Predicting Blood Lead Concentrations from Lead in Environmental Media

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Policy statements providing health and environmental criteria for blood lead (PbB) often give recommendations on an acceptable distribution of PbB concentrations. Such statements may recommend distributions of PbB concentrations including an upper range (e.g., maximum and/or 90th percentile values) and central tendency (e.g., mean and/or 50th percentile) of the PbB distribution. Two major, and fundamentally dissimilar, methods to predict the distribution of PbB are currently in use: statistical analyses of epidemiologic data, and application of biokinetic models to environmental lead measurements to predict PbB. Although biokinetic models may include a parameter to predict contribution of lead from bone (PbBone), contemporary data based on chemical analyses of pediatric bone samples are rare. Dramatic decreases in environmental lead exposures over the past 15 years make questionable use of earlier data on PbBone concentrations to estimate a contribution of lead from bone, often used by physiologic modelers to predict PbB. X-ray fluorescent techniques estimating PbBone typically have an instrument-based quantitation limit that is too high for use with many young children. While these quantitation limits have improved during the late 1990s, PbBone estimates using an epidemiologic approach to describing these limits for general populations of children may generate values lower than the instrument's quantitation limit. Additional problems that occur in predicting PbB from environmental lead by biokinetic modeling include: a) uncertainty regarding the fractional lead absorption by young children; b) questions of biodegradability of specific environmental sources of lead; and c) variability in fractional absorption values over a range of exposures. Additional sources of variability in lead exposures that affect predictions of PbB from models include differences in the prevalence of such child behaviors as intensity of hand-to-mouth activity and pica. In contrast with these sources of uncertainty and variability affecting physiologic modeling of PbB distributions, epidemiologic data reporting PbB values obtained by chemical analyses of blood samples avoid these problems but raise other issues about the validity of the representation of the subsample for the overall population of concern. State and local health department screening programs and/or medical evaluation of individual children provide PbB data that contribute to databases describing the impact of environmental sources on PbB. Overall, application of epidemiologic models involves fewer uncertainties and more readily reflects variability in PbB than does current state-of-the-art biokinetic modeling. — *Environ Health Perspect 106*(Suppl 6):1485-1493 (1998). [http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1485-1493mahaffey/abstract.html](http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1485-1493mahaffey/abstract.html)

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**Background**

The history of pediatric lead poisoning in the United States is marked by a shift from finding and treatment of individual cases of lead poisoning (sometimes referred to as the medical model) to primary prevention of lead exposure. In 1971, the U.S. Surgeon General issued a statement emphasizing the need to shift the focus of intervention from identifying poisoned children to primary prevention (1). Also in 1971, the U.S. Congress passed the Lead-Based Paint Poisoning Prevention Act (1) emphasizing prevention of lead exposures to lead-based paint in housing (2). Blood lead (PbB) concentrations have been used both as measurements of lead exposure and as metrics of health effects of lead. Nearly all risk assessments and risk statements issued during and after the 1960s have been structured around PbB concentrations (2). Programs that promote primary prevention of lead toxicity often predict the level of reduction in PbB that will be achieved by reducing lead concentrations in environmental media such as air, water, food, dust, paint.

Public health recommendations describing targeted ranges of blood lead levels for children have been issued by professional and medical groups [e.g., American Academy of Pediatrics (3)]; by the U.S. government [e.g., the U.S. Centers for Disease Control (4,5)]; and by international organizations [e.g., the World Health Organization (6)]. These policy statements and criteria documents have recommended that young children should maintain PbB concentrations less than 10 µg/dl whole blood. Maximum acceptable concentrations rather than estimates of central tendency (e.g., population means or medians) are the basis for these recommendations. Variability in data on children’s PbB levels is described by the range, mean, and error estimates. The magnitude of person-to-person variation is determined by differences in the quantity and lead concentration of ingested media, and by host characteristics of the children (e.g., age, intensity of hand-to-mouth activity, frequency of food intakes) that influence the fraction of ingested lead that is absorbed. Besides this variability in external dosages, changes in time or among individuals in clearance rates of PbB by the kidneys also influence PbB levels. Variability in the volumes of distribution would similarly force changes in PbB concentrations. The general risk assessment process used by the U.S. Environmental Protection Agency (U.S. EPA) relies on integration of hazard analysis, exposure assessment, dose-response analysis, and risk characterization (7,8). For risk assessments of lead in which women of childbearing age and young children are the subpopulations of concern, currently hazard analysis and dose–response characterization have less uncertainty and variability than exposure analysis. Exposure
assessment, as used in predicting PbB concentrations from changes in lead in environmental media, remains an area in which diverse methods are applied.

Exposure estimates for lead sum intakes from multiple sources (e.g., lead-based paints, folk remedies, consumer products) and through multiple pathways (e.g., ingestion of lead dust, food, or water; inhalation of lead aerosols). Following the phaseout of lead from gasoline, ambient air concentrations have declined dramatically so that inhalation has become a small and typically nonsignificant exposure route except in occupational exposures or situations in which the residence is located near a point source. The predominant exposure pathway among children today in the United States is through ingestion of lead. Since the mid-1990s, dietary exposures from lead have been typically less than 5 μg/day from foods and beverages (9) as a result of removal of lead from solder once used in food and beverage cans, and reduced deposition of atmospheric lead onto crops. Typically, the major sources of ingested lead are from paint, dust, and soil.

Dose for lead may be expressed as either external (an environmental dose expressed as micrograms per day or micrograms per kilogram body weight per day) or an internal dose (tissue concentration). In recent decades, internal dose estimates use PbB concentration as a biomarker of lead exposure to indicate an internal dose (2). Most of the biomedical and environmental literature on lead relies on analyses of blood samples from human subjects to evaluate environmental lead exposure and to predict health hazards. PbB concentration per se may be substituted for direct measurement of health hazards by medical or psychometric testing (2) and is a biomarker of effect.

An alternative approach to chemical or physical analyses of PbB concentration is the use of various models that predict PbB concentration from environmental lead measurements (10–12). PbB levels traditionally have been assumed to reflect concurrent or recent lead exposures (2). However, studies among women and children indicate that lead from tissue stores, largely from skeletal tissues, can be the predominant source of lead in blood among adult women of childbearing age even at PbB concentrations considerably less than 10 μg/dl (13). Maternal PbBone can be transferred to the fetus and infant from maternal breast milk (14,15). Under conditions of low environmental exposure, a significant portion of PbB may result from internal dosing rather than from contemporaneous environmental exposures. For example, Gulson et al. (13) determined that among adult women the skeleton contributes 45 to 70% of the lead in the blood. During pregnancy, PbB increases approximately 20%; skeletal contribution to this increase was on average 30% (14). Individual differences around the mean were substantial (mean of 30%, range 9–65% increase). Under conditions with relatively elevated past exposures, the fractional contribution of the skeleton to current PbB could be even greater.

**Exposure Estimates**

Predicting lead exposure from environment sources requires knowing the lead concentrations in media (e.g., food, water, soil, dust, paint, etc.) that are the sources of lead. Both statistical analyses of epidemiologic data and physiologically based models face a number of difficulties in making these estimates. One problem for both statistical analyses of empirical data and for the physiologically based models is the so-called errors in the variables (16) describing the statistical assumption that the independent variable is measured without error. In this context, errors in the variables refers to whether the lead concentrations in the media actually consumed by the individual are the same as the lead concentrations used to represent the media in the statistical or modeled analyses. The lead concentrations assumed for the environmental media may differ from those in the media actually consumed by the subjects. To an extent, these differences reflect sampling variability and homogeneity, as well as analytical errors in determining the concentrations of lead in the media. Typical solutions used to deal with errors in the variables problems include composite sampling, increasing the size of the exposure area, increasing the number and location of samples collected, and increasing the depth and intensity of sampling.

**Dose Response to Lead**

Hazard analyses for lead based on neurotoxicity as the health end point of concern has been well described and documented (2–5). Estimating dose response involves linking exposures to PbB levels. Table 1 shows questions that arise in the risk assessment process when there is an attempt to link environmental exposures with PbB levels.

**Predicting the Mean and Distribution of PbB Concentrations**

**Prediction Based on Epidemiologic Data.** In the epidemiologic approach, PbB concentrations are determined by chemical analyses of blood samples collected from a group of individuals described in the study. In most epidemiologic and clinical studies, lead in the whole blood of exposed populations remains the biologic marker of choice (2–4). Chemical measurements of total PbB include lead transferred to blood from the contemporaneous environment and from long-term tissues stores of lead, typically the skeleton. Although physical measurements of the stable isotopes of lead using thermal ionization mass spectrometry have been used successfully under selected circumstances to identify multiple sources of lead, chemical analyses of bulk or total lead cannot distinguish sources (i.e., skeletal vs environmental sources).

To interpret and generalize findings from epidemiologic studies, risk assessors ask such fundamental questions as:

- Is the population representative of the group of concern?
- Does the study have the power to identify differences?
- Are the subjects appropriately selected?

**Prediction with Physiologically Based Models.** Risk assessors have also used physiologically based models to predict the likelihood of health effects of lead from environmental lead concentrations. These are population-based predictions and are not considered applicable to individuals. The modeling procedures aim to predict the central tendency and distribution of PbB concentrations using models that rely on data describing lead concentrations in environmental media. Fundamental questions include some of the same ones faced by epidemiologic studies (e.g., is the population studied representative of the group of concern), and there are a number of additional concerns (Table 1). For example:

- Are the estimates of the quantity of lead ingested from multiple media accurate?
- Are there errors in the variables problems associated with these estimates?
- Is the fraction of lead absorbed from the gastrointestinal tract accurately known?
- Are the parameters used to predict the biokinetics of the absorbed lead as it is distributed into the blood volume and tissues known with accuracy?

Mathematic coefficients are used to represent physiologically complex events including absorption of lead as it enters the plasma and its removal to various body compartments such as erythrocytes, soft tissue, and mineralizing tissues (2,17,18). If exposure is constant, a steady state eventually occurs. Under steady-state conditions
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Table 1. Risk assessment questions on lead from dust and soil.

| Hazard analysis | Exposure assessment | Dose response | Risk characterization |
|-----------------|---------------------|---------------|----------------------|
| Relationship between PbB and pediatric neurotoxicity is well described. | What is the contribution of environmental lead that is from lead sources other than dust and soil? | Is there a linear relationship between PbB levels and various exposure levels? | Which groups of children are the susceptible subpopulations (e.g., young children, persons with marginal nutritional status, children with intense hand-to-mouth activity)? |
| Predominant questions are related to linearity of effects at PbB concentrations < 10 μg/dl. | What are the lead levels in paint, soils, and dust? | Are there differences in dose–response curves for specific subpopulations of children? | What are the sources of variability? |
| | Do chemical speciation and particle size of lead sources influence exposure? | What determines biokinetics of lead within various tissue compartments (e.g., mobilization from various skeletal stores)? | What are the sources of uncertainty? |
| | Are the samples representative of typical exposures? | What are PbB distributions (e.g., mean and 90th percentiles)? | |
| | How important are errors in the variables considerations? | | |
| | What quantities of the lead source are consumed? | | |

*Errors in the variables refers to the statistical assumption that the independent variable is measured without error. This issue applied to lead in dust and soil refers to whether a soil or dust sample used in the analysis was representative of soil or dust ingested by a child or group of children. Approaches to dealing with errors in the variables include composite sampling, increasing the size of the number and locations of samples, differences in the depth, and intensity of sampling.

(i.e., stable exposure), plasma lead and erythrocyte lead are in equilibrium. Lead is removed from whole blood, under steady-state conditions, with a half-life that depends on such factors as total body lead burden, age, magnitude of external exposure, and the method of measuring a half-life (2).

Not only is lead removed from blood to other tissues, but lead re-enters the blood from tissues, particularly bone. In 1985 Manton estimated that 70% of lead in the blood was derived from bone based on studies in a single adult female subject (19). More recent estimates have provided quantitative estimates for additional individuals. Smith et al. (20) analyzed stable lead isotopes and showed that 11 of 20 subjects had an average of 61% of the lead in their blood derived from bone stores. The remaining 9 of the 20 subjects had lead sources that did not fit a simple two-compartment (exogenous or environmental vs endogenous or tissue derived) model for lead. To date, the most extensive studies of the contribution of tissue lead to blood lead has been among adult women who are Eastern European immigrants living in Australia. Because of differences in the ratios of stable lead isotopes between Eastern Europe and Australia, estimates of lead mobilized from body stores into blood have been obtained.

Among nonpregnant adult women in their late 20s and early 30s, 45 to 75% of lead in blood came from long-term tissue stores (13). These women were part of a longitudinal study and a number of them were subsequently evaluated when pregnant. During pregnancy, PbB increased over prepregnancy values by 25% to approximately 100% (twice the prepregnancy value); with lactation, these higher bone contributions were maintained for at least 6-months postpartum (15,21).

Because such a high percentage of PbB comes from bone, physiologically based models that attempt to predict PbB concentrations from contemporaneous environmental lead data must be able to incorporate the contributions of lead from bone to obtain accurate predictions. Some of the physiologically based models do provide for a contribution of tissue lead from bone (11). Under conditions in which the individual’s body burden of lead is higher than that typical of the current environment, the predicted PbB concentrations could be dominated by PbBone stores. For example, Berlin et al. (22) found that rapid mobilization of skeletal lead secondary to skeletal disease in a previously nonsymptomatic adult male worker produced neurologically overt lead poisoning. Under conditions with low current lead exposure, skeletal lead can dominate environmental lead as the predominant source of lead to blood. The data from the immigrant studies in Australia indicate 45 to 75% of lead in blood came from tissue (probably skeletal) sources (13). Longitudinal monitoring of infants born to these mothers documented that maternal lead incorporated into the infant’s skeleton is remobilized to the infant’s PbB. When environmental lead exposures are high relative to past exposures, PbBone concentrations would be less important in predicting PbB levels.

Predicting the quantities of lead mobilized from bone requires data on PbBone concentrations for both cortical and trabecular bone. Datasets providing PbBone concentrations among adults and children date from the mid-1980s (23–25) or earlier (26–28) when lead exposures were much higher than in the 1990s. These lower lead exposures resulted in lower PbBone concentrations. Consequently, the applicability of the earlier estimates of PbBone to current predictions of PbB using physiologically based models is problematic given the substantial decline in lead exposures over the past 15 years. For example, Drasch et al. (23,24,29,30) reported PbBone concentrations from cases coming to autopsy in Munich between the early 1970s and 1994. These comparisons are for subjects living in
the same geographic vicinity in Southern Germany. Between 1974 (29) and 1994 (30) trabecular PbBone decreased from 2.5 mg/kg (1974) to 1.7 mg/kg (1984) to 0.7 mg/kg (1994). Compact bone decreased from 5.5 mg/kg (1984) to 2.8 mg/kg (1994) (30). These series are for adults. The changes in PbBone can be anticipated to be even more dramatic among young children who, unlike adults, do not have the long-term stores of lead accumulated during decades of much higher lead exposures. Young children’s PbBone can be expected to be particularly low, reflecting the greatly reduced environmental lead exposures in recent decades. Unfortunately, contemporary PbBone data based on chemical analyses have not been published for other geographic locations. Estimates have been made using X-ray fluorescence techniques (2,31); however, these methods have quantitation limits that are higher than needed for many young children and for individual determinations (32).

Data for children on the fraction of blood lead derived from tissue lead are virtually nonexistent. Lead models have relied on generalization from the calcium biokinetic literature (11). Additional studies of tissue lead mobilization by young children would provide valuable information to verify these assumptions. Short-term experiments at very low exposures to lead could provide such basic data on lead kinetics as pool size, clearance rates, and fractional absorption of lead from the gut. Models based on generations that had more severely elevated PbBone may not directly apply to those that had far lower body burdens of lead.

Bioavailability of Lead from Environmental Media

Epidemiologic Data. Because PbB itself is measured, there is no need to estimate the bioavailability of lead in environmental media to predict PbB.

Data Based on Physiologically Based Models. These models apply a series of coefficients to estimate fractional absorption of lead to the quantity of lead ingested from various environmental sources of lead (e.g., food, water, soil, dust, paint chips). Although models such as the IEUBK model specify a default value (e.g., 60%), experimental data indicate both higher and lower bioavailability from comparable samples. For example, immature swine fed two fully characterized soil samples from a Western Superfund site had bioavailability values ranging from 56 to 86% depending on the organ system used to express dose (e.g., PbB, liver lead, kidney lead, etc.) (33). These variable estimates of bioavailability argue for measuring site-specific bioavailability (33).

Another approach uses one coefficient to approximate bioavailability for all ingested sources. Uptake rates for adults are fairly well validated using long-term mass balance studies (34-38), radioactive tracers (17,39), and stable isotope tracers (40,41). Data on adult female subjects are sparse. Only James et al. (39), whose subjects (26-77 years of age) included females (12 women, 11 men), reported lead absorptions from foods and beverages. Unfortunately, the report provided no discussion of whether the retention of radiolabeled lead differed between male and female subjects.

Uptake rates for children are much less well established than those for adults. Children’s coefficients are based essentially on two mass balance studies with small numbers of children. Alexander et al. (42) conducted balance studies in eight subjects ranging in age from 3 months to 8 years, with lead intakes averaging 10.6 μg lead/kg bw/day. Absorption averaged 53% of intake and retention averaged 18% of intake. Ziegler et al. (43) investigated lead absorption by 12 infants ranging in age from 14 to 746 days whose lead intakes were greater than 5 μg lead/kg bw/day. These two studies (42,43) are from the 1970s when mean PbB levels were many times higher than current levels. Consequently, these fractional absorption estimates may not be directly applicable to current estimates of kinetics. In the absence of more appropriate data, these two datasets have been used to estimate lead absorption by young children in the age range from birth through 7 years. Physiologically based models for children have as an underlying assumption that absorption of ingested lead is in the range of 40 to 50%, based on the fractional absorption rates from the studies of infants and children less than 2 years of age. This may be an inappropriate assumption.

Based on analyses of stable lead isotope profiles of a group of nine children who were immigrants from Eastern Europe living in Australia, Gulson et al. (14) observed that the fractional absorption of ingested lead by children in the 6- to 11-year age range are comparable with the absorption patterns observed among adult females in the 29- to 37-year age range. Whether the 40 to 50% absorption values for ingested lead obtained using subjects who were typically less than 2 years of age applies to children in the 2- to 6-year age range remains a question. Lower absorption values for 2- to 6-year-old children are supported by the data of Angle et al. (44), who suggested that absorption of ingested lead among 2- to 3-year-old children was 10 to 15%.

Risk Characterization

PbB concentrations are the metric used to integrate exposure estimates and predict the likelihood of health hazards associated with lead exposure. The usefulness of PbB concentrations is broadly accepted; however, a close look at the available information emphasizes the importance of understanding how host variables influence the relationship between lead in blood and lead in environmental media.

Uncertainty and Variability in Susceptible Subpopulations

Host Factors Affecting the Relation between Environmental Lead and Blood Lead. Linking estimates of environmental lead exposures to development of adverse health effects of lead is complex because lead toxicity can result from acute or chronic exposures that reflect years of accumulated excess lead exposures. Both the young child’s in utero and early postnatal lead exposures have been found to be predictive of neurodevelopmental status based on epidemiologic data using blood lead patterns as the metric of critical lead concentrations in the nervous system. Knowing the age of the child at which the greatest biologic susceptibility to adverse effects occurs helps in selecting when environmental monitoring is most important.

Using results from environmental sampling to predict PbB has a number of difficulties. Two factors that influence the relation between environmental lead levels and PbB concentrations are a) differences in the frequency and intensity of hand-to-mouth activity and pica, which greatly affect lead exposures, and b) differences in nutritional status, which can greatly change the fraction of environmental lead that is absorbed from the gastrointestinal tract. These factors affect both statistical analyses of epidemiologic data and predictions from physiologically based models, although in different ways.

Differences in Occurrence of Hand-to-Mouth Activity. Children at different ages have marked differences in their patterns of hand-to-mouth activity, with the highest prevalence occurring among children less than 3 years of age (45,46).
Greater intensity of hand-to-mouth activity correlates with higher PbB levels (46–50), particularly when household dust is lead contaminated. For example, the increased leaded dust found during renovations of housing has been associated with increased PbB concentrations among children (57–53).

Epidemiologic studies can readily identify such variation in environmental lead exposures because blood samples are chemically analyzed. Differences in lead exposures (e.g., from pica or hand-to-mouth activity during household renovation) changes in fractional absorption from the gastrointestinal tract (e.g., increases during periods of hunger), and major mobilization of internal sources (e.g., elevated PbBone from earlier exposures) produce higher PbB values than would be predicted from knowing only lead concentrations in environmental media. Physiologically based models can predict this variability only if these sources of variation were recognized, their prevalence can be expressed with certainty, and these were successfully built into the models.

Influence of Nutritional Status on Bioavailability of Ingested Lead. Data from national epidemiologic surveys such as the National Health and Nutrition Examination Surveys (NHANES) were conducted in the United States during the 1970s through 1990s (54–56). Data from these studies demonstrate that young children from socially disadvantaged, low-income, minority families are more likely to have a greater prevalence of elevated PbB levels and of marginal nutritional status (57,58). For example, data from Phase 2 of NHANES III showed that 4.5% of all 1- to 2-year-old children had PbB levels ≥ 10 μg/dl (55). Among non-Hispanic black children, the prevalence of PbB levels ≥ 10 μg/dl was 11%. Low-income black children living in pre-1946 housing had a prevalence rate of 22% compared to 9% of all children living in such housing.

Marginal intakes of nutrients such as iron and calcium and irregular eating patterns are more common among nonwhite, low-income, minority populations [for an analysis, see Mahaffey (59)]. Marginally adequate calcium intakes have been identified more commonly among nonwhite children with higher PbB levels (58) and recently identified as a risk factor for elevated PbB levels among pregnant women in Mexico City (60). Metabolic balance studies between infants and children less than 2 years of age (43) have shown that when dietary calcium is lower, lead absorption increases. Less than optimal iron intakes are associated with increases in lead absorption [for a review of data describing this interaction, see Mahaffey (59)]. Median iron intakes from food were below recommended levels for young children 1 to 2 years of age, and for adolescent and adult females based on nationally representative surveys conducted in the United States in the late 1980s and early 1990s (57). Recent reports for specific subpopulations at elevated risk of lead toxicity show a negative statistically significant association between blood lead concentrations and dietary iron intake among urban children 9 months to 5 years of age (61). Iron therapy to treat overt iron deficiency was associated with a decrease in mean blood lead concentrations from a mean of 14.1 to 7.5 μg/dl among Spanish children (62).

Patterns of food intake are also important determinants of the proportion of ingested lead that is absorbed. Metabolic studies among adults show that when lead is ingested during fasting, the fractional absorption increases from the range of 5 to 20% to approximately 60 to 80% (36, 38,39, 41). Periods of food shortage occur among low-income families and their children, as documented by national dietary surveys in the United States (57). About 9 to 13% of people living in low-income households experience some degree of food insufficiency (57). This insufficiency was highest among groups of greatest concern for elevated PbB levels; specifically in the 1988 to 1991 survey period, Mexican Americans and non-Hispanic blacks were more likely than non-Hispanic whites to report that they sometimes or often did not have enough food to eat (57).

Generalization of Modeled Data

Because recommendations on acceptable PbB levels usually refer to maximal acceptable values (e.g., 10 μg/dl), it is important to predict the distribution of PbB, particularly at the higher percentiles of the distribution. To successfully predict this upper range, it is essential that the likelihood of events that can increase lead exposure/absorption (e.g., pica, household renovation, periods of hunger) is documented and that those building a model find a way of incorporating these recognized sources of variability.

Generalization from Epidemiologic Data. To generalize from one subpopulation to another, comparability of groups is a consideration. Differences such as nutritional status and prevalence of intense hand-to-mouth activity may help explain some of the person-to-person differences encountered in epidemiologic data. Host factors as well as differences in environmental lead exposure contribute to the overall variability acknowledged in epidemiologic data. A pooled analysis of 12 epidemiologic studies estimating the contribution of various environmental lead sources to PbB (over the range of 10–25 μg/dl) has determined that the major source of lead exposure for children was house dust (63). The pooled analysis also demonstrated that the child's age within the age range of 6 through 36 months, race, mouthing behavior, and study-site specific factors influenced the predicted PbB concentrations for a given level of environmental lead exposure.

Generalization from Physiologically Based Models. Because the percent fractional absorption can be changed in models, there is the possibility of adjusting models to reflect differences in lead exposure and absorption. The difficulty is that there is no basis to choose which absorption coefficients should be assumed if the PbB distribution is not already known. Unless some data are on the distribution of PbB concentrations, there is no way to be certain whether the physiologically based model predictions are accurate, particularly at the extremes of the distribution (e.g., less than the 10th and greater than the 90th percentiles).

The difficulties are encountered if efforts to generalize the results from a particular model also include differences between PbB concentrations predicted following episodic, short-term, and chronic exposures. LaKind (64) explored results from three physiologically based models for children and adults. The three models evaluated produced highly divergent predicted PbB concentrations when environmental lead exposures were episodic. Because no measured PbB concentrations were available for comparison, it is uncertain how well these models predicted PbB concentrations over varying time intervals.

Conclusions and Research Needs

Epidemiologic data and physiologically based models both have limitations when used to predict PbB concentrations. Additional data on variability and uncertainty in environmental sampling (e.g., errors in the variables issues) are needed to strengthen both empirical analyses and
Table 2. Risk assessment and lead exposure.

| Element of risk assessment | Epidemiologic approach                                                                 | Physiologically based model approach                                                                 |
|-----------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Hazard assessment           | Association between PbB and the likelihood of adverse health effects established. PbB is used as a metric for likelihood of adverse health effects. | Association between PbB and the likelihood of adverse health effects. PbB is used as a metric for likelihood of adverse health effects. |
| Exposure analysis           | Are the lead concentrations used to assess exposure appropriately representative of those actually consumed by the subjects? | Are the lead concentrations used to assess exposures appropriately representative of those actually consumed by the subjects? Does the model include all appropriate exposure media and pathways? Does the model assume the appropriate quantity of media consumed? Is the intensity of hand-to-mouth activity among children appropriately described? Does the model include uncommon exposures such as occur following house remodeling or pica when appropriate? |
| Dose response               | Can the dose–response curve from the study be generalized to the subgroup of interest for the risk assessment? | Is the coefficient used to calculate fractional absorption of ingested lead appropriate? Are the different absorption coefficients used to estimate absorption by children of varying ages and nutritional status? Do the same absorption coefficients apply across a wide range of total daily exposures? Are appropriate PbBone data available to estimate the contribution of internal body stores to PbB? Is there a basis to adjust biokinetic coefficients used in the model to appropriately reflect differences depending on nutritional status, age, and genetic variability of the subjects? Is there a basis to adjust coefficients to reflect differences in previous body burden of lead? |
| Risk characterization       | Uncertainty in the extent to which lead concentrations established by direct analyses of blood reflect person-to-person variability in blood lead. | Person-to-person variability in media consumed by the subjects is not identifiable. Uncertainty in the extent to which lead concentrations used in the exposure estimates reflect lead concentrations is not identifiable in the media actually consumed by the subjects. Uncertainty in coefficients used to calculate PbB concentrations at different age groups (especially among children 2 to 6 years of age). Uncertainty as to the applicability of model coefficients to particular subpopulations. Variability in the distribution is not established. Generalizability of default coefficients is not determined. Applicability of selected coefficients cannot be established a priori unless the distribution of observed PbB concentrations is known. |
modeled predictions of the distribution of PbB levels. The ability to use practical measures of lead exposure (e.g., dust loading vs dust lead concentrations) is another element to consider in the usefulness of approaches.

Physiological models currently do not permit input of certain environmental parameters considered to be of practical importance, such as dust-lead loading. Table 2 provides a summary of sources of uncertainty and variability in the two approaches.

Epidemiologic data typically include chemical analyses of blood samples for lead so that prediction of PbB levels from physiologically based models is not necessary. Using epidemiologic data from previous studies to predict PbB levels in a different environment requires careful consideration of a number of issues by experts in multiple disciplines (statistics, epidemiology, analytical measurements, biology). These problems have been addressed in a pooled analysis of 12 epidemiologic investigations of the relation between environmental and PbB among 6- to 36-month-old children living in the United States (63). This report provides broad-based data from geographically diverse areas of the United States.

Physiologically based models have been used to predict PbB concentrations (estimates of central tendency and distributions) from environmental lead data. To provide for the contribution of long-term tissue stores of lead to PbB for children, additional data on PbBone concentrations among contemporary children are necessary and do not appear to be available in the published literature. The PbBone data currently used by modelers were obtained prior to the substantial decline in lead exposure that has taken place in the 1980s and 1990s. Another source of uncertainty in these models is the data on the fractional absorption of ingested lead by 2- to 6-year-old children. It is unknown whether children in this age range absorb lead at the 40 to 50% rate observed for infants or the 3 to 15% range typical of older children and adults. However, at least two reports (14,44) suggest children older than 2 years have lower fractional absorption rates than the 40 to 50% used in most physiologically based biokinetic models.

Child-based factors (including marginal nutritional status and intensity of hand-to-mouth activity) can increase variability in PbB levels, particularly when environmental lead exposures are higher. A solid advantage of measured PbB concentrations is that the observed distribution will reflect such differences. Currently it does not appear that adequate data exist to predict in a quantitative way the likelihood of multiple child-based variables that increase risk of ingesting lead occur simultaneously. Comparisons provided by Lanphear et al. (63) and LaKind (64) demonstrated that risk factors do not occur independently within the overall population of children, which adds to the complexity of modeling efforts.

In summary, limitations exist for both approaches that may be resolved through additional research (Table 3). In view of such considerations, the relative strengths and weaknesses of either approach should be considered in their application to risk assessments. Ideally both approaches, if sufficiently developed, should converge on the same pattern.

Table 3. Issues and research needed to resolve areas of uncertainty and variability.

| Issue | Research needs |
|-------|----------------|
| Statistical analyses of epidemiologic data | To analyze existing data that address issues of variability between studies |
| Generalizability across multiple subpopulations | | |
| Physiologically based biokinetic models | Human studies to determine the fractional absorption of lead by children |
| Can the results be generalized across multiple subpopulations? | Autopsy studies to determine PbBone concentrations |
| What are the appropriate absorption coefficients for children in the 2- to 6-year-old age range? | May not be resolvable by activity, pica, patterns of food consumption, and marginal nutritional status |
| What is the contribution of tissue lead stores to PbB? | |
| How do child-dependent variables, including the intensity of hand-to-mouth activity, affect PbB levels? | |

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