The ICRP Age-Specific Biokinetic Model for Lead: Validations, Empirical Comparisons, and Explorations

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The objective of this manuscript is to provide a description of the International Commission for Radiation Protection (ICRP) model and a comparison to other models (the integrated exposure uptake biokinetic [IEUBK] and O'Flaherty models), including the software used with the models, and a comparison of the model predictions for selected situations. The ICRP biokinetic model for Pb is a multicompartmental model for Pb uptake and disposition in children and in adults. The model describes deposition and retention of absorbed Pb in numerous tissues, removal from tissues to plasma, and movement along various routes of excretion. Long-term skeletal behavior of Pb is described in terms of age-specific rates of restructuring of compact and trabecular bone. The ICRP model is more flexible and has wider applicability than the IEUBK model. The major disadvantages are that application of the computer model requires some basic computer skills, and the user must convert the Pb concentrations in food, air, soil, dust, paint, or other media to the amount of Pb ingested or inhaled per day. Direct comparisons between the ICRP model and the IEUBK model are provided by modeling blood Pb levels using the IEUBK vs. 0.99d default Pb uptakes and intake values. The model is used to simulate occupational exposure cases and a controlled Pb inhalation experiment in adult humans. Finally, use of the model to explore situations with limited data is illustrated by simulating the kinetics and disposition of Pb during acute Pb poisoning and chelation therapy in a child. — Environ Health Perspect 106(Suppl 6):1505–1511 (1998). http://ehpnet1.niehs.nih.gov/docs/1998/suppl-6/1505-1511pounds/abstract.html

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The populations and the exposure scenarios defining risk for Pb poisoning are exceedingly diverse. The fetus, infant, adolescent, and adult in the workplace are at risk for Pb poisoning. Pb exposure may range from low environmental levels to high levels associated with leaded paint or occupational exposure. The exposure duration may be chronic, acute, or intermittent. The most important routes of exposure are via inhalation, ingestion, or both. The media for Pb exposure include air, food, soil, dust, paint chips, and many others. Clearly, the data requirements to support risk assessment for these diverse exposure scenarios and populations at risk are enormous. Physiologically based biokinetic models are effective tools for synthesizing existing data, designing new research, supporting risk assessment decisions, and exploring real or hypothetical situations for which no data exist.

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Abbreviations used: BAL, British antilisthenis; EDTA, calcium disodium ethylenediamine tetraacetate; ICRP, International Commission for Radiation Protection; IEUBK, integrated exposure uptake and biokinetic (model); PbB, blood lead concentration (ug/dl); PBPK, physiologically based pharmacokinetic model; RBC, red blood cells; XRF, X-ray fluorescence.

Description of the ICRP Model

The International Commission on Radiological Protection (ICRP) model is the minimal system needed to synthesize a wide variety of data from diverse studies related to the biokinetics of Pb in humans (Figure 1). These include studies of healthy adult humans receiving Pb tracers by injection, ingestion, or inhalation; postmortem measurements of Pb in environmentally exposed men, women, and children; Pb balance studies conducted in humans; and bioassay and autopsy measurements on occupationally exposed subjects. Data on the behavior of Pb in human subjects were supplemented with findings from Pb studies on laboratory animals at different stages of life and with experimental, occupational, environmental, and medical data on the biokinetics of elements with physicochemical properties similar to those of Pb. Finally, modeling of the long-term retention of skeletal deposits of Pb was based on age-dependent data on the rate of bone restructuring, an approach that is supported by human and animal data on many bone-seeking radionuclides (1).

The ICRP model describes the age- and time-dependent distribution and excretion of Pb injected directly into blood or absorbed from the gastrointestinal tract and/or lung. The schematic diagram of the compartments used in the systemic model and the directions of Pb movement among compartments is shown in Figure 1. The transfer rates between compartments and the age-dependent physiologic parameters are provided in Leggett (2). The transport of Pb between compartments follows first-order kinetics, provided the concentration in the erythrocytes stays below a nonlinear threshold concentration. A nonlinear threshold concentration of 60 μg Pb/g red blood cells (RBC), corresponding to about 25 μg Pb/dl whole blood, has been suggested as a default value (2,3), but the threshold level may vary substantially from one person to another and may also depend on the duration of exposure.

Advantages of the ICRP Model

The ICRP model has several distinct differences, advantages, and disadvantages compared with other biokinetic models for Pb (Table 1). The advantages and disadvantages may vary in importance depending on the questions asked of the model and the knowledge and experience of the user. A particularly important advantage
for many applications is that age-dependent parameter values are provided for young, middle-aged, and older adults as well as for infants, children, and adolescents. Thus, modeling is not restricted to children but can include lifetime or occupational exposure scenarios. A second important advantage is that the user has versatile and nearly complete access to almost all model input and output parameters. For example, the user is able to redefine the default biokinetic and Pb uptake parameters as required, as illustrated later in this paper. Other advantages include the facile import of model output into a spreadsheet or graphics software for further analysis and presentation. Finally, the source code is short and is written in elementary FORTRAN, and the computational steps within the code are easy to follow. This allows the nonprogrammer with knowledge of a few basic FORTRAN commands to modify the code for special applications. An example of code modification to simulate the biokinetics of Pb during chelation treatment is provided in this report. Note that the ease of altering the source code by a nonprogrammer may also be considered a disadvantage, in that it can lead to a proliferation of slightly different source codes developed for different applications. Also, the introduction of coding errors is always a possibility, even for an experienced programmer.

Disadvantages of the ICRP Model
The disadvantages of the model for applications to Pb as a chemical toxicant generally stem from the facts that a) the model was designed primarily for use in radiation protection, where the starting point is often an intake level rather than environmental concentration, and b) the computer code was not originally intended for dissemination to the public. For applications to Pb as a chemical toxicant, an important disadvantage of the ICRP model is that Pb input is defined in micrograms per day to the gastrointestinal tract and to the respiratory tract. Thus, the user must convert the Pb concentrations in food, air, soil, dust, paint, or other media to the amount of Pb ingested or inhaled per day. This conversion requires both effort and judgment. This disadvantage may be relatively unimportant when the Pb uptake is experimentally defined or the situation is hypothetical, but, depending on the user’s knowledge and experience, may be debilitating for site-specific blood-Pb modeling.

The ICRP model has other disadvantages and differences from the integrated exposure uptake biokinetic (IEUBK) and O’Flaherty models. The ICRP program is not menu driven but is run from a command line prompt using an input file (described below). It does not incorporate a statistical treatment to estimate population values. It should be noted that the omission of an error estimate for population values is not necessarily a disadvantage. Use of general U.S. population-based statistics to generate error estimates for a subpopulation (that may have very different patterns of Pb exposure and biokinetics) may provide an inappropriate estimate for the subpopulation. Finally, graphic display of output is not integrated into the program; output data must be imported into a spreadsheet or graphic software for further analysis and visual presentation.

Operation of the ICRP Model
A 53-line, free-form ASCII input file is used to provide the datastream (4). This input file is prepared by the user with the aid of any ASCII file editor. Lines 1 through 5 contain the computational parameters, including the age at which modeling starts and ends and the time-stepping for model computation. Line 6 identifies five output variables to be printed to an ASCII file. Lines 7 through 12 are used to define the intake scenario by selecting acute or chronic exposure, the number of time periods with different Pb intakes, and the daily Pb intakes to the respiratory and gastrointestinal tracts during these time periods. Lines 13 through 52 provide age-dependent transfer rates and other model parameters that are not normally changed by the user. Line 53 selects for chelation and defines the
duration and timing of chelation treatment with the chelation efficacy.

Applications

Comparison to IEUBK Model

The IEUBK model is the most commonly used physiologically based pharmacokinetic (PBPK) model for Pb in children. To provide direct comparisons between the IEUBK and the ICRP models, the IEUBK daily Pb intake (micrograms Pb per day taken into respiratory and gastrointestinal systems) or Pb uptake (micrograms Pb per day absorbed into blood) values for air, food, water, soil, and dust (5,6) were used as input to the ICRP model respiratory and gastrointestinal uptake modules or directly into the blood (Table 2). The default values were used for all Pb absorption, distribution, and other biokinetic parameters in both models. The mother's blood was set to 2.5 µg/dl for both models and the biokinetics of Pb was simulated from birth to 7 years of age. The ICRP model-predicted blood Pb level at each age is approximately twice the IEUBK model-predicted Pb value when IEUBK Pb uptake is used to define the Pb input to the ICRP model (Figure 2 and Table 3). The default bioavailability of Pb in water and diet is 50 and 30% for soil and dust in the IEUBK model. The IEUBK model-predicted absorption of the default Pb uptake is between 32 and 35% (Table 2). The default bioavailability of all gastrointestinal Pb is 45% from birth to 1 year of age and 30% to 5 years of age in the ICRP model. The daily uptake of Pb from the gastrointestinal and respiratory tracts was very similar, except for the period from 6 to 12 months of age (Figure 3). Thus, the difference in predicted Pb values is due mainly to differences in the systemic biokinetics.
Table 3. Blood lead levels predicted by the IEUBK v0.98d and ICRP models using the IEUBK default lead exposure values.

| Age, years | IEUBK | ICRP
|-----------|-------|-------|
| 1         | 4.1   | 6.2   |
| 2         | 4.5   | 8.7   |
| 3         | 4.2   | 8.8   |
| 4         | 4.0   | 8.6   |
| 5         | 3.4   | 7.3   |
| 6         | 2.9   | 6.6   |
| 7         | 2.7   | 6.3   |

*Model-predicted PbB values using the IEUBK default Pb intake (µg Pb/day to the gastrointestinal and respiratory systems) values from Table 2. Model-predicted PbB values using the IEUBK default Pb uptake (µg Pb absorbed into blood/day) values from Table 2. The IEUBK default values are from the U.S. EPA Technical Support Document (6). Parameters and equations used in the IEUBK model (6) were used for both models. Mother’s PbB values set to 2.5 for all runs.

Simulated Occupational Lead Exposure

The kinetics of Pb in the human skeleton is under investigation in several laboratories using noninvasive X-ray fluorescence (XRF) techniques. In particular, long-term XRF studies on retired Pb workers have provided information on the turnover rate of Pb in bone (7–9). In these studies, the observed turnover rate of bone Pb has varied with the length of the follow-up period and the bone selected for measurement. Based on measurements of Pb in finger bone, a mean half-time of 6.7 years was estimated for subjects followed for 5 years after retirement from Pb work, and a mean half-time of 8.2 years was estimated for subjects followed from year 7 to year 13 after retirement (7). In retired workers followed for over 18 years after the end of exposure, the asymptotic mean half-time of Pb in finger bone was 16 years (8). In active and retired Pb workers followed for many years, the estimated mean half-times of Pb in the tibia (largely cortical bone) and calcaneus (a mixture of trabecular and cortical bone) were 27 years and 16 years, respectively (9).

Immediately after subjects were removed from Pb work, PbB levels declined, with a half-time of 30 to 40 days (7,8). Descriptions of the long-term decline of PbB after retirement depended on the number of exponential terms used and the length of the follow-up period, but eventually the decline in PbB roughly paralleled that in the skeleton (7,8).

Only broad comparisons between these data and model predictions can be made because the precise time course and level of exposure of the subjects to Pb are not known, and model predictions vary somewhat with the assumed pattern and duration of exposure. For presumably realistic occupational exposure scenarios, however, model predictions are consistent with the findings of the XRF and PbB studies summarized above. Model predictions for one such scenario are shown in Figures 4 and 5. For this scenario, occupational exposure was assumed to begin at 20 years of age and end at 45 years of age (age of retirement). Chronic Pb input to blood (micrograms per day) during occupational exposure was arbitrarily adjusted to maintain PbB levels between 40 and 45 µg/dl, and input to blood from all external sources after retirement was assumed to be 10 µg/day. For this scenario, the decline in total skeletal Pb in the 15-year period after retirement was best described by a biexponential curve, with half-times of about one and three decades. The loss of Pb from the trabecular bone compartment was best fit by a biexponential model wherein 23% of trabecular Pb was associated with a half-time of 4 years and 77% was lost with a half-time of 22 years. The loss of Pb from the cortical bone compartment was best described by a monoexponential function, with a half-time of 34 years. The loss of Pb from blood was best described by a triexponential function in which 42% of blood Pb was lost with a half-time of 57 days, 16% with a half-time of 1.3 years, and the remainder with a half-time of 24.4 years. The 1- and 25-year half-times are consistent with the input of soft tissues and the skeleton to the blood. These half-times are also consistent with the half-times of Pb in retired workers reviewed above.

Investigation of the Potential Contribution of Bone Lead to Blood Lead

The ICRP model may be used to investigate the importance of long-term stores of Pb in bone as a source of blood Pb. In the computer code used to implement the model, the time-dependent flow rate into blood is expressed as a sum of flow rates from sites of absorption (respiratory and gastrointestinal tracts) and from each of the internal compartments that feed blood, including the two long-term storage compartments in bone (nonexchangeable cortical and trabecular bone volume). The calculation steps through a series of thousands of short time intervals.
periods of length no greater than a few days, and the average flow from each compartment to blood is calculated over each period. For a given exposure scenario, relative contributions of Pb to blood from gastrointestinal absorption, resorption of cortical bone, resorption of trabecular bone, and turnover of Pb in nonskeletal tissues during each period can be isolated and written to an output file.

Model simulations indicate that the importance of bone Pb as a source of blood level depends strongly on the assumptions concerning the pattern and level of exposure, fractional absorption of ingested or inhaled Pb to blood, bone turnover rates, and for high exposure levels, the nonlinear threshold for uptake by RBC. The model predicts that for persons exposed only to gradually changing levels of environmental Pb and having typical rates of mobilization from the skeleton as represented by the baseline turnover rates, exogenous sources are generally more important contributors than bone stores to PbB. On the other hand, model predictions indicate that long-term stores of Pb in bone can be the dominant source of PbB during the first few years after removal from high, long-term exposures such as those experienced by many Pb workers, or in situations in which there may be increased mobilization of skeletal stores, such as in pregnant or postmenopausal women.

As indicated in the preceding example, retired Pb workers usually show a rapid rate of decline of PbB soon after removal from exposure, but the rate of decline slows over a period of months and eventually parallels that of skeletal Pb (7,10–12). In these subjects, PbB levels generally have remained substantially higher than the average background levels in a matched population for at least a few years, suggesting that bone Pb represents the dominant source of PbB in the retired workers during this period. As in the preceding example, only broad comparisons between these data and model predictions can be made because of inadequate information on the time course and level of exposure of the subjects before, during, and after occupational exposure, and the proper nonlinear threshold (if any) to apply to these exposures. However, for presumably realistic occupational exposure scenarios, model predictions are generally consistent with the conclusion that bone Pb represents the most important source of PbB for at least a few years (Figures 4, 5) and sometimes for several years after retirement.

Simulated Controlled Lead Exposure

Griffin and co-workers (13) determined changes with time in PbB levels in several healthy adult male volunteers who were exposed to elevated levels of airborne Pb for 23 hr/day for about 18 weeks. The average concentration of Pb in air in the exposure chamber varied only slightly with time and averaged 10.9 μg/m³ over the entire exposure period. These PbB levels increased to about 37 μg/dl during the exposure compared with a mean of 20.4 μg/dl prior to exposure. PbB levels returned to nearly normal levels about 2 months after the men left the exposure chamber.

To simulate this controlled exposure, input to blood (assumed to represent primarily Pb absorbed from the gastrointestinal tract) was arbitrarily set at a constant, chronic level such that PbB gradually increased over several years (2000 days) to the pre-exposure mean PbB value of 20.4 μg/dl. When this background PbB value was attained, 58 μg/day was assigned to the lungs over the next 125 days, based on a concentration in air of 10.9 μg/m³, an air intake rate of 15 m³/day, an intake time of 23 hr/day, and a lung deposition fraction of 0.37 (2). Model predictions are compared with observations in Figure 6.

Simulated Chelation Therapy

Metal-chelating drugs have been used for many years for diagnosis of metal toxicity and to enhance metal diuresis. The major action of chelators is to facilitate the transfer of Pb in blood to urine. Although several studies have been conducted in laboratory animals (14–16), little is known regarding the tissue and cellular source of the Pb excreted during chelation in children or in adults (17–20).

Chelation is most simply modeled by increasing the deposition fraction of Pb in urine (default 0.015) and uniformly decreasing the total transfer rate from plasma to all other tissues, keeping the total transfer rate from plasma to all destinations at 2000/day. This approach is illustrated and validated by a case report of a Pb-poisoned child. The child lived in an environment of uncharacterized Pb contamination to 421 days of age. He then moved to a home containing Pb paint in a deteriorated condition. His blood Pb reached 40 μg/day at about 1150 days of age and peaked at 57 μg/dl on day 1228. He was treated with EDTA and BAL for 5 days as an inpatient and then released.

To simulate this exposure, daily Pb intake was adjusted to give PbB levels approximating 40 μg/dl, with a higher intake for 2 months just before the chelation (Figure 7). Chelation efficiency, defined in the model as the fraction of the total outflow of Pb from plasma that is assigned to the urinary bladder contents, was empirically set to 0.85 to provide the best fit to the PbB measurements during the chelation period. Table 4 and Figures 7 and 8 show urinary Pb excretion and the ICRP model-predicted Pb burden of selected tissues.

![Image](attachment://image.png)

**Figure 6.** ICRP model-predicted and observed blood Pb levels in human volunteers exposed by inhalation to controlled levels of Pb. Data are the observed PbB from Griffin et al. (13) (●) and the curve is ICRP model-predicted PbB.
Although model-predicted and observed PbB levels are comparable, it is apparent that model-predicted and observed urinary excretion of Pb during chelation are not comparable. Even if chelation efficacy is set at 100%, the model significantly underestimates the amount of Pb excreted in urine. This discrepancy may be due in part to the omission from the chelation model of extracellular, nonplasma forms of Pb that are labile to chelation. Examples of such labile Pb pools would include Pb associated with the glycocalyx of erythrocytes and tissue parenchymal cells, Pb associated with extracellular matrix proteins, and Pb associated with bone surfaces accessible to the plasmaborne chelator. It is also conceivable that the chelator has limited access to an intracellular Pb pool or to cells of a given phenotype, neither of which is included in the chelation model.

Research Needs for Biokinetic Models

PBPK modeling is a powerful toxicologic tool to convert exposure into target tissue dose. Improvement in both model realism and in our understanding of Pb toxicity and kinetics is necessary for any of the available models to achieve their full potential for risk assessment. Needed improvements include:

- Refine models to accommodate lifetime exposures by extending mathematical descriptions of age-dependent to 70 years of age or more. This effort would require information pertaining to bone mineral metabolism, bone formation, resorption, and bone mass, and Pb kinetics associated with pregnancy and lactation, nutritional perturbation, aging, or osteoporosis and other skeletal disease.
- Develop better data to validate the target tissue dose response. That is, blood is not the critical target tissue for Pb poisoning. Thus, all models must also be validated to the Pb content of target tissues including brain and kidney and other target tissues.
- Models should be refined to accommodate gender, race, and ethnicity-dependent differences in tissue mass and skeletal dynamics and Pb kinetics.
- Data should be developed describing the biokinetics of Pb and the chelator-Pb complex during chelation so that models may more fully accommodate chelation and some of the mysteries of chelation (17) may be addressed.
- Improved data for validation of models should be developed in humans with low levels of Pb exposure. That is, all of the Pb models have been constructed largely from data derived from relatively high human Pb exposures, resulting in very high PbB levels—between 20 and 50 mg/dl. Lead models should be recalibrated to appropriate data for the lower Pb exposure levels more common today and expected in the future.
- Skeletal Pb metabolism and kinetics is a major component in the biokinetics of Pb. Current models were developed using skeletal Pb concentrations resulting from the higher Pb exposures common before the 1980s and 1990s. The biokinetic models should be refined using the wealth of human bone Pb measurements made in recent years using noninvasive technology of X-ray fluorescence (21–24).
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