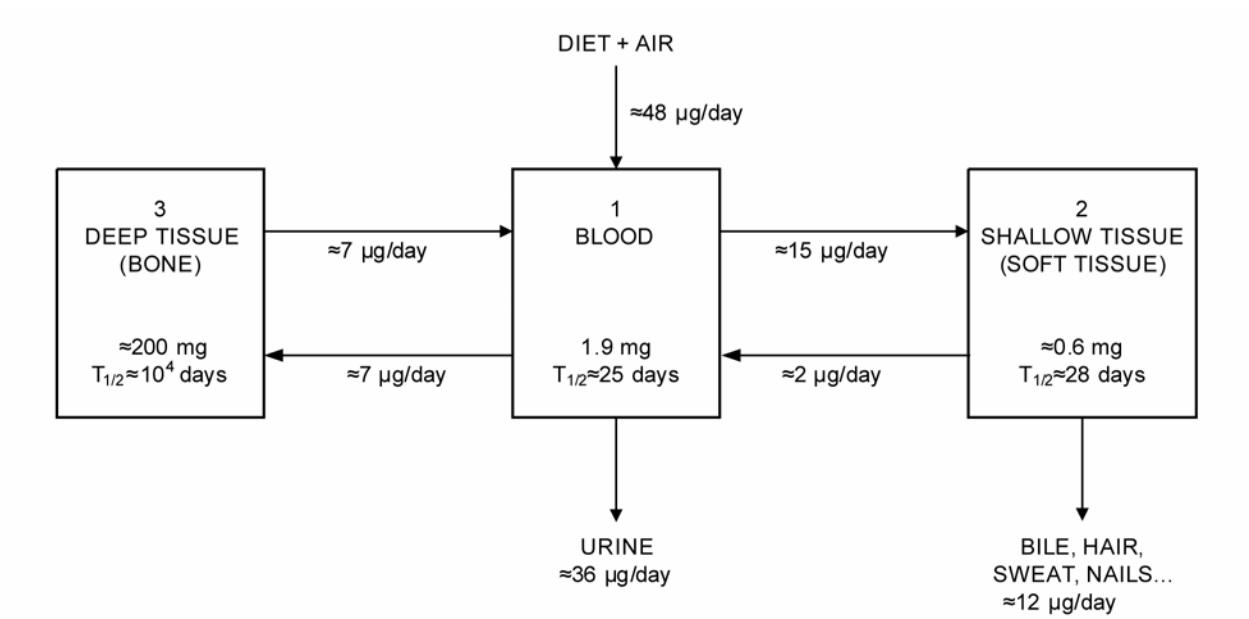


Figure 1. Lead Biokinetics Based on Rabinowitz et al. (1976). Half-times are based on reported residence times for compartments 1, 2, and 3: 36, 40, and 10^4 days, respectively (half-time – 1n(2)/(1/residence time).

2.2 MARCUS MODEL(S)

Marcus (1985b) reanalyzed the data from the Rabinowitz et al. (1976) stable isotope tracer studies and derived an expanded multicompartment kinetic model for lead (Figure 2). The model included separate compartments for cortical (slow, $t_{1/2}$ 1.2H10^4–3.5H10^4 days) and trabecular (fast, $t_{1/2}$ 100–700 days), an approach subsequently adopted in several models (O'Flaherty, 1995; U.S. Environmental Protection Agency, 1994a,b; Leggett, 1993a; O'Flaherty, 1993; Bert et al., 1989). A more complex representation of the lead disposition in bone included explicit simulation of diffusion of lead within the bone volume of the osteon and exchange with blood at the canaliculus (Marcus, 1985a; Figure 3). The bone diffusion model was based on lead kinetics data from studies conducted in dogs. A similar approach to simulating radial diffusion of lead in bone, expanded to include eight concentric diffusion shells, was implemented in O'Flaherty (1995, 1993). Marcus (1985c) also introduced nonlinear kinetics of exchange of lead between plasma and erythrocytes. The blood model included four blood subcompartments: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool (see Figure 4). This model predicted the curvilinear relationship between plasma and blood lead concentrations observed in humans (deSilva, 1981).

2.3 BERT MODEL

Bert et al. (1989) adopted the bone model from Marcus (1985b), in which the bone compartment is subdivided into slow cortical bone and faster trabecular bone compartments (Figure 5). The central compartment (denoted as blood) is assumed to be 1.5 times the volume of whole blood, with the whole blood volume varying in direct proportion with body weight. The model includes a discrete pathway for excretion of unabsorbed lead from the gastrointestinal (GI) tract into feces. Secretion of lead in bile, gastric secretions, and saliva are represented as transfers from the soft tissue compartment to the GI tract. Compartment transfer coefficients were based on average values estimated for four individuals from the Rabinowitz et al. (1976) study. Initial average values for lead in cortical bone for a given age at the start of a simulation were derived from Barry (1975).

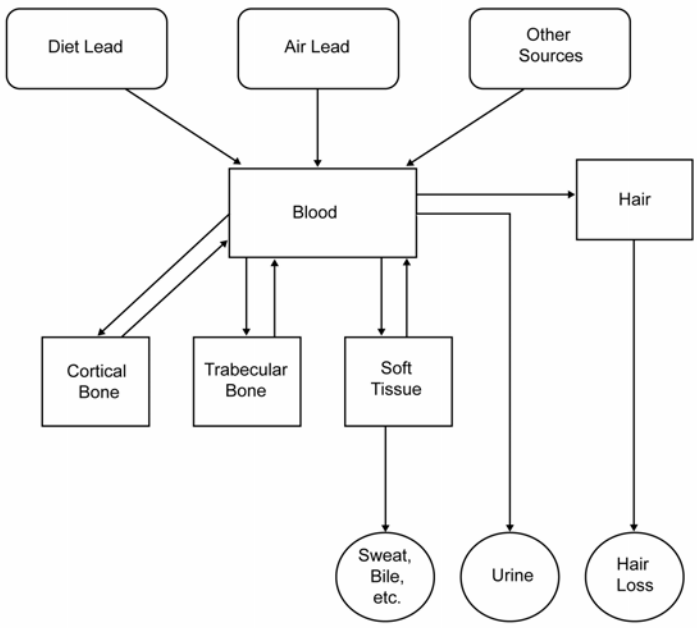


Figure 2. Lead biokinectics based on Marcus (1985b). Bone is represented as a slow cortical compartment ($T_{1/2}$) and a faster, trabecular compartment ($T_{1/2}$).

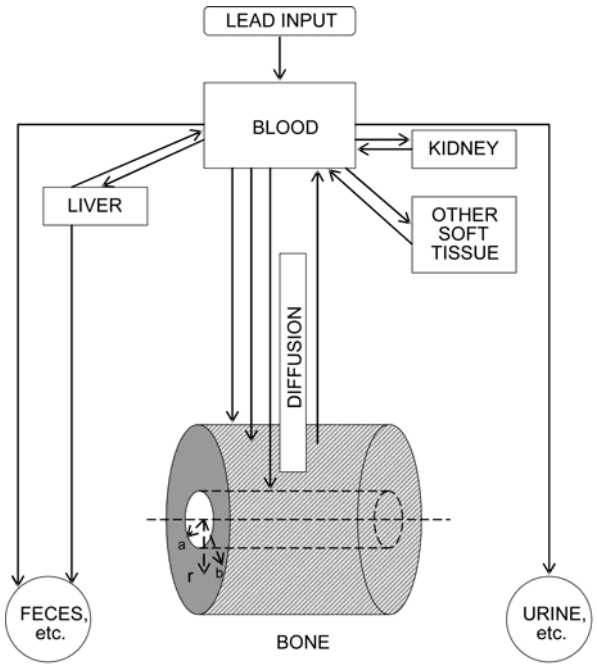


Figure 3. Lead biokinetics based on Marcus (1985a). Bone is represented as an extended cylindrical canalicular territory. The canalicular territory has a radius b and surrounds the canaliculus of radius a. Lead diffuses across radius library, between fluid in the canaliculus (which is in communication with blood in the Haversian canal, not shown) and the bone volume of the canalicular territory.

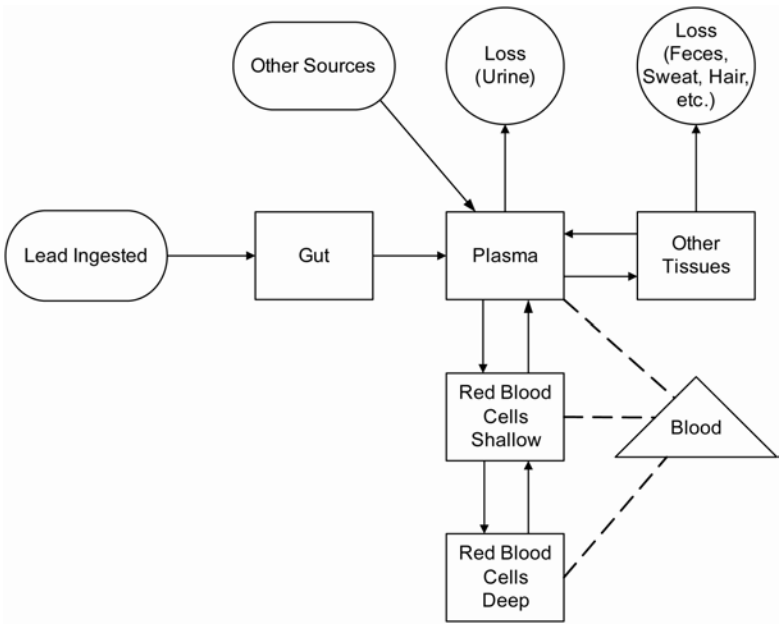


Figure 4. Lead biokinetics based on Marcus (1985c). Blood is represented with a plasma (central exchange) compartment and a red blood cell compartment, the latter having shallow and deep pools.

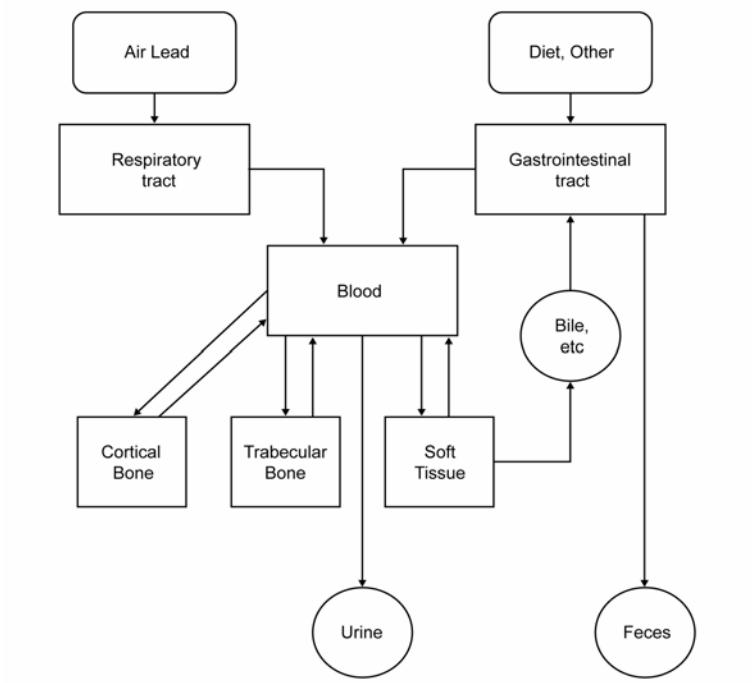


Figure 5. Lead biokinetics based on Bert et al. (1989).

3.0 CONTEMPORARY MODELS

Additional information on lead biokinetics, bone mineral metabolism, and lead exposures has led to further refinements and expansions of the above earlier modeling efforts. Three pharmacokinetic models, in particular, are currently being used or considered for broad application in lead risk assessment: (1) the Integrated Exposure Uptake BioKinetic (IEUBK) model for lead in children developed by EPA (U.S. Environmental Protection Agency, 1994a,b; White et al., 1998); (2) the Leggett model, which simulates lead kinetics from birth through adulthood (Leggett, 1993a); and (3) the O'Flaherty model, which simulates lead kinetics from birth through adulthood (O'Flaherty, 1993, 1995). Of the three approaches, the O'Flaherty model has the fewest lead-specific parameters and relies more extensively on physiologically based parameters to describe volumes, flows, composition, and metabolic activity of blood and bone that determine the disposition of lead in the human body. Both the IEUBK model and the Leggett model are more classical multicompartmental models; that is, the values of the age-specific transfer rate constants for lead are based on kinetics data obtained from studies conducted in animals and humans and may not have precise physiological correlates. Thus, the structure and parameterization of the O'Flaherty model is distinct from both the IEUBK model and Leggett model. All three models represent the rate of uptake of lead (i.e., amount of lead absorbed per unit of time) as relatively simple functions (f) of lead intake:

$$Uptake = Intake \cdot AF \qquad \textbf{(Equation 1)}$$

$$Uptake = Intake \cdot f_{(Intake)} \qquad \textbf{(Equation 2)}$$

Values assigned to AF or other variables in $f(_{Intake})$ are, in general, age-specific and, in some models, environmental medium-specific. However, the models do not modify the representation of uptake as functions of the many other physiologic variables that may affect lead absorption (e.g., nutritional status). While this could be viewed as a limitation of the models, it also represents a limitation of the data available to support more complex representations of lead absorption.

The IEUBK model simulates multimedia exposures, uptake, and kinetics of lead in children ages 0–7 years; the model is not intended for use in predicting lead pharmacokinetics in

adults. The O'Flaherty and Leggett models are lifetime models, which include parameters that simulate uptake and kinetics of lead during infancy, childhood, adolescence, and adulthood. Lead exposure history (e.g., residence-specific environmental lead concentrations, childhood activity patterns) is not readily described by current versions of the O'Flaherty and Leggett models. By contrast, the IEUBK model includes parameters for simulating exposures and uptake to estimate average daily uptake of lead (μg/day) among populations of children potentially exposed via soil and dust ingestion, air inhalation, lead-based paint chip ingestion, tap water ingestion, and diet.

The above three models have been individually calibrated, to varying degrees, against empirical physiological data on animals and humans and data on blood lead concentrations in individuals and/or populations (U.S. Environmental Protection Agency, 1994a,b; Leggett, 1993a; O'Flaherty, 1993). However, risk assessment applications typically require that the models accurately predict blood lead distributions in real populations, in particular those in the "upper tails" (e.g., 95th percentile) of the distributions, when input to the models consists of data that describe site-specific exposure conditions (e.g., environmental lead concentrations, physicochemical properties of soil and dust) (Beck et al., 2001; Griffin et al., 1999a,b). In evaluating models for use in risk assessment, exposure data collected at hazardous waste sites have been used to drive model simulations (Bowers and Mattuck, 2001; Hogan et al., 1998). The exposure module in the IEUBK model makes this type of evaluation feasible.

3.1 INTEGRATED EXPOSURE UPTAKE BIOKINETIC (IEUBK) MODEL FOR LEAD IN CHILDREN

3.1.1 Model Structure

The IEUBK model for lead in children (see Figure 6) is a multicompartmental pharmacokinetics model linked to an exposure and probabilistic model of blood lead concentration distributions in children (U.S. Environmental Protection Agency, 1994a,b; White et al., 1998). The model simulates exposure and biokinetics of lead from birth to age 7 years (84 months) and was developed for predicting average quasi-steady state blood lead concentrations corresponding to daily average exposures, averaged over periods $1 year.

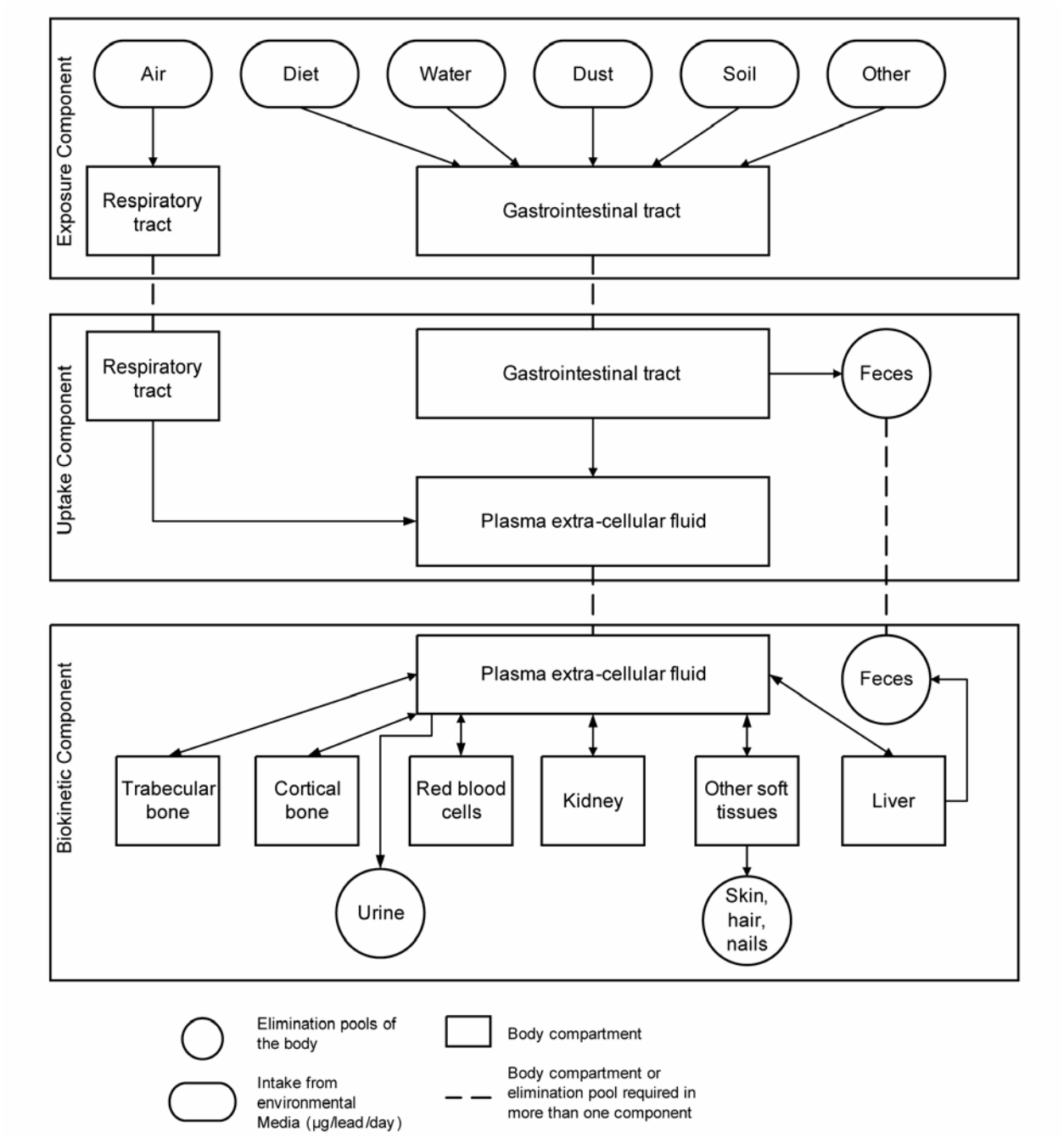


Figure 6. Structure of the Integrated Exposure Uptake Biokinetics Model for Lead in Children (U.S. Environmental Protection Agency, 1994a,b; White et al., 1998).

The model has four major submodels:

- Exposure model, in which average daily intakes of lead (μg/day) are calculated for each inputted exposure concentration (or rates) of lead in air, diet, dust, soil, and water;
- Uptake model, which converts environmental media-specific lead intake rates calculated from the exposure model into a media-specific time-averaged rates of uptake (μg/day) of lead to the central compartment (blood plasma);
- Biokinetic model, which simulates the transfer of absorbed lead between blood and other body tissues, elimination of lead from the body (via urine, feces, skin, hair, and nails), and predicts an average blood lead concentration for the exposure time period of interest; and
- Blood lead probability model, which applies a log-normal distribution (with parameters geometric mean and geometric standard deviation) to predict probabilities for the occurrence of a specified blood lead concentration in a population of similarly exposed children.

Exposure Model. The exposure model simulates intake of lead (μg/day) for inputted exposures to lead in air (μg/m^3), drinking water (μg/L), soil-derived dust (μg/g), and diet (μg/day). The temporal resolution of the exposure model is 1 year; exposure inputs are intended to represent annual averages for an age-year time step (e.g., ages 1, 2, 3...years). Exposure inputs that represent the average daily value for an age-year yield corresponding daily average intakes for the same age-year. The spatial resolution of the exposure model is intended to be a child's residence (e.g., the home and yard). The model accepts inputs for media intake rates (e.g., air volume breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway partitions exposure to outdoor air and indoor air; with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to lead in soil-derived dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates lead absorption for the gastrointestinal tract as the sum of a capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear relationship). These two terms are intended to represent two different mechanisms of lead absorption, an approach that is in accord with limited available data in humans and animals that suggest a capacity limitation to lead absorption (Mushak, 1991). One of the parameters for the capacity-limited absorption process

(that represents that maximum rate of absorption) is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested lead as a function of total lead intake as well as an age-dependence of fractional lead absorption. Absorption fractions are also medium specific (Figure 7). At 30 months of age, at low intakes (<200 μg/day) below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested lead in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, >5000 μg/day). For lead ingested in soil or dust, fractional absorption is 0.35 at low intakes (<200 μg/day) and decreases to 0.09 (intake, >5000 μg/day).

The uptake model assumes that 32% of inhaled lead is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active lead smelter; size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions (Table 1). Lead deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas lead deposited in the nasopharyngeal and tracheobronchial regions is assumed to be transported to the gastrointestinal tract where absorption (approximately 30%) occurs.

Biokinetics Model. The biokinetics model includes a central compartment, plasma and extracellular fluid combined (plasma-ECF), six peripheral body compartments, and three elimination pathways. The temporal resolution of the biokinetics model is 1 month and, as discussed below, parameter values for bone-plasma-ECF exchanges were assigned with the objective of simulating the quasi-steady state condition of months, rather than short-term kinetics of days. The body compartments include kidney, liver, trabecular bone, cortical bone, and other soft tissue. The model simulates growth of the body and tissues, compartment volumes, and lead masses and concentrations in each compartment. Blood lead concentration at birth (neonatal) is assumed to be 0.85 of the maternal blood lead. Neonatal lead masses and concentrations are assigned to other compartments based on a weighted distribution of the neonatal blood lead concentration. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate coefficients. Rate coefficients are allometrically scaled as a power function of body weight ($BW^{0.33}$).

1

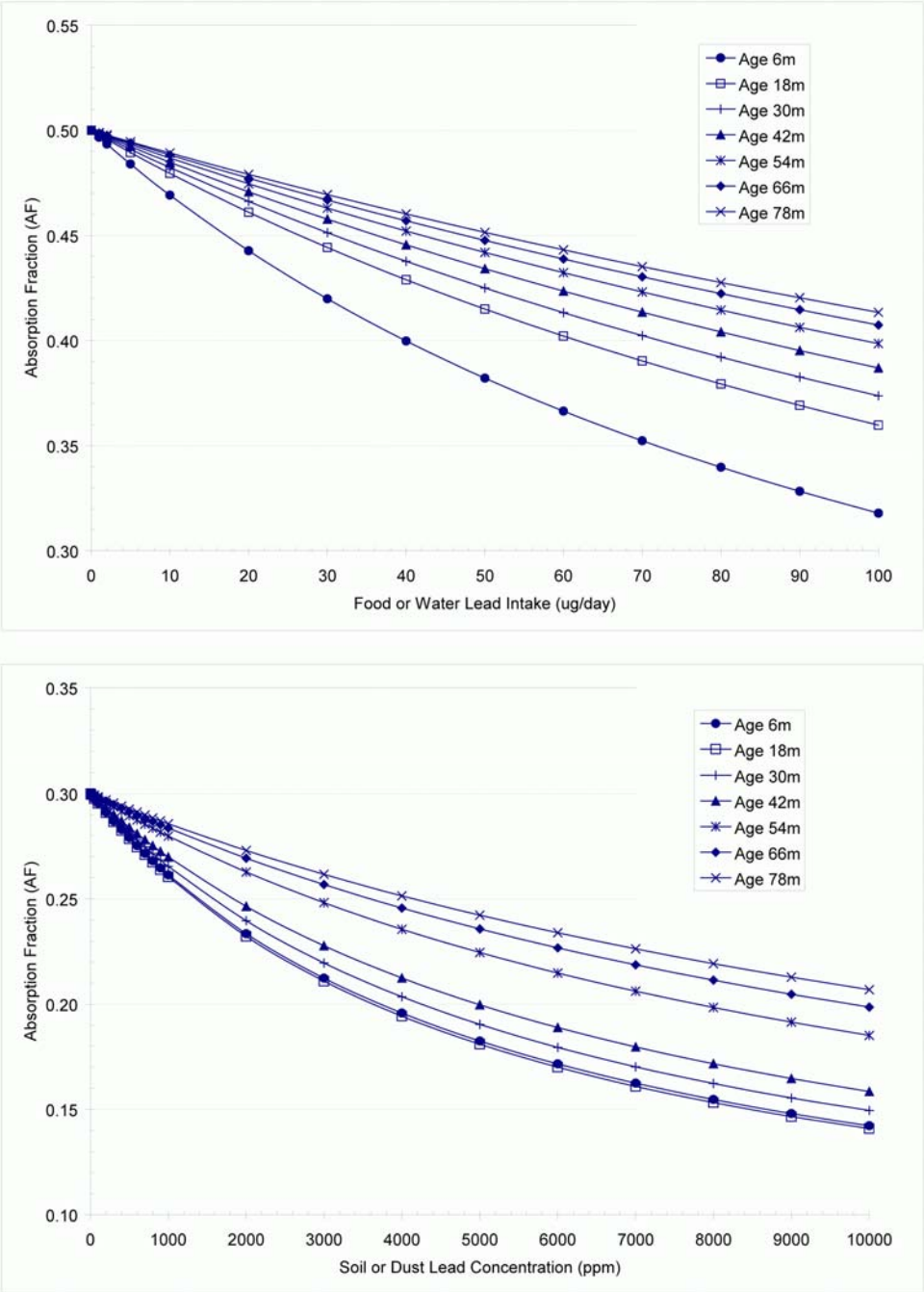


Figure 7. Age-dependency of Absorption Fraction for Ingested Lead in the IEUBK Model for Lead in Children. Absorption fraction for food and water (top panel); soil and dust (bottom panel).

Saturable uptake of lead into erythrocytes is simulated, with a maximum erythrocyte lead concentration of 120 µg/L. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway representing losses from skin, hair and nail, from the other soft tissue compartment.

Bone is simulated as a trabecular bone compartment, representing 20% of bone volume, and a cortical bone compartment, representing 80% of the bone volume. Rate constants for the two bone compartments are assigned values that result in a 4:1 cortical lead:trabceular lead mass ratio, within one biokinetics time step (one month). This is achieved by assigning the two bone compartments identical rate coefficients for transfer of lead from bone to plasma-ECF (half-time 8.5 days, at age 2 years), and *faster* (cortical, half-time 0.0083 days) and *slower* transfer (trabecular, half-time 0.035 days) from the plasma-ECF (cortical:trabecular rate ratio is approximately 4:1). Note, this approach is different from previous and subsequent modeling approaches, in which cortical bone-to-plasma (or blood) transfer is assumed to occur slowly, relative to trabecular bone-to-plasma transfer (Marcus, 1985b; Bert et al., 1989; Leggett, 1993; O'Flaherty, 1993, 1995). For predictions of quasi-steady state conditions, the intended use of the IEUBK Model, the two general approaches can be expected to yield similar distributions of lead between the cortical and trabecular bone compartments.

Blood Lead Probability Model. Inputs to the IEUBK model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central tendency estimate of blood lead concentration for children who might experience the inputted average exposures. However, within a group of similarly exposed children, blood lead concentrations would be expected to vary among children as a result of inter-individual variability in media intakes (e.g., daily average intakes of soil-derived dust, drinking water, or food), absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of blood lead concentration for which the geometric mean (GM) is given by the central tendency blood lead concentration outputted from the biokinetics model, and the geometric standard deviation (GSD) is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given blood lead concentration within a population of similarly exposed children:

P_X = probability of exceeding a blood lead concentration of X µg/dL

P_{10} = probability of exceeding a blood lead concentration of 10 µg/dL

The model can be iterated for varying exposure concentrations (e.g., a series of increasing soil lead concentration) to predict the environmental media concentration that would be associated with a probability of 0.05 for the occurrence of a blood lead concentration exceeding 10 μg/dL ($P_{10} = 0.05$).

3.1.2 Model Calibration and Evaluation

An evaluation of the IEUBK model has been carried out via comparison of model predictions of blood lead concentrations in children with observations from epidemiologic studies of hazardous waste sites (Hogan et al., 1998). Data characterizing residential lead exposures and blood lead concentrations in children living at four Superfund National Priorities List (NPL) sites were collected in a study designed by EPA and the Agency for Toxic Substances and Disease Registry (ATSDR). The residential exposure data were used as inputs to the IEUBK model and the resulting predicted blood lead concentration distributions were compared to the observed distributions in children living at the same residences. The IEUBK model predictions of geometric mean blood lead concentrations for children whose exposures were predominantly from their residence (e.g., who spent no more than 10 hours/week away from home) were within 0.7 μg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have blood lead concentrations exceeding 10 μg/dL were within 4% of the observed percentage at each site. This evaluation provides support for the validity of the IEUBK model for estimating blood lead concentrations in children at sites where their residential exposures can be adequately characterized. Similar empirical comparisons of the IEUBK model have shown that agreement between model predictions and observed blood lead concentrations at specific locations can be influenced by numerous factors, including (a) the extent to which the exposure and blood lead measurements are adequately matched and (b) site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect lead intake or uptake in children (Bowers and Mattuck, 2001; U.S. Environmental Protection Agency, 2001).

3.1.3 Model Applications

Biomarkers Simulated. The IEUBK model computes masses of lead in bone and various soft tissues, and excretion of lead, all of which are used in the computation of blood lead concentration. However, the model was not developed for the purpose of predicting lead masses

in these tissues or in excreta. Blood lead concentration is the only lead biomarker output that is accessible to the IEUBK model user.

Exposure Inputs. The IEUBK model was developed to predict the probability of elevated blood lead concentrations in children exposed to user-specified annual average exposures to lead in air, food, drinking water, soil, and dust. As noted above, the exposure model has an age-year time step (the smallest time interval for a single exposure event) and, therefore, is more suited to applications in which long-term (i.e., >1year) average exposures and quasi-steady state blood lead concentrations are to be simulated. Intermittent exposures (e.g., weekend or seasonal) can be simulated as time-weighted average exposures (U.S. Environmental Protection Agency, 2003a). Shorter-term dynamics of blood lead concentration that may result from exposures that are highly variable on time scales of days or weeks will not be captured with this approach (Lorenzana et al., 2005; Khoury and Diamond, 2003).

Modeling Variability and Uncertainty. As noted above, the IEUBK model uses a lognormal probability model to simulate inter-individual variability in blood lead concentrations attributable to variability in media intakes, absorption, and biokinetics. The model uses a generic default value of 1.6 for the blood lead concentration individual GSD (GSD_i). This value was derived from an analysis of exposure (soil lead)-stratified variability in blood lead concentrations in various cohorts of children (U.S. Environmental Protection Agency, 1994a; White et al., 1998). Griffin et al. (1999b) explores various statistical methods for estimating for calculating GSD_i (regression, box modeling, structural equation modeling).

A variation of the IEUBK model utilizes a Monte Carlo approach to simulate and propagate variability and uncertainty in exposure and absorption through IEUBK model simulation of blood lead concentrations (Goodrum et al., 1996). This extension of the model provides an alterative to the blood lead probability model for incorporating, explicitly, and estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of blood lead concentrations. A quantitative uncertainty analysis of IEUBK model-based estimates of the P_{10} for a smelter site in Utah revealed that parameters specifying soil ingestion rate were a dominant contributor to uncertainty in the P_{10}; however, the contribution of soil ingestion uncertainty, relative to uncertainty in other model parameters (i.e., mean soil lead concentration, absorption fraction) varied across individual locations (Initial Study Zones) at the site (Griffin et al., 1999a).

3.1.4 Validation/Verificaiton of IEUBK Implementation Code

The IEUBK model was initially released to the public in 1994 as a compiled DOS-based C program (IEUBK v99d). This version was subjected to an independent validation and verification study which verified that the code accurately implements the model (Mickle, 1998; Zaragoza and Hogan, 1998). A 32-bit C++ (IEUBKwin32) version of the model is available for download from an EPA website (http://www.epa.gov/superfund/programs/lead/ieubk.htm).

3.2 LEGGETT MODEL

3.2.1 Model Structure

The Leggett model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP), for calculating radiation doses from environmentally important *bone-seeking* radionuclides, including radioisotopes of lead (Leggett, 1993b, 1992a,b). The model has been used to develop cancer risk coefficients for internal radiation exposures to lead and other alkaline earth elements that have biokinetics similar to those of calcium (ICRP, 1993; U.S. Environmental Protection Agency, 1997). The model includes a central exchange compartment, 15 peripheral body compartments, and 3 elimination pools (Figure 8). The central exchange compartment is the *diffusible* pool of lead in plasma. The model simulates a bound pool in plasma (i.e., lead bound to plasma proteins); that has an equilibrium ratio (bound:free) of approximately 5. Transport of lead from plasma to tissues is assumed to follow first-order kinetics. The temporal resolution of the model is 1 day. Transfer rate constants vary with age and blood lead concentration. The latter adjustment accounts for the limited uptake of plasma lead into red blood cells and the resulting shift in distribution of lead from plasma-ECF to other tissues. Above a nonlinear threshold concentration in red blood cells (assumed to be 60 µg/dL), the rate constant for transfer to red blood cells declines and constants for all other tissues increase proportionally (Leggett, 1993a). This replicates the nonlinear relationship between plasma and red blood observed in humans (Smith et al., 2002; Manton et al., 2001; Bergdahl et al., 1999, 1998, 1997). The model simulates blood volume as an age-dependent function, which allows simulation of plasma and blood lead concentrations. However, volumes of other tissues are not simulates; therefore, only lead masses in these tissues, but not concentrations, are simulated.

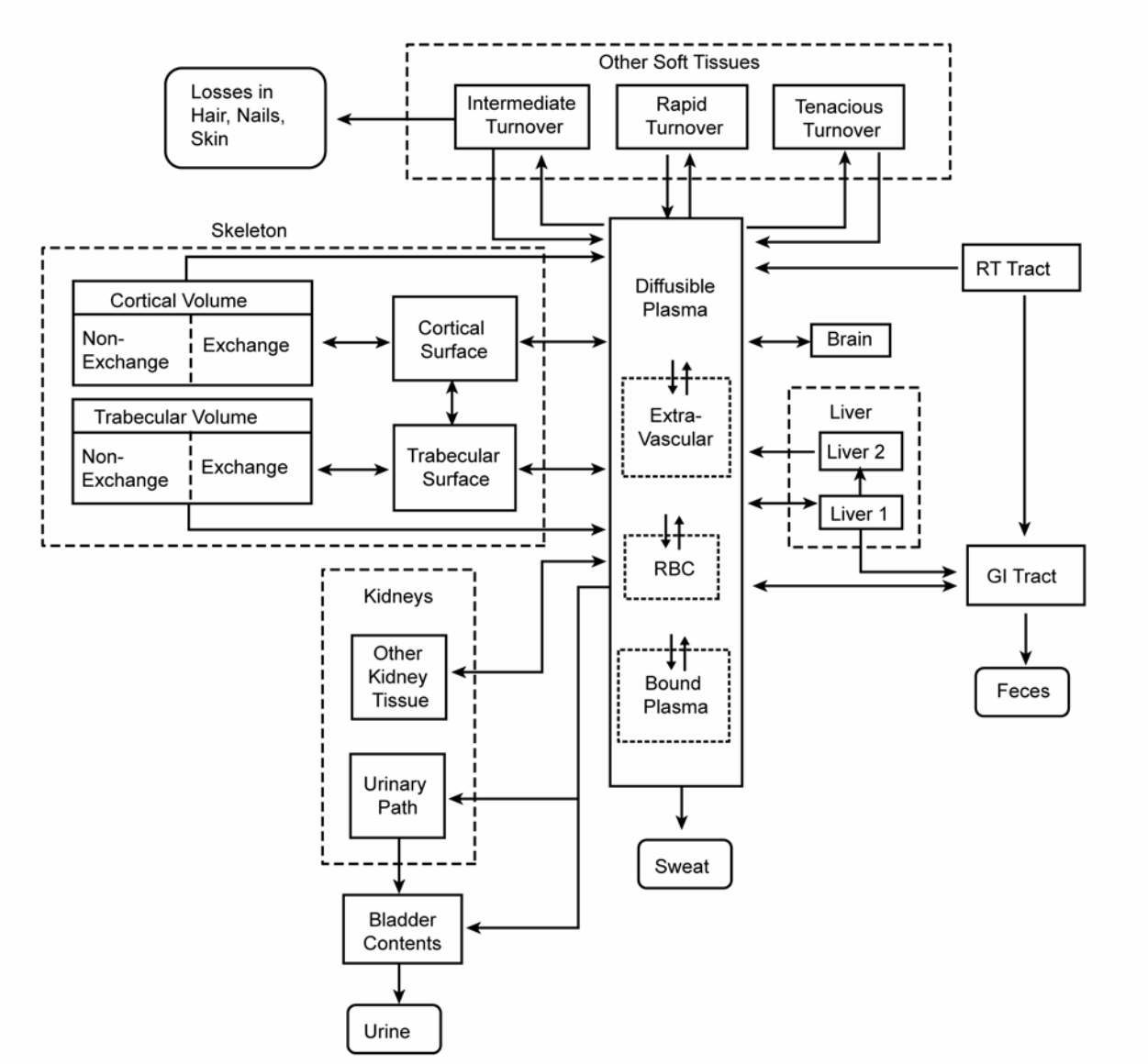


Figure 8. Structure of the Leggett Lead Biokinetic Model (Leggett, 1993a). The central exchange compartment is *diffusible* plasma. Bone is represented as having surface (which rapidly exchanges with plasma) and volume compartments; the latter stimulates slow exchange with the surface and slow return of lead to the plasma from bone resorption.

Unidirectional, first-order transfer coefficients (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. The total transfer rate from diffusible plasma to all destinations (TPALL) combined is assumed to be 2000 day^{-1}, based on isotope tracer studies in humans receiving lead

via injection or inhalation. Values for transfer coefficients from plasma to tissues and tissue compartments are based on measured deposition fractions (DF) or instantaneous fractional outflows of lead between tissue compartments (Leggett, 1993a), where the transfer coefficient to a specific tissue or compartment (TP_i) is given by:

$$TP_i = DF_i \cdot TPALL \qquad \textbf{(Equation 3)}$$

This approach establishes mass balance with respect to the transfer rates from plasma:

$$\sum TP_i = TPALL \qquad \textbf{(Equation 4)}$$

The model simulates both rapid exchange of lead with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchanges with lead in plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Lead enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the plasma only when bone is resorbed. Transfers from plasma to bone surface, return from bone surface to plasma, and bone surface to exchangeable bone volume are assumed to be relatively fast processes (adult $t_{1/2}$ = 3.85, 1.4, and 1.4 days, respectively). Return of lead from the exchangeable bone volume is slower (adult $t_{1/2}$ = 30 days); however, the dominant transfer process determining long-term accrual of bone lead burden are slow rate coefficients for transfer of lead from the nonexchangeable pools of trabecular and cortical bone to plasma (adult $t_{1/2}$ = 3.8 and 23 years, respectively). Bone transfer coefficients vary with age (faster in children) to reflect the age-dependence of bone turnover. The slow, nonexchangeable, bone volume compartment is much more labile in infants and children than in adults (e.g., cortical $t_{1/2}$ = 68 days at birth and 1354 days at age 15 years; trabecular $t_{1/2}$ = 68 days at birth and 725 days at age 15 years). Other physiological states (such as pregnancy and menopause) that affect bone turnover and, therefore, bone lead kinetics are not simulated, although such states could be accommodated with adjustments to tissue (e.g., bone) transfer coefficients.

The liver is simulated as two compartments: one compartment has a relatively short removal half-life (days) for transfers to plasma and to the small intestine by biliary secretion (adult $t_{1/2}$ = 10 days); a second compartment simulates a more gradual transfer to plasma of approximately 10% of lead uptake in liver (adult $t_{1/2}$ = 365 days). The kidney is simulated as two compartments, one that exchanges slowly with blood plasma and accounts for lead accumulation kidney tissue (adult $t_{1/2}$ = 365 days) and a second compartment that receives lead from blood plasma and rapidly transfers lead to urine (adult $t_{1/2}$ = 5 days), with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates, without specific physiologic correlates (adult $t_{1/2}$ = 0.3, 100, and 1824 days, respectively). Other excretory pathways (hair nails and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett model simulates lead intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled lead is deposited and absorbed with half-times of 1, 3, 10, and 48 hours, respectively. Four percent of the inhaled lead is assumed to be transferred to the GI tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron lead-bearing particles (Morrow et al., 1980; Chamberlain et al., 1978; Wells et al., 1975; Hursh and Mercer, 1970; Hursh et al., 1969). These assumptions would not necessarily apply to exposures to larger airborne particles. Absorption of ingested lead simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years) and to 0.15 after age 25 years (Figure 9).

3.2.2 Model Calibration and Evaluation

Leggett (1993a) and Pounds and Leggett (1998) describe various qualitative empirical comparisons of model predictions against observations made on adults (e.g., Skerfving et al., 1985; Campbell et al., 1984; Manton and Cook, 1984; Barry, 1981; deSilva, 1981; Chamberlain et al., 1978; Rabinowtiz et al., 1976; Barry, 1975; Griffin et al., 1975; Gross et al., 1975; Hursh and Mercer, 1970; Hursh et al., 1969; Schroeder and Tipton, 1968). Age-specific changes in parameter values that specify the biokinetics of lead in children were assigned values that

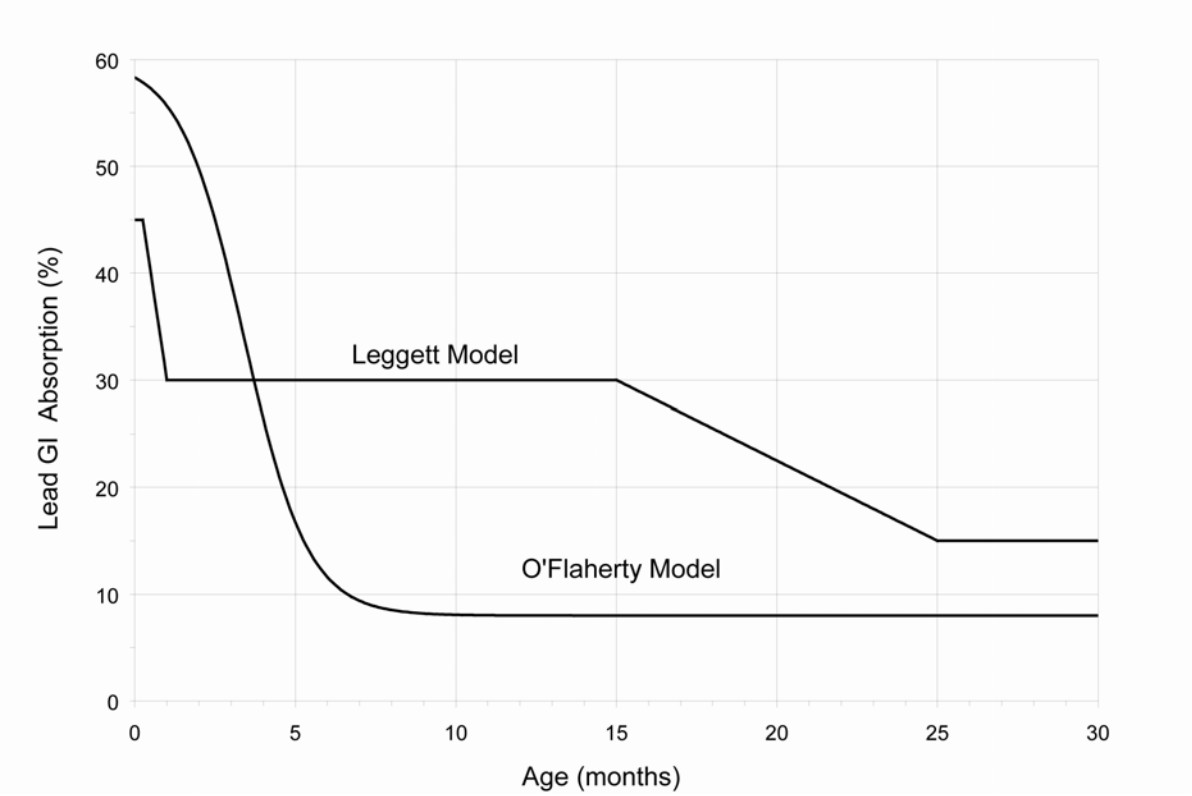


Figure 9. Age-dependency of Absorption Fraction for Ingested Lead in the Leggett and O'Flaherty models.

resulted in agreement between predicted age-specific lead distribution (fraction of body burden) in blood, bone, brain, kidney, liver, and other tissues, and reported post-mortem values (Schroeder and Tipton, 1968; Barry, 1975, Gross et al. 1975; Barry, 1981).

3.2.3 Model Applications

Biomarkers Simulated. The Leggett model simulates the concentrations of lead in blood and plasma, lead masses of lead in bone and various soft tissues, and excretion of lead in urine that correspond to lifetime exposures (in terms of daily lead intakes).

Exposure Inputs. The model does not contain a detailed exposure module (although it can be linked to an exposure model); lead exposure estimates are incorporated into the simulations as age-specific point estimates of average daily intake (µg/day) from ingestion, inhalation, or injection. The model operates with a lead intake time step of 1 day, which allows simulation of

rapidly changing (i.e., daily) intermittent exposures (Lorenzana et al., 2005; Khoury and Diamond, 2003). Assumptions of blood lead concentrations at birth can also be introduced into the simulations, from which levels in other tissue in the first time step after birth are calculated.

Dose reconstruction is possible with this model, since intakes, and corresponding tissue lead burdens accrued at any period in the lifetime, prior to an exposure event of interest, can be simulated. Pounds and Leggett (1998) illustrate this in a study of a childhood lead poisoning case, in which the exposure is followed by chelation. Chelation was simulated as a short-duration increase in the plasma lead deposition fraction to urine, with corresponding proportional decreases in deposition fractions to other tissues.

3.2.4 Validation/Verification of Leggett Model Implementation Code

The Leggett model was initially developed as a Fortran code, which can be run without compiling from various platforms, including DOS and Windows (see Pounds and Leggett, 1998 for a description). A version compiled in Advanced Continuous Simulation Language (ACSL) has also been reported (Lorenzana et al., 2005). Confirmation of the Leggett model code was carried out by a panel of experts (ICRP, 1990, 1993).

3.3 O'FLAHERTY MODEL

3.3.1 Model Structure

The O'Flaherty model simulates lead exposure, uptake, and disposition in humans, from birth through adulthood (O'Flaherty, 1995, 1993). Figure 10 shows a conceptualized representation of the model. Important novel features of the O'Flaherty model are the simulation of growth, bone formation, and resorption. Growth curve is simulated with a logistic expression relating body weight to age in males or females. The full expression relating weight to age has five parameters (constants), so that it can readily be adapted to fit a range of standardized growth curves for males and females. Tissue growth and volumes are linked to body weight; this provides explicit modeling of concentrations of lead in all tissues simulated. Other physiologic functions (e.g., bone formation) are linked to body weight, age, or to both. The model can be implemented with a temporal resolution of 1 day; however, as originally configured, the rate parameters are expressed in time units of years.

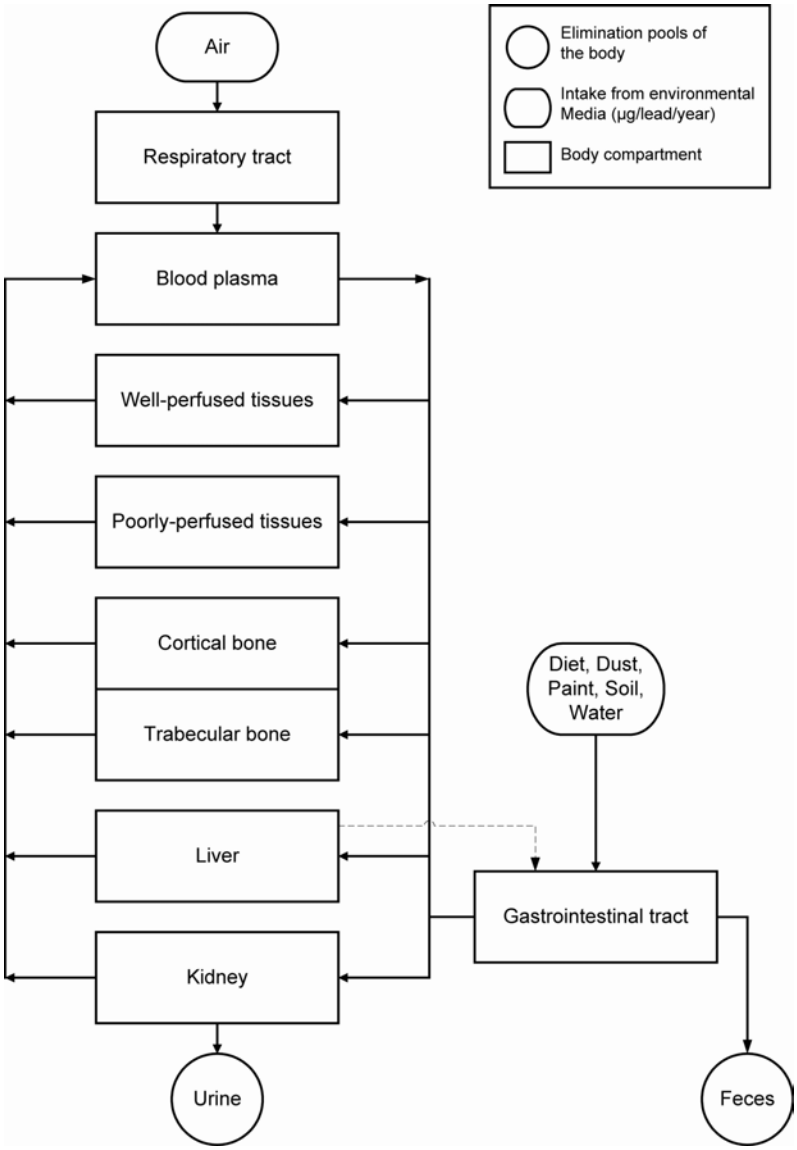
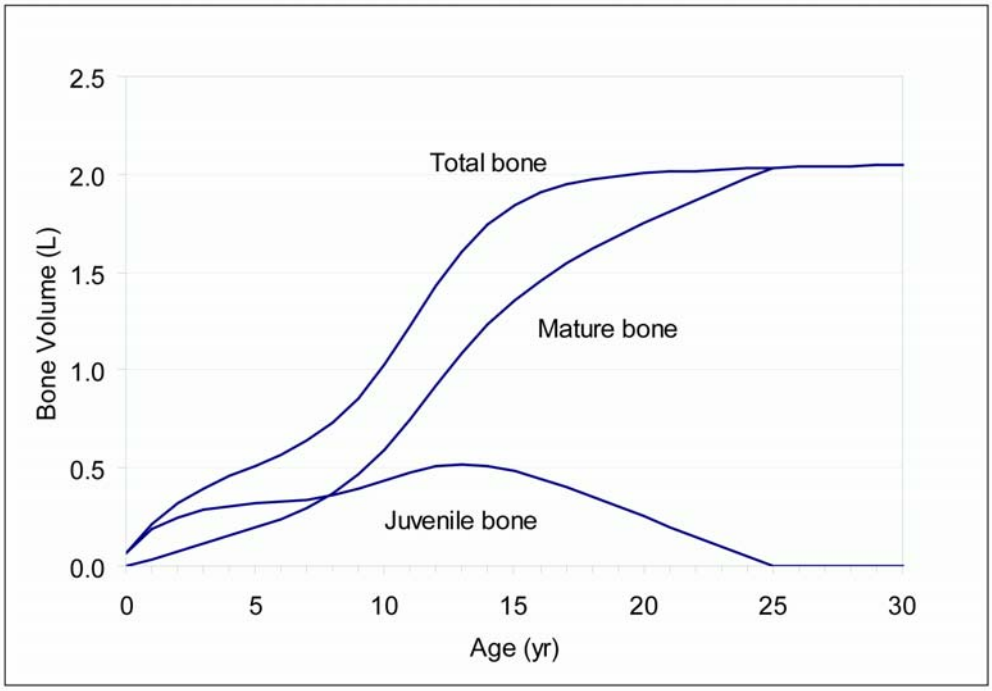


Figure 10. Structure of the O'Flaherty lead exposure biokinetics model (O'Flaherty, 1993, 1995). The central exchange compartment is *diffusible* plasma. Lead distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone. The model simulates tissue growth with age, including growth and resorption of bone mineral.

Rates of bone formation and resorption are simulated as age-dependent functions (Figure 11). Uptake and release of lead from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively; this establishes the



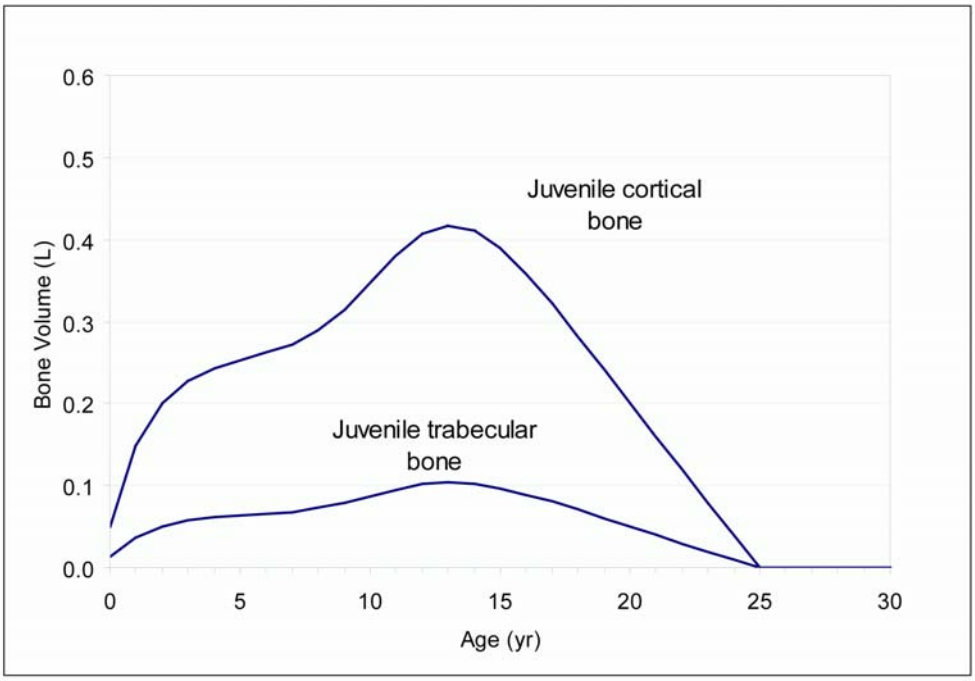


Figure 11. Bone Growth as Simulated by the O'Flaherty Lead Exposure Biokinetics Model (OFlaherty, 1993, 1995). The model simulates an age-related transition from juvenile bone, in which bone turn-over (formation and resorption) rates are relatively high, to mature bone, in which turn-over is relatively slow. Cortical bone comprises approximately 80% of total bone volume.

age-dependence to the lead kinetics in and out of bone. Lead exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). The model simulates an age-related transition from immature bone, in which bone turnover (formation and resorption) rates are relatively high, to mature bone, in which turnover is relatively slow. Changes in bone mineral turnover associated with senescence (e.g., postmenopausal osteoporosis) are not represented in the model. Metabolically active regions of bone, in which lead uptake and loss is dominated by bone formation and loss, a region of slow kinetics in mature cortical bone is also simulated, in which lead uptake and release to blood occur by heteroionic exchange with other minerals (e.g., calcium). Heteroionic exchange is simulated as a radial diffusion in bone volume of the osteon. All three processes are linked to body weight, or the rate of change of weight with age. This approach allows for explicit simulation of the effects of bone formation (e.g., growth) and loss, changes in bone volume, and bone maturation on lead uptake and release from bone. Exchanges of lead between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of lead in erythrocytes (maximum capacity is 2.7 mg Pb/L cell volume); this replicates the curvilinear relationship between plasma and erythrocyte lead concentrations observed in humans (Smith et al., 2002; Manton et al., 2001; Bergdahl et al., 1999, 1998, 1997). Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of age-dependent glomerular filtration rate. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively.

The O'Flaherty model simulates lead intake from inhalation and ingestion. Inhalation rates are age-dependent. Absorption of inhaled lead is simulated as a fraction (0.5) of the amount inhaled, and is independent of age. Gastro-intestinal absorption of lead in diet and drinking water is simulated as an age-dependent fraction, declining from 0.58 of the ingestion rate at birth to 0.08 after age 8 years (Figure 9). These values can be factored to account for relative bioavailability when applied to absorption of lead ingested in dust or soil.

3.3.2 Model Calibration and Evaluation

The O'Flaherty model was initially calibrated to predict blood, bone, and tissue lead concentrations in rats (O'Flaherty, 1991a,b,c), and subsequently modified to reflect anatomical

and physiological characteristics in children (O'Flaherty, 1995), adults (O'Flaherty, 1993), and Cynomolgus monkeys (*M. fasicularis*) (O'Flaherty et al., 1998a). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. Empirical comparisons (largely qualitative) of model predictions against observations made in adults (e.g., Van de Vyver et al., 1988; Kehoe, 1987; Marcus, 1985c; Manton and Malloy, 1983; Sherlock et al., 1982; deSilva, 1981; Moore et al., 1977; Cools et al., 1976; Rabinowitz et al., 1976; Azar et al., 1975) are provided in O'Flaherty (1993); and comparisons against observations made in children (e.g., Sherlock and Quinn, 1986; Bornschein et al., 1985; Chisolm et al., 1985; Lacey et al., 1985) are described in O'Flaherty (1995). Additional discussion of model evaluation can be found in O'Flaherty (1998).

3.3.3 Model Applications

Biomarkers Simulated. The O'Flaherty model simulates lead concentrations in blood and plasma, bone, and various soft tissues, and excretion of lead in urine that correspond to lifetime exposures (in terms of daily lead intakes). The model predicts blood lead concentrations for a broad age range, including infants, children, and adults, which allows for simulated dose reconstruction, since intakes and corresponding tissue lead burdens accrued at any period in the lifetime, prior to an exposure event of interest, can be simulated. Physiological states (such as pregnancy and menopause) that affect bone turnover and, therefore, bone lead kinetics are not simulated, although such states could be accommodated with adjustments to the physiological bone formation and resorption models.

Exposure Inputs. The O'Flaherty model simulates lead intake from inhalation and ingestion. The model simulates ingestion exposures from infant formula, soil and dust ingestion, and drinking water ingestion. Rates of soil and dust ingestion are age-dependent, increasing to approximately 130 mg/day at age 2 years, and declining to <1 mg/day after age 10 years. However, the ACSL implementation code allows constructions of simulations with an exposure time step as small as 1 day, which would allow simulation of rapidly changing intermittent exposures (e.g., an acute exposure event).

Modeling Variability and Uncertainty. The O'Flaherty model, as described in O'Flaherty (1995, 1993), utilizes point estimates for parameter values and yields point estimates as output; however, a subsequent elaboration of the model has been reported that utilized a Monte Carlo

approach to simulate variability in exposure, absorption, and erythrocyte lead binding capacity (Beck et al., 2001). This approach could be used to predict the probability that children exposed to lead in environmental media will have blood lead concentrations exceeding a health-based level of concern (e.g., 10 μg/dL).

3.3.4 Verification/Validation of O'Flaherty Model Implementation Code

The O'Flaherty model was developed in ACSL. A compiled C program has also been developed (personal communication, E. O'Flaherty). The extent to which code verification and validation studies have been conducted for the O'Flaherty model is unclear at this time. However, analogs of certain components of the O'Flaherty model (e.g., parameters related to bone growth) have been incorporated into the EPA All Ages Lead Model as a potential option for evaluation.

3.4 EPA ALL AGES LEAD MODEL

3.4.1 Model Structure

The EPA All Ages Lead Model (AALM) currently under development simulates lifetime lead exposures and biokinetics in humans. The model simulates exposure and biokinetics of lead from birth to age 90 years and is expected to incorporate, at some near-future time, a pregnancy model that simulates transplacental transfer of lead from the mother to the fetus.

Exposure Model. The exposure component of the AALM incorporates and extends the exposure component of the IEUBK model. The AALM exposure model defines a receptor in terms of age, sex, date of birth, and activity pattern profile. The age specification establishes age ranges (e.g., infant, child, adolescent, adult, etc.) for which various exposure (and biokinetic) parameter values can be applied. This provides a means for varying parameter values with age. The sex specification links the receptor to the appropriate growth algorithm (see below). The date specification links the receptor to historical exposure levels (e.g., air, diet) for the selected age range. The activity pattern specification sets the relative amount of time the receptor spends in various exposure settings (e.g., residential, school, recreational, occupational) for which exposure concentrations can be specified. Parameters that can be set include sleep (hours/day),

hours/week spent at the residential, school, occupational, and recreational settings, and fraction of time spent indoors at each setting.

The exposure model simulates an average daily intake of lead (µg/day) based on user defined exposure levels in air, diet, dust (ingestion and dermal), drinking water, soil, or paint chips (pica scenario). The air exposure model allows the user to define exposure levels in terms of outdoor air, and indoor residential, school, or occupational air, all as a fraction of the outdoor air concentration. Ventilation rates (i.e., m^3 air inhaled/day) can be set for each exposure scenario (e.g., residential, recreational, occupational). The model calculates a weighted average amount of lead inhaled (µg/day) for the combined scenarios and passes this intake rate to the biokinetic model (see below).

The diet exposure model accepts inputted values (current or historical) for lead levels (µg/g) in market basket fruits, vegetables, meat and fish; recreational- or subsistence-harvested fish and meat; and corresponding food intakes for each food type (µg food/day). Lead intakes from drinking water are calculated from inputted concentrations (µg/L) in tap water (first draw and/or flushed), fountain water, and/or bottled water; and corresponding source water intake rates (L/day).

The dust exposure model accepts inputted values for dust concentrations (µg/g) in various settings (e.g., residential, school, recreational, occupational) or dust loadings (µg/m^2) and corresponding dust ingestion rates (µg dust/day) or contact rates (m^2/day, the lead ingestion rate for a given loading is calculated as the product of loading and contact rate. Dermal exposure to lead in dust can also be simulated with inputted values for dust lead level (µg/g), dust loading on the skin (mg/cm^2), and skin exposure rate (cm^2/day). Pica ingestion or soil and/or paint chips can be simulated with inputted values for lead levels in soil (µg/g) or paint (µg/cm^2) and corresponding pica ingestion rates (g soil/day, cm^2 paint/day).

Calculated lead intakes for each exposure pathway are summed to calculate total intake (µg/day) to the respiratory tract, gastrointestinal tract, and dermal absorption pathway, respectively (see description of biokinetics model). The exposure model time step is 1 day (the smallest time interval for a single exposure event).

Biokinetics Model. The biokinetics model for the AALM is based on (Leggett, 1993a) with the following modifications and enhancements (see Figure 8 for diagram of the Leggett model):

1. A simulation of dermal absorption is implemented that calculates transfer of lead from the skin to the central compartment, as a function of rate of dermal contact with lead (μg/day) and a dermal absorption fraction.
2. Male and female growth algorithms for body weight, soft tissues, and cortical and trabecular bone are included, based on O'Flaherty (1995, 1993). This allows simulation of tissue growth and volumes, and concentrations of lead in all tissues simulated.
3. A simulation of maternal-fetal transfer is being incorporated that will simulate lead levels in fetal tissues, which also establishes blood and tissue lead levels for any ensuing post-natal simulation. This feature provides a means for multi-generation simulation of exposure and lead biokinetics.

3.4.2 Model Calibration and Evaluation

The AALM currently under development incorporates key exposure model features from the IEUBK model (plus age-related extensions) and key biokinetic model features from the Leggett model. To the extent that model validation evaluations have indicated reasonably good matches between IEUBK or Leggett model outputs and empirical observations, the same can likely be expected for the AALM.

3.4.3 Model Applications

Biomarkers Simulated. The AALM simulates the concentrations of lead in blood and plasma, bone, and various soft tissues, and excretion of lead in urine that correspond to lifetime exposures (in terms of daily lead intakes). Algorithms for transplacental transfer of lead are also soon to be incorporated, so that concentrations of lead in fetal tissues resulting from maternal-lead exposures can be simulated.

Exposure Inputs. The model simulates daily lead intakes based on inputted current or historic levels of lead in environmental media (e.g., air, diet, drinking water, dust, soil) in various exposure settings (e.g., residential, school, recreational, occupational). The model operates with a lead intake time step of 1 day, which allows simulation of rapidly changing (i.e., daily) intermittent exposures.

Multi-generation dose reconstruction will be possible with this model, since intakes, and corresponding lead burdens accrued at any period in the lifetime prior to an exposure event of interest, can be simulated, including lead burdens received *in utero*.

3.4.4 Validation/Verification of AALM Implementation Code

The AALM is implemented as a compiled C++ program. Code verification and validation is being performed with each iteration of the model code as part of the model development and is tracked by a formal tracking process.

4.0 MODEL COMPARISONS

Table 1 summarizes the major features of various mechanistic models of human exposure that predict tissue lead burdens. These include the currently available models discussed above (IEUBK, AALM, Leggett, O'Flaherty).

Lead uptake-blood lead concentration relationships in children, predicted by the IEUBK Leggett and O'Flaherty models are shown in Figure 12. In the range of uptakes shown (0.1-100 µg lead absorbed/day), non-linearity of the relationship is apparent in the Leggett and O'Flaherty models simulations. This reflects assumptions in each model regarding the limited capacity of red blood cells to take up lead. Regression slopes (µg/dL blood per µg/day uptake) for the predictions #10 µg/dL are: Leggett model: 0.88; IEUBK model: 0.36; O'Flaherty model: 0.29.

The models predict an average blood lead concentration of 10 µg/dL for the age range 2–3 years, in association with average lead uptakes (µg/day) for the same period of approximately: Leggett model: 12; IEUBK model: 29; O'Flaherty model: 36.

A similar comparison of uptake-blood lead concentration relationships predicted in adults is shown in Figure 13. Regression slopes for adults predicted by the Leggett and O'Flaherty models (at blood lead concentrations #10 µg/dL) are more similar for adults than for children: Leggett model: 0.54; O'Flaherty model: 0.72. The models predict an average blood lead concentration of 10 µg/dL for the age range 31–32 years, in association with average lead uptakes, for the same period, of approximately 18 and 13 µg/day, Leggett and O'Flaherty models, respectively.

Comparisons of predicted bone and soft tissue lead burdens are shown in Figure 14. Leggett and O'Flaherty models predict bone lead burdens. Both the Leggett and O'Flaherty models predict a bone lead burden in adults of approximately 90 and 98% of total body burden, respectively. Regression slopes (mg lead in bone per µg uptake/day) are 1.2 for the Leggett model and 2.1 for the O'Flaherty model.

Table 1. Summary of Mechanistic Models of Human Exposure Biokinetics that Predict Tissue Distribution of Lead

Model	Age Range	Exposure Pathways	Exposure Time Step	Biokinetics Simulation	Biomarkers Predicted	Variability and Uncertainty Simulation
U.S. Environmental Protection Agency IEUBK Model White et al. (1998)	0-7 yr	Air Diet Soil/dust Water Other	1 year	Multi-compartmental	Blood lead	Variability: blood lead GSD_i Variability/uncertainty: MCA (Griffin et al., 1999b)
U.S. Environmental Protection Agency AALM	0-90 yr	Air Diet Soil/dust Water Other	1 day	Multi-compartmental	Blood Bone Brain Fetus Kidney Liver Urine	NA
Leggett (1993)	0-Adult	Intakes (inhaled, ingested, injected)	1 day	Multi-compartmental	Blood Bone Brain Kidney Liver Urine	NA
O'Flaherty (1993, 1995)	0-Adult	Air Diet Soil/dust Water Other	1 year (code supports 1 day)	Multi-compartmental	Blood Bone Brain Kidney Liver Urine	Beck et al., (2001)

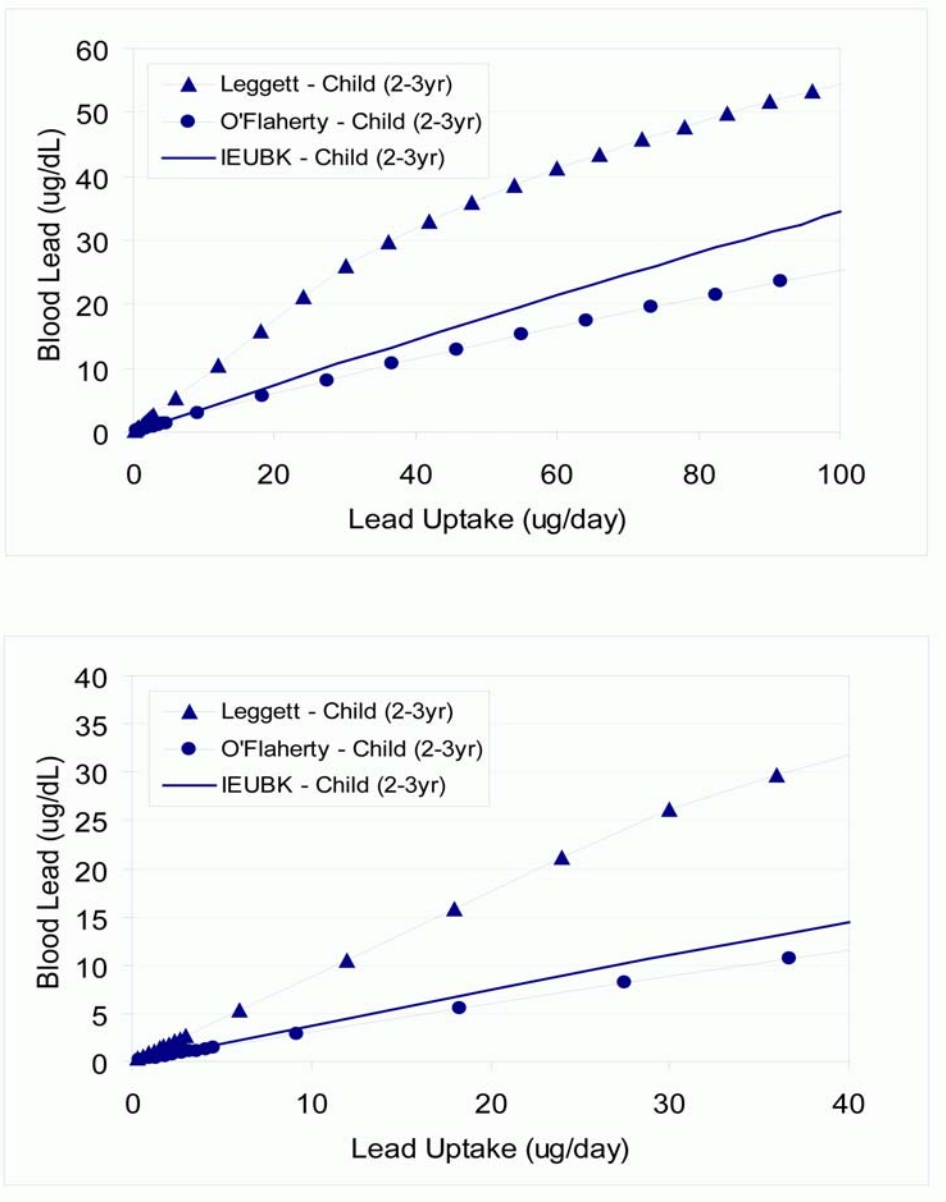


Figure 12. Model Comparison of Predicted Lead Uptake-Blood Lead Concentration Relationship in Children. In the range of uptakes shown, the non-linearity of the relationship is apparent in the Leggett and O'Flaherty Models simulations, reflecting the simulation of the limited capacity of red blood cells to take up lead. Regression slopes (µg /dL blood per µg/day uptake) for the predictions #10µg/dL are: Leggett Model: 0.88; IEUBK Model: 0.36; O'Flaherty Model: 0.29.

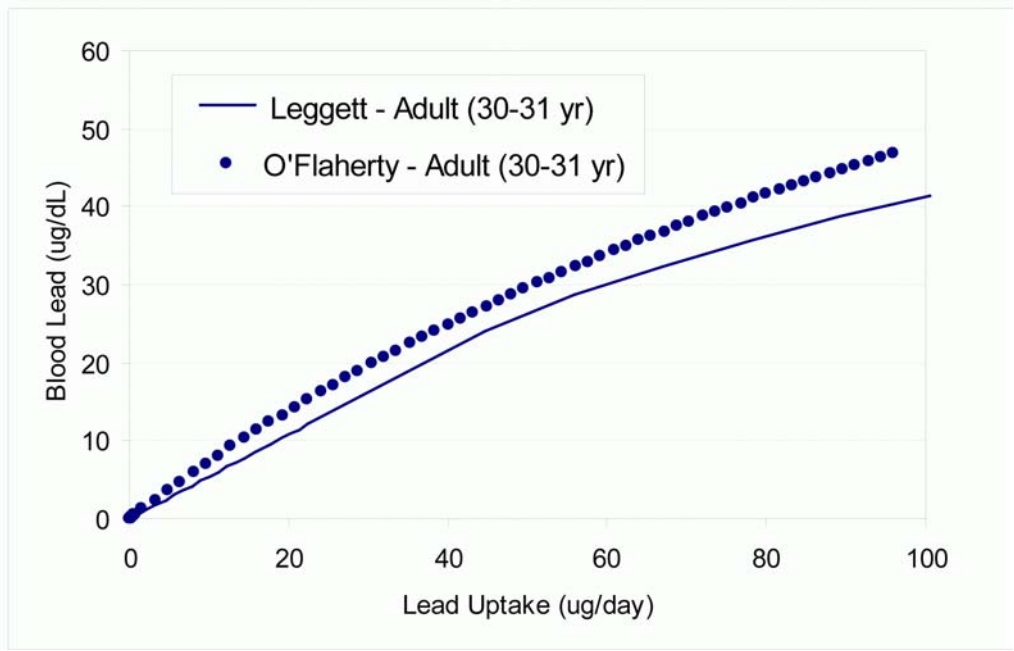


Figure 13. Model Comparison of Predicted Lead Uptake-Blood Lead Concentration Relationships in Adults. The non-linearity of the relationship is apparent in both the Leggett and O'Flaherty Models. Regression slopes (µg /dL blood per µg/day uptake) for the predictions #10µg/dL are: Leggett Model: 0.54; O'Flaherty Model: 0.72.

Figures 15 and 16 compare model predictions for blood lead concentration for hypothetical childhood or adult exposures. The hypothetical child (Figure 15) has a blood lead concentration of 2 µg/dL at age 2 years, and then experiences a 1-year exposure to 100 µg Pb/day. All three models (Leggett, IEUBK, and O'Flaherty) predict a similar temporal pattern of increase in blood lead concentration at the start of exposure, attainment of a quasi-steady state, followed by a decrease in blood lead concentration, with fast and slower phases of the decline in blood lead concentration after the exposure ceases. However, differences in the predicted kinetics of the blood lead changes and the predicted quasi-steady state blood lead concentrations are evident. For this hypothetical scenario, the Leggett model predicts the highest blood lead concentrations (23 µg/dL) compared to the O'Flaherty model (12 µg/dL) and IEUBK model (10 µg/dL). These differences are not solely the result of different values for the absorption fraction in 2–3 year old children (Figure 9): Leggett model, 30%; O'Flaherty model; 45% (descending from 49% at age 2 years to 39% at age 3 years); IEUBK model, 25% (at a soil lead

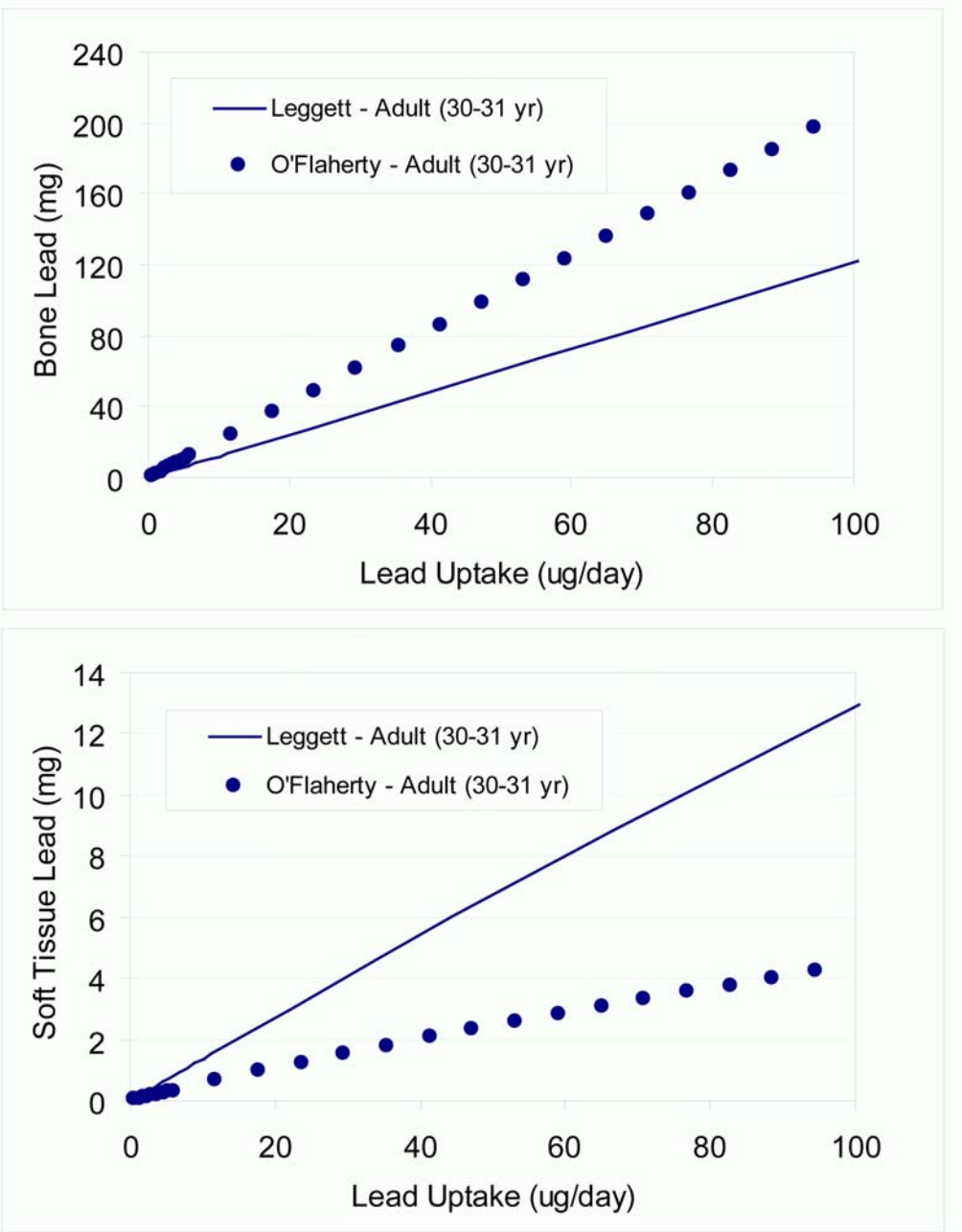


Figure 14. Model Comparison of Predicted Lead Uptake-Bone and Soft Tissue Lead Burden Relationship in Adults. Both the Leggett and O'Flaherty Models predict a bone lead burden of approximately 90% and 98% of total body burden, respectively. Soft tissue burdens shown include blood. Regression slopes (mg Pb per µg uptake/day) for uptake-bone burden relationship is: Legget: 1.2; O'Flaherty Model: 2.1.

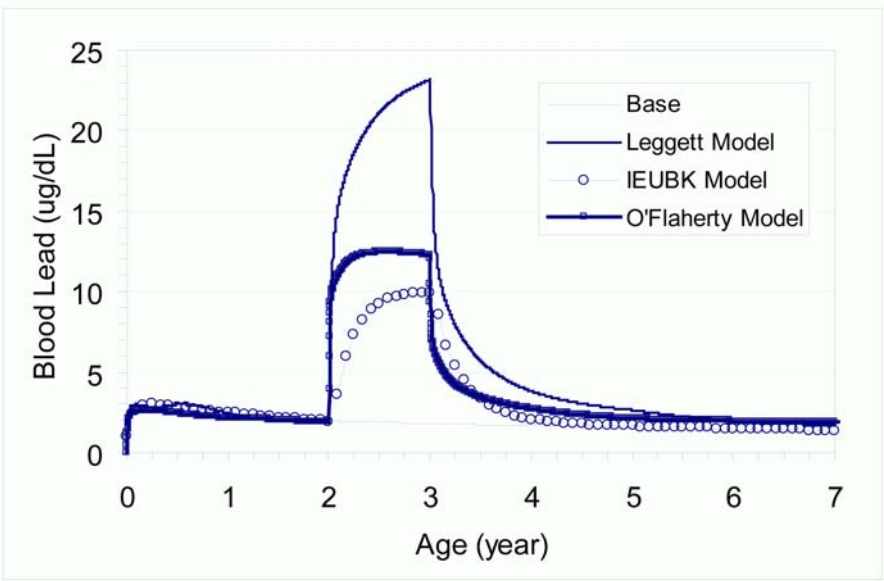


Figure 15. Comparison of Model Predictions for Childhood Lead Exposure. The simulations are of a hypothetical child who has a blood lead concentration of 2 µg/dL at age 2 years, and then experiences a 1-year exposure to 100 µg Pb/day. Default bioavailability assumptions were applied in all three models.

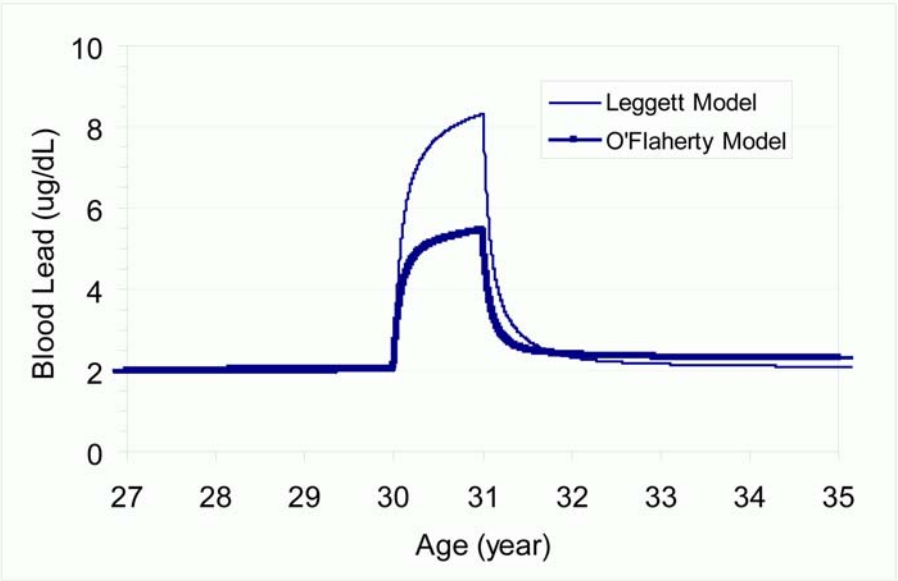


Figure 16. Comparison of Model Predictions for Adult Lead Exposure. The simulations are of a hypothetical adult who has a blood lead concentration of 2 µg/dL at age 30 years, and then experiences a 1-year exposure to 100 µg Pb/day. Default bioavailability assumptions were applied in the Leggett and O'Flaherty models.

intake of 100 µg/day). A similar pattern is evident in the simulation of the same exposure (100 µg/day for 1 year) in an adult (age 30 years; Figure 16). The Leggett model predicts a quasi-steady state blood lead concentration of approximately 8.2 µg/dL and the O'Flaherty model predicts 5.4 µg/dL. However, most of this difference is accommodated by the value for the absorption fraction in adults in the two models; 15% in the Leggett model and 8% in the O'Flaherty model.

5.0 CONCLUSIONS AND FUTURE DIRECTIONS

Modeling of relationships between lead exposures and lead levels in tissues has advanced considerably during the past 25years or so. Three multi-compartmental exposure-biokinetics models (predecessors to the AALM) have been developed and evaluated to varying degrees for predicting associations between exposure and body burden (IEUBK model, Leggett model, O'Flaherty model). The IEUBK model has had the most extensive application in the regulatory context, as EPA requires that risk estimates for residential exposures to lead at hazardous waste sites be based on IEUBK model predictions of blood lead concentrations in children. Although these models are constructed very differently (e.g., the O'Flaherty biokinetics model has only 17 lead parameters, compared to 65 in the Leggett biokinetics model, and 47 in the IEUBK biokinetics model), the three models yield remarkably similar predictions of blood lead concentration for similar hypothetical exposure scenarios (e.g., Figures 15 and 16). The three models predict similar kinetics of change of blood lead concentrations in association with a change in lead exposure. Both the Leggett and O'Flaherty models predict similar rates of accrual of lead in bone, for the same rates of uptake of lead into the body. Predictions of quasi-steady state blood lead concentrations for the scenarios are simulated in Figures 15 and 16 and differ across models by a factor of approximately 2. While this magnitude of difference may be substantial in the context of regulatory use of the models (e.g., for establishing cleanup goals at hazardous waste sites), it represents a remarkable convergence of various approaches taken to reduce the complex biokinetics of lead to tractable, relatively simple, mathematical expressions. Given that the AALM incorporates and combines key features from predecessor models (especially exposure components of the IEUBK and the Leggett biokinetics components) it is reasonable to expect likely convergence of its outputs with those of such predecessor models.

Several major challenges remain to be confronted in further developing our ability to simulate lead exposure-tissue level relationships in real individuals or populations. The three earlier mechanistic models described above do not simulate the kinetics of lead in pregnancy or in senescence (e.g., menopause). Only one of these three models (Leggett) simulates lead levels in brain, a potential target organ for lead toxicity. None of the models have been rigorously evaluated for accuracy of predictions of bone lead levels in humans, for which there is a rapidly expanding set of observations of importance to dose-response assessment. On the other hand, the fourth multi-compartmental model, the EPA AALM currently under development, has been designed to simulate lead kinetics out to age 90 years and is being further expanded to simulate both maternal and fetal lead biokinetics. In addition to these useful features of the biokinetics model, the AALM also has a life-time exposure model that simulates complex life-time exposure patterns (i.e., complex temporal patterns of exposure to multiple exposure media and in multiple exposure settings). These exposure simulations can be used to drive simulations of lead biokinetics, based on the AALM biokinetics model, or any other biokinetics model.

While extending the functionality of available lead models, as noted above, the AALM also provides important insight with regard to desirable future directions in model development. Of great importance for regulatory uses of the models, for example, is the need for more rigorous quantitative assessment of confidence (i.e., uncertainty) in model predictions. To date, such assessments have not been applied uniformly in a manner that allows cross-model comparisons of confidence for specific regulatory uses. The IEUBK Model has undergone the most extensive and thoroughly reported evaluation of a regulatory use of the model, i.e., quantitative evaluation of predictions of blood lead concentrations in children who live in areas for which cross-sectional measurements of environmental lead levels were available, and an independent verification of the implementation code (Hogan et al., 1998; Zaragoza and Hogan, 1998). However, a similar level of evaluation of the Leggett and O'Flaherty models has not been reported, although specific predictions of the models have been evaluated against observations (e.g. experimentally –observed kinetics of change in blood lead following a change in intakes). To a large extent, this important information gap regarding model confidence derives from a lack of observational data and/or public access to observational data on which various predictions could be evaluated. An additional challenge for applications of the models in a regulatory context relates to uncertainties in exposure data from which exposure model inputs are derived.

Model development and uncertainty assessment could be substantively advanced by assembling verified (for accuracy) sets of data on lead biokinetics against which models could be uniformly evaluated. Examples of the types of data that would be valuable include data on the kinetics of change in blood, tissue, or excreta lead concentrations, or stable lead isotope ratios, in response to a change in exposure. Measurements of exposure levels that are paired with blood, tissue, or excreta lead measurements would also be extremely valuable for cross-model evaluations.

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APPENDIX

ACRONYMS AND ABBREVIATIONS

AALM	All Ages Lead Model
ACSL	Advanced Continuous Simulation Language
AF	absorption fraction
ATSDR	Agency for Toxic Substances and Disease Registry
DF	deposition fractions
ECF	extracellular fluid
GM	geometric mean
GSD	geometric standard deviation
ICRP	International Commission on Radiological Protection
IEUBK	Integrated Exposure Uptake Biokinetic
ISK	intake slope factor
NPL	National Priorities List
PbB	blood lead concentration
USF	uptake slope factor