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Modeling Interindividual Variation in Physiological Factors Used in PBPK Models of Humans

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ABSTRACT: Modeling interindividual variation in internal doses in humans using PBPK models requires data on the variation in physiological parameters across the population of interest. These data should also reflect the correlations between the values of the various parameters in a person. In this project, we develop a source of data for human physiological parameters where (1) the parameter values for an individual are correlated with one another, and (2) values of parameters capture interindividual variation in populations of a specific gender, race, and age range. The parameters investigated in this project include: (1) volumes of selected organs and tissues; (2) blood flows for the organs and tissues; and (3) the total cardiac output under resting conditions and average daily inhalation rate. These parameters are expressed as records of correlated values for the approximately 30,000 individuals evaluated in the NHANES III survey. A computer program, Physiological Parameters for PBPK Modeling (P^3M), is developed that allows records to be retrieved randomly from the database with specification of constraints on age, sex, and ethnicity. P^3M is publicly available. The database and accompanying software provide a convenient tool for parameterizating models of interindividual variation in human pharmacokinetics.

KEYWORDS: breathing rate, Monte Carlo, P^3M, surface area.

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I. INTRODUCTION

A. Background

Physiologically based pharmacokinetic models (PBPK) have proved to be useful tools for the assessment of risks from human exposure to chemicals that occur from the use of chemicals and from environmental media contaminated by unintended releases of chemicals. Over the last decade, a number of researchers have investigated the range of internal doses that occur in humans from exposures to chemicals as a result of interindividual variation in metabolism and the physiology of the exposed individual (Portier and Kaplan, 1989; Spear and Bois, 1994; Slob and Krajnc, 1994; Dankovic and Bailer, 1994; Thomas et al., 1996; Bois et al., 1996; Simon 1997; Brown et al., 1998; Clewell et al., 1999). These investigations have been performed using Monte Carlo PBPK models to simulate the variation in uptake, kinetics, metabolism, and elimination of chemicals.

Such models require information on the variation of the physiology of individuals. Specifically, the models require data on the interindividual variation in the values of physiological parameters across the target population. In addition, to properly predict the distribution of internal doses, the models require the consideration of correlations between the values of the parameters. This characterization can be performed using correlation matrices or other tools. An alternative approach is to use records of parameter values where the values in a single record reflect the values for an actual individual. These records by definition capture the correlations between the parameters. This project has taken the latter approach.

B. Approach

This project develops a database of values for physiological parameters often used in PBPK models of humans.[1] Specifically, the project creates a database of "records." Each record contains a set of internally consistent values of compartment and organ volumes, resting blood flows, and the average breathing rate. Ideally, such records would come from detailed physiological analyses of individuals; however, such a survey has not been performed at this time.

Records are created based on data from the NHANES III survey. There are two advantages to using NHANES III data. First, this survey provides a number of concurrently measured physiological parameters on each individual that capture the actual correlations of height, weight, and other factors. Second, the survey includes the anthropometry data that provide the basis for the estimation of the unmeasured physiological parameters for the individual. Thus while the NHANES III survey did not measure the volumes or blood flow for specific organs, it did collect data that provide a basis for predicting the values of these parameters.

[1]The collection and organization of data on physiological parameters has been performed a number of times (U.S. EPA, 1988; Brown et al., 1997; also see ICRP, 1975, 2002); however, these attempts have sought to define a single value for the parameters applicable to a "typical" or reference individual at specific ages. In contrast, this project seeks to provide data on the variation of the values of parameters that occur because of differences across individuals.

The predicted values are the most likely values for an individual, given the reported anthropometry. Where the predictive equations explain the majority of the observed variance of the parameters (R^2 values close to 1.0) the values of the predicted parameters should capture the majority of the variation of the parameter values across the population.[2] However, the values are not actual measurements and will always fail to capture some portion of the variation in the parameters. As a result, the variation in parameters will tend to underestimate the true interindividual variation.

The population for this project is defined by the target population of the NHANES III survey. The NHANES III target population excludes the ill, pregnant women, and infants below the age of 2 months or people older than 90 years. Thus, the population excludes individuals with genetic disorders that affect physiology, illnesses that could affect body composition, and pregnant women.

The database consists of approximately 31,000 records.[3] Each record includes three types of information:

1. Volumes and masses of selected organs and tissues.
2. Blood flows for the organs and tissues.
3. The total resting cardiac output and the average inhalation rate.

Finally, a computer program, Physiological Parameters for PBPK Modeling (PPPM or P^{3}M), is developed that generates "sets" of records of correlated parameter values for groups of individuals of specified age ranges, genders, and ethnicities. These sets are generated by sampling, with replacement, the database records. These output sets can be used as inputs to Monte Carlo-based PBPK models of interindividual variation in dose. P^{3}M can be down loaded without charge at http://www.thelifelinegroup.org or by contacting the lead author.

[2]Note the majority of the studies reported the value of R or R^2 for the regression equation. In a few instances, other measures such as the standard error of the estimates are also reported. In no case are the actual data provided. Because of the lack of access to the original data and the lack of a consistent reporting of data beyond the R^2 value, this study relied on the R^2 as the basis for the evaluation of the relative quality of alternative models.

[3]Because many of the records in the NHANES III data contain missing values, the final number of values for any one parameter is less than 31,000.

II. DEFINING THE VOLUMES OF RELEVANT COMPARTMENTS, ORGANS, AND TISSUES

A. Existing Models of Body Composition

Body composition has been a subject of scientific study for more than a century (Tanner, 2000). Models of body composition have been developed that reflect the available ways of measuring composition and the needs of various fields of study. These include the development of new analytical techniques, public health (such as obesity-related health issues), organ transplants, anthropological studies, and forensics. As a result, there are a number of models of body composition. These models range from 2 to more than 50 compartments and reflect multiple levels of organization (Ellis, 2000; Brodie and Stewart, 1999).

The simplest body composition models sought to investigate the change in the percent body fat since this measurement is directly related to health outcomes relevant to many disciplines. In order to facilitate the accurate modeling of the fat compartment, more complicated models of the nonlipid portion of the body (the body mass minus fat) have been developed that distinguish between bone mineral content, water, and protein. This has led to three- and four-compartment models (Wang et al., 1993).

An overarching framework for the various approaches of organizing body composition has been proposed by Wang (Wang et al., 1993, 1995, 1998) (see Figure 1).

Each of the models of body composition has been explored using a variety of measurement techniques (Ellis, 2000). These include cadaveric dissection, infrared interactance, skin fold measurements, computerized tomography (CT), magnetic resonance imaging (MRI), total body potassium, nuclear based methods such as neutron activation analysis, dual-energy x-ray absorptiometry (DXA), and dual-energy photon absorptiometry (DPA), total-body electrical conductivity or bioimpedance analysis (BIA), and clinical measurements such as 24-h urinary creatinine.

In the last 15 years, there has been a significant increase in studies of body composition because of the advent of noninvasive techniques for directly

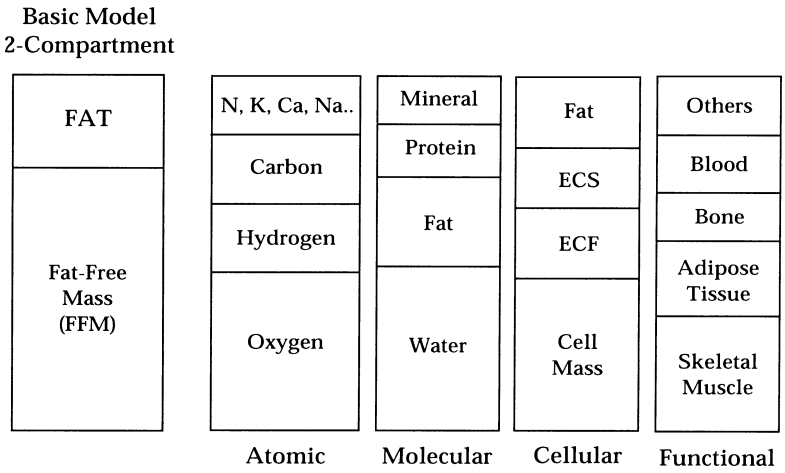

FIGURE 1. Overarching framework for various appraches to models of body composition (diagram adapted from Wang et al., 1993). ECS is extracellular solids. ECF is extracellular fluids.

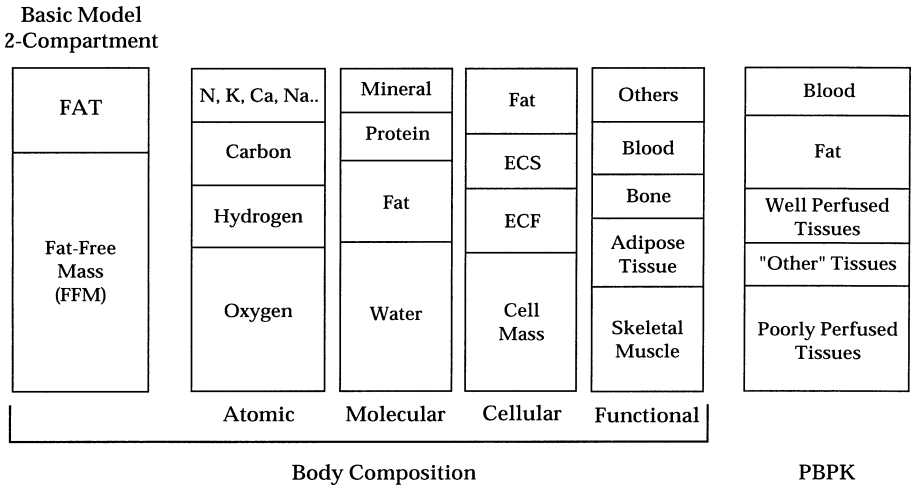

FIGURE 2. Comparison of the compartments of body composition models with those of PBPK models.

measuring tissue or organ volumes such as DXA, CT, and MRI.

B. PBPK Perspective

None of the existing models of body composition directly correspond to the compartments of the body in PBPK assessments (see Figure 2). In PBPK assessments the compartments are defined in terms of their relationship to the circulatory system and are traditionally divided into three categories: fat, poorly, and well-perfused tissues (Andersen et al., 1987). In addition, PBPK models consider those organs that determine the rate that a substance enters the circulatory system (lung, skin, and the gastrointestinal organs), those associated with the metabolism of the compounds (liver), and those that remove the substance (kidney and lung). Fat may also be divided into subcompartments (Andersen et al., 2001). The portions of the body that do not interact with the circulatory system (teeth, cartilage, tendons, fascia, periarticular tissue, hair, and nails) are typically not included in the models.[4] Table 1 presents the PBPK-relevant compartments and the organs and organ systems that compose the compartments.

[4]Such tissues can be important for PBPK models of minerals (metals and other inorganics such as fluoride and phosphorus) and are important in matching PBPK results to biomonitoring studies (hair and nails).

TABLE 1
PBPK Compartments and Organ Systems

Blood	
Plasma	Cells
Fat	
Subcutaneous fat	Yellow marrow
Visceral and intramuscular fat	
Well-Perfused Tissues	
Red marrow	Adrenals
Liver	Breasts
Spleen	Thyroid
Thymus	Pancreas
Kidney and other urogenital organs	Gastrointestinal organs
Brain	Lungs
Other Components of the Body	
Skeleton (bone, cartilage, and related tissues)	Stratum corneum
Dense connective tissues	Teeth, hair, nails
Poorly Perfused Tissues	
Muscle	Smooth muscle
Skeletal muscle (minus intramuscular fat)	Epidermis
Heart (cardiac muscle)	Dermis

III. ESTIMATING ORGAN AND TISSUE VOLUMES USING NHANES III ANTHROPOMETRY

The literature on physiology and body composition includes numerous studies of the variation of the size of tissues, organs, and organ systems across individuals. In many instances, these studies have correlated organ size with one or more anthropometric measurements. As a result there are a number of published equations relating organ size to body measurements such as age, weight, height, and gender. In this section, we review the most recent studies and the predictive equations that have been developed for the compartments and organs identified in Table 1. Where multiple equations were identified, preference was given to those equations that were derived from studies that:

1. Involve large numbers of participants.
2. Have a higher reported correlations.
3. Involve the appropriate age ranges.
4. Are based on direct rather than indirect measurements of organ weights or volumes.

This project does not attempt to estimate the volume for all materials, tissues and organs. Some materials such as interstitial fluids were evaluated as part of specific organs. In addition, no data were found for predicting the mass or volume of certain organs and structures, including connective tissues and ligaments, nasal-pharyngeal tissues, salivary glands, the organs of the gastrointestinal, and urogenital system (other than the kidney), ears, and eyes.

A. Blood and Blood Components

Blood volume is reported here for the entire body. It should be noted that the volume of the tissues and organs estimated in subsequent sections of this report also reflects the volume of blood contained in those organs.

Adults

Blood, blood cell, and plasma volumes in adults have been investigated by Sprenger et al. (1987) using previously published relationships of plasma volume (PV) to height, weight, and gender. The equations were tested in 80 adults individuals including individuals with abnormal hematocrit values.

Males:

Plasma volume (ml)

$$= (13.1\text{BH} + 18.05\text{BW} - 480) \times (1 - \text{hct} \times 0.91)/0.5723 \quad (R^2 = .69)$$

Blood volume (ml)

$$= (13.1\text{BH} + 18.05\text{BW} - 480)/0.5723$$

Blood cell volume (ml)

$$= \text{blood volume} - \text{plasma volume}$$

where BW is weight (kg), BH is body weight (cm), and hct is the venous hematocrit.

Females:

Plasma volume (ml)

$$= (35.5\text{BH} + 2.27\text{BW} - 3382) \times (1 - \text{hct} \times 0.91)/0.6178 \quad (R^2 = .69)$$

Blood volume (ml)

$$= (35.5\text{BH} + 2.27\text{BW} - 3382)/0.6178$$

Blood cell volume (ml)

$$= \text{blood volume} - \text{plasma volume}$$

Children

The relationship between blood volume and anthropometric measurements has been explored in children by Linderkamp et al. (1977) using 125-iodated human serum. A total of 160 infants and children were measured. Other measurements include age, length/height, surface area, weight, and venous hematocrit. The children were divided into three groups: infants <2 years, boys 2–14 and girls 2–6 years, and girls aged 7–14. The results are summarized in the following equations.

Ages 0–1 year, both sexes:

$$\log \text{BV} = 0.7891(\log \text{BW}) + 0.004132(\text{BH}) + 1.8117 \quad (R^2 = .95)$$

where log BV is the $\log_{10}$ of blood volume (ml) and log BW is the $\log_{10}$ of weight (kg).

Ages 2–14 males and 2–6 females:

$$\log \text{BV} = 0.6459(\log \text{BW}) + 0.002743(\text{BH}) + 2.0324 \quad (R^2 = .96)$$

Ages 7–14 females:

$$\log \text{BV} = 0.6412(\log \text{BW}) + 0.001270(\text{BH}) + 2.2169 \quad (R^2 = .94)$$

Plasma and blood cell volumes are defined using the reported venous hematocrit (hct) values for the individuals (Linderkamp et al., 1977):

Plasma volume (ml)

$$= (1 - \text{hct} \times 0.91) \times \text{blood volume}$$

Blood cell volume

$$= \text{blood volume} - \text{plasma volume}$$

B. Fatty Tissues

Fatty tissue is not a discrete organ and occurs in a variety of locations. The largest amounts of fatty tissue are the adipose tissues occurring in subcutaneous deposits and in visceral and intramuscular deposits.[5] Fatty tissues also include the fatty or yellow marrow. The derivation of the estimate of the volume of the yellow marrow is described in a separate section of this report. The amount of adipose tissue is greatly affected by individual's behavior and diet. In addition, it is influenced by age and genetic factors. As a result, there is a high degree of interindividual variation in the size of this compartment.

Because of the wide implications for health, body composition studies have long focused on the determination of the amount of fat in the body. This determination has resulted in a number of different but interrelated body composition measurements that include mass of fat, lean body mass (LBM), fat free mass (FFM), percent body fat, and volumes of fat rich tissues (adipose tissues and yellow marrow). Body composition studies have used a wide variety of methods for characterizing fat in the body (Ellis, 2000). These methods include direct measurement of fat in cadavers or animal models by dissection or by physical rendering, indirect measurements of fat using body density, skin folds, conductivity, dilution, or nuclear methods, and direct measurement of tissue volumes using DXA, MRI, and CT.

Estimates of fat volume made by the DXA, MRI, and CT are highly correlated. MRI has

[5]In this project, we determine the total adipose tissue. Future work may wish to develop estimates of these subcompartments.

been validated using animal models (whole carcass lipid extraction) (Ross et al., 1991), and dissection (Fowler et al., 1992).

The indirect measurements of fat are properties of the human body that are related to the fat compartment (whole body density, skin folds, and conductivity). These measurements are then validated using animal models, cadavers, or basic physics.

In many instances, the direct or indirect measurements of an individual's body fat are too invasive or expensive. As a result, the different measures of body fat have been correlated to anthropometry data. These correlations fall into the following categories:

1. Prediction of percent body fat estimated from body density measurements correlated with anthropometrics (race, height, weight, body mass index (BMI), age, and gender).
2. Predictions of percent body fat estimated from body density measurements or other techniques correlated with a combination of bioimpedance or skinfold data and anthropometrics.
3. Prediction of the volumes of specific fatty tissues measured by CT and MRI.

The relationship between the mass of fat in an individual's body and the volume of adipose tissue can be established based on the percent fat in adipose tissue and the density of adipose tissue (Kvist et al., 1988). The following are the equations that are used in this project.

Adipose tissue volume (L)

= total adipose tissue (kg)/density of adipose tissue (0.923 kg/L)

Total adipose tissue (kg)

= body fat (kg)/fat fraction of adipose tissue (0.83)

It should be noted that this estimate of adipose tissue includes the volume of the blood in the adipose tissue.

The NHANES III database include four types of data that have been included in published equations:

1. Basic demographics (age, gender, and race).
2. Basic measurements (height, weight, and body circumferences).
3. Skinfold measurements.
4. Bioimpedence data.

Because of the potential errors associated with skinfold measurement, such as variation in where measurements are taken, variation in calipers, and difficulties in accurately measuring in obese individuals (Brodie and Stewart, 1999), skinfold-based approaches for estimating adipose tissue volume were not investigated in this project.

Adipose Tissue Volume in Adults and Children Over the Age of 12

The following is an assessment of five equations for estimating adipose tissue volume in adults that were identified in the recent literature.

Model of CT Based Measurement of Adipose Tissue Volume

Kvist et al. (1988) investigated the volume of total adipose tissue in adults using CT. Regression models of the anthropometry and the measurement of total adipose tissue for the individuals were developed based on a group of 17 men and 10 women with cross-validation in a second group of 7 men and 9 women. While this study involves a relatively small number of individuals, the correlation coefficients of the regression are quite high.

Males:

Adipose tissue volume (L)

$= 1.36\text{BW (kg)/BH (cm)} - 42 \quad (R^2 = .93)$

Females:

Adipose tissue volume (L)

$= 1.61\text{BW (kg)/BH (cm)} - 38.3 \quad (R^2 = .96)$

Models Based on Indirect Measurements of Adipose Tissue Volume (Estimates based on Body Fat as Predicted by Body Density)

Percent body fat has been indirectly measured using body density measurements (underwater weighing or plethysmography). Measures of percent body fat are related to total adipose tissue by

the following equation:

$$\text{Total adipose tissue volume (L)} = \text{percent body fat} \times \text{body weight (kg)}/0.923\ \text{kg/L}$$

Values of percent body fat have been correlated with anthropometry in a number of populations. Two recent publications that predict percent body fat in adults are Gray and Fujioka (1990) and Deurenberg et al. (1991). Gray and Fujioka (1990) studied 29 males and 75 females with widely varying weights. The following predictive equations were developed for adults.

Males:

$$\text{Percent body fat} = 0.99\text{BMI} - 1.32 \quad (R^2 = .68)$$

Females:

$$\text{Percent body fat} = 0.94\text{BMI} + 10.77 \quad (R^2 = .74)$$

where BMI is the body mass index and is equal to BW (kg)/[BH (m)]^2.

Deurenberg et al. (1991) studied 521 males and 708 females, ages 7–83, with widely varying BMI values (13.9–40.9 kg/m^2).

Males:

$$\text{Percent body fat} = 1.20\text{BMI} + 0.23\ \text{Age (years)} - 16.2 \quad (R^2 = .79)$$

Females:

$$\text{Percent body fat} = 1.20\text{BMI} + 0.23\ \text{Age (years)} - 5.4 \quad (R^2 = .79)$$

Models of Adipose Tissue Volume Based on FFM as Predicted by Anthropometry and Bioimpedence Data

Adipose tissue volume can be estimated from measures of the FFM of the individual:

$$\text{Total adipose tissues volume (L)} = [\text{body weight (kg)} - \text{FFM (kg)}]/0.90\ \text{kg/L}$$

Measures of the FFM have been estimated based on bioimpedance data. Ellis (2000) reported on 10 published equations for estimating FFM. The equation that is based on the largest number of adults (Segal et al., 1988) is as follows:

$$\text{FFM (kg)} = 0.0013\text{BH (m)}^2 - 0.044R\ \text{(ohm)} + 0.305\text{BW (kg)} - 0.168\ \text{Age (years)} + 22.668 \quad (R^2 = \text{not reported})$$

A second equation been proposed by Brodie and Stewart (1999) based on the work by Houtkooper et al. (1992) in young adults. Houtkooper et al. (1992) estimated FFM using a three-compartment model. The equation was cross-validated with three other groups.

$$\text{FFM (kg)} = 0.61(H^2/R)(\text{cm}^2/\text{ohm}) + 0.25\text{BW (kg)} - 0.62 \quad (R^2 = .91)$$

Comparison of Models

The five models were developed using independent methods produce similar, but not identical, predictions of adipose tissue volume. Table 2 presents

TABLE 2
Correlation Matrix for the Five Methods of Estimating Adipose Tissue Volume

	Kvist et al. (1988)	Gray and Fujioka (1990)	Deurenberg et al. (1991)	Segal et al. (1988)	Houtkooper et al. (1992)
Kvist et al. (1988)	—	0.982	0.947	0.877	0.919
Gray and Fujioka (1990)		—	0.964	0.883	0.924
Deurenberg et al. (1991)			—	0.947	0.897
Segal et al. (1988)				—	0.922
Houtkooper et al. (1992)					—

the correlation matrix for volume of adipose tissue in adults and teenagers produced using five equations: CT (Kvist et al., 1988), anthropometry (Gray and Fujioka, 1990; Deurenberg et al., 1991), and bioimpedance (Segal et al., 1988; Houtkooper et al., 1992). As Table 2 indicates, the predicted values are highly correlated. This finding is encouraging since the equations were developed based on different populations using measuring different endpoints. However, the mean values of the estimates for the NHANES records of adults is about 24% higher in the highest of the models (Deurenberg et al., 1991), than in the lowest model (Kvist et al., 1988).

The preferred approach for predicting total adipose tissue would be to use regression equations of anthropometry to direct measures of tissue volume such as Kvist et al. (1988). However, the limited number of individuals included in the Kvist et al. (1988) survey raises concerns about the ability to accurately predict values in the extreme portions of the NHANES III survey population. The bioimpedance equations and the anthropometric equations both start with density-based measure of body fat and then use anthropometric data to predict results. The bioimpedance equations would be expected to perform better since they have an additional independent measurement (bioimpedance) that can be used to predict body fat. This appears to be the case for Houtkooper et al. (1992), which has a higher R^2 value than either Gray and Fujioka (1990) or Deurenberg et al. (1991).

Based on the data just reviewed the model of body fat based on body weight minus FFM as estimated by Houtkooper et al. (1992) was selected to derive the values of total adipose tissue in adults. This study had median values that were closest to the median values for the direct measurement of adipose tissue reported by Kvist et al. (1988). The study has been cross-validated and has a large R^2. The study, however, was based on young adults and does not include the elderly. Additional work may be required in this area to determine the impact of alternative models on outcomes.

This model of body fat predicts amounts of less than 0.1 kg for the lower tail of the NHANES III records distribution (the lowest 0.015% of adults). Such values are physiologically implausible. The values may have occurred because of the application of the equation to a much larger and more diverse population than the original study. In addition, errors in the NHANES III records or measurements could also affect the data. Finally, the Houtkooper et al. (1992)-based approach defines adipose tissue volume by subtracting estimates of FFM. Under this approach, the errors are cumulative and transfer directly to the estimate of body fat.

In order to address this issue, a minimum value of adipose tissue was assumed for all individuals. This value was arbitrarily set at 0.5% body weight.

Adipose Tissue Volume in Children Ages 3–11

A much smaller pool of equations was identified for children. NHANES III did not perform bioimpedance in children under the age of 12. Thus, Houtkooper et al. (1992) and other equations using bioimpedance data could not be applied to children under the age of 12. Deurenberg et al. (1991) did include children aged 7 and above; however, the R^2 for predicting body fat in children was low, .38.

The best study identified was the work by Ellis and coworkers (Ellis, 1997; Ellis et al., 1997). In this study, 313 female and 297 male children ages 3–18 had body fat, bone mineral content, and lean tissue mass measured using dual-energy x-ray absorptiometry (DXA). The results were regressed against age, weight, and height. This study examined three different ethnic populations (White,[6] African American, and Hispanic). No significant ethnic differences were identified in body fat. However, the relatively low R^2 values for male children for this study suggest the need for additional work for this parameter in children.

Males:

$$\text{Total fat (kg)} = 0.534\text{BW} - 1.59\ \text{Age (years)} + 3.03 \quad (R^2 = .57)$$

Females:

$$\text{Total fat (kg)} = 0.642\text{BW} - 0.12\text{BH} - 0.606(\text{age}) + 8.98 \quad (R^2 = .86)$$

Ellis (Ellis, 1997; Ellis et al., 1997) predicts very small volumes (<0.1 L) for the lower tail of adipose tissue volumes distribution (the lowest 0.4% of

[6]While the older literature uses a number of different terms for various racial groups, for purposes of this article, computer programs, and database, the OFCCP Equal Opportunity Survey categories (U.S. Department of Labor, 2003) are used. The term Caucasian is replaced with White and the term Black is replaced with African American regardless of the term used by the original author.

children aged 3–12). The values may have occurred because of the application of the equation on a much larger and more diverse population than the original study. In addition, errors in the NHANES III records or measurements could also affect the data. In order to address this issue, a minimum weight of adipose tissue of 0.5% body weight is assumed for all children ages 3 to 12.

Adipose Tissue Volume in Infants and Young Children (<3 Years)

Data on fat mass in infants under the age of 1 year are taken from Koo et al. (2000). This study evaluated 214 infants of approximately equal numbers of Whites and African Americans. The group consisted of 155 boys and 99 girls. The group was studied using DXA. The study determined fat mass and DXA-derived lean mass. No differences in the predictive equations were seen for race or gender.

$$\begin{aligned}\text{Fat mass (g)} = {} & 908.4 + 0.706\text{BW (g)} \\ & - 53\text{BL (cm)} + 358.5\text{ (gender)} \\ & - 3.057\text{ Age (days)}\end{aligned}$$

where gender is specified as 0 for males and 1 for females.

No published models of fat mass were identified for children ages 1–2. Therefore, the Koo et al. (2000) equation was used for children in this age. The model equation was modified to limit the values of the age parameter to 1.1 years. This modified equation was found to give values for 3-year-olds that are similar to the values for the Ellis et al. (1997) model. The estimates of the adipose tissue volumes should be revisited in the future when studies of children ages 1–2 become available.

C. Poorly Perfused Compartment

This compartment is composed of two organ systems (skeletal muscle and skin) and all or part of a number of organs. Two organs are predominantly muscular, the heart, and the tongue. The cardiac muscle is the major component of the heart, and tongue is largely composed of striated muscle. In addition, smooth muscles occur as a significant fraction of the volume of the organs of the gastrointestinal and urogenital systems.

Skeletal Muscle

Skeletal muscle is the largest single component of the poorly perfused compartment. The size of the compartment is influenced by the individual's behavior. As a result, there is considerable variation in the size of this organ system.

The skeletal muscle includes tissues that belong in both the fat and poorly perfused compartments. Muscles consist of interstitial adipose tissue (IAT) comprising 2–8% by volume of the muscle and the adipose tissue free skeletal muscle (ATFSM) comprising 92–98%. The amount of adipose tissue in the muscle varies in the individual and increases with age and with obesity (Mitsiopoulos et al., 1998). In young males, the mass of IAT is about 10% of the total adipose tissue mass and is therefore small in comparison to other adipose tissues (Heymsfield et al., 1995; Chowdhury et al., 1994).

The volume of the IAT is included in the estimate of the total adipose tissue volume calculated earlier.

Estimates of ATFSM can be developed using a number of approaches (Heymsfield et al., 1995), including:

1. An assumption of a fixed ratio of ATFSM to FFM.
2. Regressions of measures of ATFSM volumes made using DXA, MRI, or CT against creatinine levels in urine.
3. Regressions of measures of ATFSM volumes made using DXA, MRI, or CT against anthropometry.
4. Regressions studies of ATFSM volumes made using DXA, MRI, or CT against bioimpedance and anthropometry.

Approach 1 is dependent on the existence of a fixed ratio of ATFSM to FFM, which has been questioned in the literature (Wang et al., 1997). Option 2 is a possibility since NHANES III did measure creatinine levels in the urine. However, a number of questions have been raised concerning this approach (Wang et al., 1993; Heymsfield et al., 1995). In addition, the published methodologies for estimating skeletal muscle from creatinine measurements require a meat free diet for the 24 h prior to the testing and a 24-h urine sample. Neither of these protocols was followed in NANHES III. Option 3 or 4 would be preferable since DXA, CT, and MRI can directly measure the volume of ATFSM (Mitsiopoulos et al., 1998).

Adults (Age 18 and Above)

Three predictive equations were identified for adults. The first is the application of a single ratio to an estimate of FFM (derived from Houtkooper et al., 1992). This value of FFM is assumed equivalent to the LBM.[7] Following Clarys et al. (1984), the ATFSM is assume to be 54% of the adipose tissue free body mass for men and 48.9% for women. The volume of the ATFSM is calculated from the ATFSM mass based on a density of 1.04 kg/L (ICRP, 1975).

Males:

$$\text{ATFSM volume (L)} = \text{FFM (kg)} \times 54/100/1.04\ \text{(kg/L)}$$

Females:

$$\text{ATFSM volume (L)} = \text{FFM (kg)} \times 48.9/100/1.04\ \text{(kg/L)}$$

The second equation was developed by Lee et al. (2000). This study regressed anthropometric data against ATFSM measured using MRI in 324 adults ages 20 and older. Approximately 25% of the group was obese.

Males:

$$\text{ATFSM volume (L)} = [0.244\text{BW (kg)} + 7.8\text{BH (cm)} - 0.098\ \text{Age (years)} + 3.3 + \text{race}]/1.04\ \text{(kg/L)}$$

Females:

$$\text{ATFSM volume (L)} = [0.244\text{BW (kg)} + 7.8\text{BH (cm)} - 0.098\ \text{Age (years)} - 3.3 + \text{race}]/1.04\ \text{(kg/L)}$$

where race equals 1.2 for Asian, 1.4 for African American, and 0 for Whites and Hispanics.

The third equation was developed by Janssen et al. (2000). This study developed predictive equations for ATFSM measured using MRI. The test subjects also had bioimpedance measurements taken. The predictive equations used both the anthropometry and the bioimpedance data. The predicted value of ATFSM was converted to volume using a density of 1.04 kg/L.

Males:

$$\text{ATFSM volume (L)} = [4.01\text{BH}^2/R - 0.071(\text{age}) + 8.927]/1.04\ \text{(kg/L)}$$

Females:

$$\text{ATFSM volume (L)} = [4.01\text{BH}^2/R - 0.071(\text{age}) + 5.102]/1.04\ \text{(kg/L)}$$

[7]The FFM is slightly smaller (5%) than the LBM, which includes the essential fat (lipids contained in cells).

TABLE 3
Correlation Matrix for Clarys, Janssen, and Lee Approaches to Estimating Adipose Tissue from Skeletal Muscle in Adults

	Clarys	Janssen	Lee
Clarys	—	0.9299	0.9112
Janssen		—	0.9051
Lee			—

The correlation coefficients among the three models are given in Table 3.

As Table 3 indicates, there is a high degree of correlation between the three approaches. The Janssen et al. (2000) approach gives estimates that are about 7% lower than the other two approaches. The predictive equation of Clarys et al. (1984) is used, since it is the simplest model and the more complicated models do not produce significantly different results.

Children and Infants (Ages <18 Years)

No models of ATFSM or skeletal muscle (SM) were identified in children. Because of the absence of any specific equation, the approach used in this analysis is to assume an age dependent ratio of FFM to ATFSM. As discussed earlier, Clarys et al. (1984) reported that ATFSM was 54% of FFM for adult males and 48.9% for adult females. Norgan (1998) reported that the fraction of the body that is muscle increases with age until the age of 17. ICRP (2002) reports that the fraction of the FFM represented by SM ranges from 30% in the newborn to 42% in 10-year-olds. Since the amount of AT in SM is believed to be small in children, SM should be a reasonable estimate of ATFSM.

In this project, the ratio of ATFSM is assumed to vary linearly with age from 30% at birth to 48.9%

TABLE 4
Assumptions Used in the Estimation of Volume of Dermis and Epidermis (Based on Data From U.S. EPA, 1997; ICRP, 1975, 2002)

	Epidermis thickness (um)	Dermis thickness (um)	Fraction of body area
		Adults 20 years	
Head and trunk	45	2055	75
Upper arms and legs	45	1109	9
Lower arms and legs	91	1109	10
Palms and fingers	364	1200	2.5
Soles of feet	727	1500	3.5
		Children 1–10 years	
Head and trunk	45	618	75
Upper arms and legs	45	618	9
Lower arms and legs	45	618	10
Palms and fingers	364	1200	2.5
Soles of feet	727	1500	3.5
		Infant <1 year	
All body parts	45	618	100

at age 18 for females and from 30% to 54% at age 18 for males. This assumption results in an ATFSM fraction of 43% for males and 40.5% or females at age 10.

As discussed earlier, Ellis and coworkers (Ellis, 1997; Ellis et al., 1997) investigated LBM in children ages 3–12 using DXA. In this project, LBM and FFM are assumed to be identical.[8] FFM in children below the age of three is estimated based as body weight minus adipose tissue in infants using the model proposed by Koo et al. (2000). See the discussion earlier in section III,B.

Smooth Muscle

Smooth muscle occurs in a number of organs. Estimates of the volume of the smooth muscle associated with specific organ systems are not performed since historically blood flows for organs with significant amounts of smooth muscle have been adjusted to account for these tissues.

Skin (Dermis and Epidermis)

The volume and mass of the skin can be estimated from the thickness of the various components of the skin on various portions of the body and the surface area of the body. The skin is divided into three compartments: the dermis, epidermis, and stratum corneum. In this article, only the epidermis and the dermis are evaluated.

The thickness of the epidermis and dermis varies by body part ICRP (1975, 2002). This variation can be captured by assigning thickness to five general regions of the body: head and trunk; upper arm and leg; lower arm and leg; back of hand, top of the foot, fingers, and palm; and soles of the foot.

In this project we have used the values reported by ICRP (1975, 2002) and the U.S. EPA (1997); see Table 4.

Models of surface area have been established by many researchers. Two recent models of surface area are Haycock et al. (1978) and the work of Gehan and George (1970), as cited in Bailey and Briars (1996). This model is based on measurements of 401 individuals ranging from infant to adults collected by Boyd (1935). The Gehan and George (1970) equation is recommended by the U.S. EPA in the *Exposure Factors Handbook* (U.S. EPA, 1997):

$$\text{Surface area } (\text{m}^2) = e^{[-3.751+0.422 \ln \text{BH (cm)} + 0.515 \ln \text{BW (kg)}]} \quad (R^2 = \text{not given})$$

[8] LBM includes the small amounts of lipids that occur in cells (essential fat); FFM does not.

The Haycock et al. (1978) equation is based on measurements made on 81 individuals from infant to adults of varying body types:

$$\text{Surface area (m}^2\text{)} = \text{BW (kg)}^{0.5378} \times \text{BH (cm)}^{0.3964} \times 0.024265 \quad (R^2 = .998)$$

The two equations produce very similar values (correlation coefficient between the estimates produced with the two equations is .999). This project uses the Gehan and George equation cited in Bailey and Briars (1996).

The equations for the volume of the skin components for both genders and all ages are as follows:

$$\text{Dermis volume (L)} = [\text{surface area (m}^2\text{)}/1000] \times \sum [\text{fraction surface area}_i \times \text{dermis thickness}_i\ (\mu\text{m})]$$

$$\text{Epidermis volume (L)} = [\text{surface area (m}^2\text{)}/1000] \times \sum [\text{fraction surface area}_i \times \text{epidermis thickness}_i\ (\mu\text{m})]$$

where fraction surface area$_i$ is the fraction of the body's surface area of the ith body portion and epidermis thickness$_i$ (μm) is the thickness of the dermis and the epidermis for the ith body portion.

Heart

The volume of the heart determined is the volume of the heart tissues alone and does not include the volume of the chambers of the heart. The heart is largely composed of the cardiac muscle. Studies of the relationship between the size of the heart and anthropometry are based on three types of studies: cadaveric, CT or MRI, and echographic. A number of publications have reported predictive equations for cardiac factors such as left ventricular muscle volume, aortic root dimension, and left atrial dimension. These measures, while directly relevant to the prediction of cardiac health and capacity, cannot be related to the volume of the heart as an organ.

Four studies were identified that include predictive equations for heart weight in adults. Three of the studies were based on autopsy data (Siebert et al., 1986; Ogiu et al., 1997; Seo et al., 2000). The fourth is Chowdhury et al. (1994), who reported the average volume in 8 adult males (age 21–42) to be 0.61 L using CT. This volume includes the volume of the heart's chambers and thus cannot be used in this project.

All three of the autopsy studies use similar protocols where the organs were weighed immediately after removal from the cadaver and following the removal of any remaining blood in the chambers. No attempt was made to separate adipose tissue from cardiac muscle. Thus, the heart weights reflect a combination of both adipose tissue and muscle. ICRP (1975) reported that the heart contains approximately 2% lipids. Therefore, failure to separate out the adipose is not a serious source of error. The three autopsy studies reported the heart weight in grams. This weight is converted to volume by assuming that heart tissue like other muscles has a density of 1.04 g/cm^3. The volume is then converted to liters by dividing by 1000.

Ogiu et al. (1997) reported that the equations that best fit the heart weight for ages 0 to 19 are:

Males:

$$\text{Heart weight (g)} = 22.81\text{BH (m)} \times \text{BW (kg)}^{0.5} - 4.15 \quad (R^2 = .98)$$

Females:

$$\text{Heart weight (g)} = 19.99\text{BH (m)} \times \text{BW (kg)}^{0.5} - 1.53 \quad (R^2 = .96)$$

Seo et al. (2000) reported on the correlation of various anthropometry and heart weight in 422 Koreans (215 male and 207 female) ages 1–76. Surface area of the individuals was found to be the best predictor of heart weight. Surface area was calculated based on the height and weight of the individual.

Males:

$$\text{Heart weight (g)} = 155.18[\text{BH (cm)}^{0.725} \times \text{BW (kg)}^{0.425} \times 71.84]^{1.29} \quad (R^2 = .81)$$

Females:

$$\text{Heart weight (g)} = 124.13[\text{BH (cm)}^{0.7763} \times \text{BW (kg)}^{0.4081} \times 71.84]^{1.242} \quad (R^2 = .83)$$

Siebert et al. (1986) examined 87 infants and children (ages 0–11 years).

Males and females:

$$\text{Heart weight (g)} = 4.289\text{BH (cm)} + 0.494\text{BW (kg)} \quad (R^2 = .92)$$

The models of heart volume from the three cadaveric studies produced highly correlated estimates for children ages 0–11 (correlations between all three models were >.96). However, Siebert et al. (1986) predicted values that were 25% greater than Ogiu et al. (1997) and Seo et al. (2000). The reason for this difference is not clear. Both Seo et al. (2000) and Ogiu et al. (1997) are based on Asian populations and Siebert et al. (1986) on White populations. It is possible that there are racial differences in the relationship between heart weight and height and body weight. Heinemann et al. (1999) has reported evidence of such differences in models of liver volume. Future work should investigate this issue. An additional problem with the Siebert et al. (1986) and Ogiu et al. (1997) models is that they are based only on children under the age of 11 for Siebert et al. (1986) and 18 for Ogiu et al. (1997). In this study, we use the model proposed by Seo et al. (2000) since this study is the only study to report a model based on adults.

Tongue

The volume of the tongue and its relationship with body weight and gender has been investigated by Lauder and Muhl (1991) using MRI in 26 subjects of varying ages. The volume of the tongue was found to be correlated to body weight ($R^2 = 0.67$).

$$\text{Tongue volume (L)} = 0.00119\text{BW (kg)} - 0.00043$$

D. Well-Perfused Compartment

The well-perfused tissues are composed of a series of organs, which may be solid (kidneys, liver, brain) or hollow (stomach, lung, intestines). Many of these organs contribute little to the total volume of the well-perfused tissues but are important as target organs. This section addresses all of these organs with the exception of red marrow, which is discussed in section III,E.

There are two problems in the estimation of the volume of well-perfused tissues. First, we were unable to identify predictive equations for the weight or volume of a number of organs. Second, studies of a number of the organs have shown that their volumes are poorly correlated with the NHANES anthropometry in adults. Correlations when they occur typically only explain a fraction of the observed variation (Ogiu et al., 1997; Ho et al., 1980).

To address these issues we have used a tiered approach. Where possible we have used predictive models. Where these are not available and the organs are believed to be directly related to metabolic processes (inhalation and ingestion) the volumes have been estimates using an assumption that the organ weights are a fixed fraction of LBM. Finally, a number of the smaller organs are not modeled.

Liver

Studies in Adults

Heinemann et al. (1999) studied liver volume in cadavers (1332 individual ages 30 and above) and derived the following model:

$$\text{Liver volume (L)} = 1.0728[\text{surface area (m}^2)] - 345.7$$

Noda et al. (1997) studied liver volume in 54 children and young adults (ages range from 10 days to 22 years) using CT.

$$\text{Liver volume (L)} = 0.05012\text{BW (kg)}^{0.78}$$

Studies in Children

Ogiu et al. (1997) reported a strong correlation with height and weight for children and adolescents. The predictive equations for males and females ages 0 to 19 reported by Ogiu et al. (1997) are as follows:

Males:

$$\text{Liver weight (g)} = 576.9\text{BH (m)} + 8.9\text{BW (kg)} - 159.7 \quad (R^2 = .92)$$

Females:

$$\text{Liver weight (g)} = 674.3\text{BH (m)} + 6.5\text{BW (kg)} - 214.4 \quad (R^2 = .94)$$

This value of liver weight can be converted to volume by dividing by the density of liver of 1.08 g/ml (Heinemann et al., 1999).

Urata et al. (1995) investigated the correlation of body surface area (BSA) to liver volume (LV) in 96 patients (ages 1–27). Liver volume was estimated using CT. The approach used to estimate BSA varied with weight. The formula used to calculate

body surface area for individuals with bodyweights under 15 kg was Haycock et al. (1978). The Du Bois formula (Du Bois and Du Bois, 1916) is used for individuals with body weights above 15 kg. The reported model is as follows:

$$\text{Liver volume (L)} = 0.7062\text{BSA} + 2.4 \qquad (R = .692)$$

The four models are all highly correlated, with R^2 values greater than .98. The values fell within a range of about 20% for adults. On average, Urata et al. (1995) gave the lowest volumes and to Heinemann et al. (1999) the largest. There was excellent agreement with the Ogiu et al. (1997), Urata et al. (1995), and Noda et al. (1997) studies in children. The Noda et al. (1997) model was chosen for this project. It gave similar prediction to Ogiu et al. (1997) in children and Heinemann et al. (1999) in adults. Noda et al. (1997) is based on a direct measurement of volume in living individuals using CT, while Ogiu et al. (1997) and Heinemann et al. (1999) were based on autopsy data.

Spleen

The spleen has been studied by a number of researchers using CT and cadaveric methods. Autopsy studies of spleens are complicated by the rapid rate of decomposition of the organ after death. The driving force for the studies of the organ is to establish the normal range of the spleen for use in the diagnosis of splenomegaly.

Ogiu et al. (1997) reported a strong correlation with height and weight for children and adolescents. Little or no correlation was observed for adults. The predictive equations for males and females ages 0 to 19 reported by Ogiu et al. (1997) are as follows:

Males:

$$\text{Spleen weight (g)} = 8.74\text{BH (m)} \times \text{BW (kg)}^{0.5} + 11.06 \quad (R^2 = .74)$$

Females:

$$\text{Spleen weight (g)} = 9.36\text{BH (m)} \times \text{BW (kg)}^{0.5} + 7.98 \quad (R^2 = .79)$$

Schlesinger et al. (1993) studied spleen volumes in 48 children ages 1 day to 18 years using CT. Only individuals weighing less than 75 kg were included. Volumes were related to age and weight. Weight was found to be a better predictor than age.

$$\text{Spleen volume (cm}^3\text{)} = 0.7 + 4.6\text{BW (kg)} \qquad (R = .72)$$

Watanabe et al. (1997) studied the volume of the spleen using CT in 49 Japanese children, adolescents, and young adults (age range from 9 days to 25 years). Spleen volume was related to age and body weight. Body weight was found to be a better predictor than age.

$$\text{Spleen volume (cm}^3\text{)} = 6.516\text{BW (kg)}^{0.797} \qquad (R = .81)$$

The results of the three models of the spleen volume differ by more than a factor of 2. The smallest of the estimates are from Ogiu et al. (1997). Ogiu et al. (1997) found that young adults had spleen weights of approximately 100–150 g. This corresponds to a volume of roughly 0.1–0.15 L. This estimate of weight is similar to the results of earlier cadaveric studies (see ICRP, 1975). In contrast, the models proposed by Schlesinger et al. (1993) predict the range of adult spleen volumes from 0.22 to 0.4 L. The Watanabe et al. (1997) model falls in between the two estimates at 0.15–0.25 L. The differences in the range of spleen volumes for children were smaller but still significant.

The reasons for the differences in the models' prediction are not clear. ICRP (2002) reported racial differences in the size of the liver and Schlesinger et al. (1993) is a survey of Whites, while Ogiu et al. (1997) and Watanabe et al. (1997) are studies of Japanese. However, part of the differences may be due to the use of the CT versus the autopsy. Ogiu et al. (1997) notes that the reported weights of spleens varied widely because the organ is "composed of spongy tissue and much blood." Sprogoe-Jakobsen and Sprogoe-Jakobsen (1997) in a review of spleen weight in adults noted the need to consider the potential for decomposition of the spleen in cadavers. CT avoids any loss of blood from the spleen that may occur during or following death. In this report, we use the Watanabe et al. (1997) estimates. The prediction of spleen volumes should be reevaluated when additional research becomes available.

Kidneys

Studies in Adults

Gilja et al. (1995) reported a regression model of the right kidney based on three-dimensional ultrasound of 20 fasting adults ages 22 to 36. Right kidney volume was correlated with gender, weight, and height. To arrive at the volume of both kidneys, the Gilja et al. (1995) equation was multiplied by 2.

$$\begin{aligned}\text{Total volume of Kidneys (ml)} &= [5.04 \times \text{gender (male} = 1, \text{female} = 2) \\ &\quad + 2.53 \times \text{age} + 1.31\text{BW (kg)} + 1.36\text{BH (cm)} \\ &\quad - 255.7] \times 2 \quad (R^2 = .75)\end{aligned}$$

Kasiske and Umen (1986) studied the relationship of age, race, and anthropometry on kidney weight in autopsy data from 357 normal adults (mean age 37). The majority of these individuals (298) were greater than 18 years of age. Kidney weight was best predicted by the following equation:

$$\begin{aligned}\text{Total weight of kidneys (g)} &= 15.4 + 2.04\text{BW} \\ &\quad + 51.8\text{BH (m)}^2 \quad (R^2 = .64)\end{aligned}$$

The values predicted by Gilja et al. (1995) result in estimates that are very similar to Kasiske and Umen (1986) of individuals aged 20–30. The model overpredicted kidney volume for older adults. This is not surprising since the study group was limited to individuals in their 20s and 30s. In addition, the study was based on a limited number of adults. Therefore, the Kasiske and Umen (1986) model is used in this project.

Studies in Children

Ogiu et al. (1997) reported a strong correlation with height, weight, age, and surface area were observed for children and adolescents. Kidney size peaked at age 40 and decreased by one-third at age 80. Little or no correlation was observed for adults. The predictive equations for males and females ages 3–19 reported by Ogiu et al. (1997) are as follows:

Males:

$$\begin{aligned}\text{Left kidney (g)} &= 10.24\text{BH (m)} \times \text{BW (kg)}^{0.5} \\ &\quad + 7.85 \quad (R^2 = .92)\end{aligned}$$

$$\begin{aligned}\text{Right kidney (g)} &= 9.88\text{BH (m)} \times \text{BW (kg)}^{0.5} \\ &\quad + 7.2 \quad (R^2 = .92)\end{aligned}$$

Females:

$$\begin{aligned}\text{Left kidney (g)} &= 10.65\text{BH (m)} \times \text{BW (kg)}^{0.5} \\ &\quad + 6.11 \quad (R^2 = .92)\end{aligned}$$

$$\begin{aligned}\text{Right kidney (g)} &= 9.88\text{BH (m)} \times \text{BW (kg)}^{0.5} \\ &\quad + 6.55 \quad (R^2 = .92)\end{aligned}$$

Dinkel et al. (1985) investigated kidney volume using two-dimensional ultrasound in 325 children ages 3 days and 15 years. Kidney lengths and widths were measured and the volume calculated using the volume formula of an ellipsoid. The estimates of kidney volume were well correlated with both height and weight. The best equations are:

$$\begin{aligned}\text{Left kidney volume (ml)} &= 4.214\text{BW (kg)}^{0.823} \quad (R^2 = .97) \\ \text{Right kidney volume (ml)} &= 4.456\text{BW (kg)}^{0.795} \quad (R^2 = .97)\end{aligned}$$

Troell et al. (1988) investigated kidney volumes in 43 children ages 8 months to 15 years using two-dimensional ultrasonography. Total kidney volume was reported to be well correlated with body weight.

$$\begin{aligned}\text{Total volume of kidneys (ml)} &= 4.0\text{BW (kg)} \quad (R^2 = \text{not reported})\end{aligned}$$

The results of Dinkel et al. (1985) are used in the project. The study used a direct measure of organ size in vivo and in a reasonably large population. The predictions from Dinkel et al. (1985) were essentially identical to those of Ogiu et al. (1997).

Brain

In total, four studies of brain weight in cadavers and one using MRI were identified. There was general agreement that brain weight increased rapidly with age for children ages 0 to 2 and increase more slowly until age 12–15. Brain weights begin to decline in the fifth decade and by age 80 have lost an average of 11% of their weight.

Ogiu et al. (1997) reported the following predictive equations for males and females ages 3–19:

Males:

$$\text{Brain weight (g)} = [-90.7\text{BH (m)} + 178.1] \times \text{BW (kg)} \quad (R^2 = .90)$$

Females:

$$\text{Brain weight (g)} = [-97.5\text{BH (m)} + 181.2] \times \text{BW (kg)} \quad (R^2 = .88)$$

Application of these equations to the NHANES III population results in a number of implausibly high values for brain volume (volumes greater than 1.8 and in children ages 4–12). This tendency to overestimate the range is likely to be due to the grater range in height and body weights in the NHANES III population than in the Japanese population.

Dekaban (1978) studied brain weight in 2773 male and 1963 female cadavers, ages 1–80. The data are binned in 5-year age ranges, and the average brain weight for each age was determined. These age-specific averages were found to follow the following equation:

$$\text{Brain weight (kg)} = 1.449 - 3.62/[\text{BW (kg)}] \quad (R^2 \text{ not reported})$$

Since this model was calibrated using the age-specific averages, it is likely to underestimate the interindividual variance. In fact, the variance in brain size produced by this model is significantly smaller than the reported range of brain sizes in Whites and African Americans (Ho et al., 1980) and Japanese (Ogiu et al., 1997).

Scammon and Dunn (1922) (as reported in ICRP, 1975) proposed the following equation for brain weight measured in cadavers based only on age for children and young adults (ages 0–20):

$$\text{Brain weight (g)} = 10,000(\text{age} + 0.315)/(9 + 6.92\text{age})$$

Iwasaki et al. (1997) reported a similar equation age-based equation using MRI:

$$\text{Brain volume (ml)} = 1/[0.00098 + 0.00023/\text{Age (years)}]$$

Both of these models produce a single value for each age and underestimate the variation reported to occur in children and adults.

The Ogiu et al. (1997) model is the only model available for children and young adults that models interindividual variation using measurements other than age. Therefore, this model is used in this project. This model produces reasonable estimates of the mean brain volume but appears to have result in more variance than is actually observed. In order to minimize the impact of this overestimation the maximum size of the brain is capped at 1.7 kg. This weight is based on the mean plus two standard deviations for male children ages 2–17 years old as reported by Ogiu et al. (1997).

None of the identified publications reported a model correlating brain volume with individual anthropometry for adults. Because of the lack of a model relating brain size to individuals anthropometry, the volume of the adult brain size is estimated based on gender and race. Gender and race were found to be predictors of a small, but statistically significant, differences in brain volumes (Ho et al., 1980). Based on Ho et al. (1980), the values in Table 5 are assigned to adult brain volumes (density of the brain is assumed to be 1.04 kg/L).

It should be noted that in adults the variation in brain volume is not large. The coefficient of variance reported by Ho et al. (1980) is approximately 0.2 for adult populations of African Americans and Whites.

Lungs

Lungs are hollow organs. The volume of interest is the tissue volume, not the volume of the airspaces contained in the lung. As a result, CT-based estimates of the volume of lungs (including both tissue and air) are not relevant. Data in NHANES include measures of lung capacity such as peak expiratory flow, forced expiratory volume, and the maximum midexpiratory flow. However, no model was identified for relating these measures of lung capacity to lung tissue volume.

Studies of lung weights in cadavers have been reported by Ogiu et al. (1997) and by three older studies (Spencer, 1968; Whimster, 1971; Whimster and MacFarlane, 1974). The weights of

TABLE 5
Values Assigned for Brain Volume (Ho et al., 1980)

Demographics	Weight (g)	Volume (L)
White male	1392	1.338
White female	1252	1.204
African American male	1286	1.237
African American female	1158	1.113

the lungs reported in these studies include a substantial amount of blood in addition to the lung tissue.

Ogiu et al. (1997) reported the following equation based on lung weight for children and young adults, aged 0 to 19.

Males:

$$\text{Left lung (g)} = 29.08\text{BH (m)} \times \text{BW (kg)}^{0.5} + 11.06 \quad (R^2 = .70)$$

$$\text{Right lung (g)} = 35.47\text{BH (m)} \times \text{BW (kg)}^{0.5} + 5.53 \quad (R^2 = .75)$$

Females:

$$\text{Left lung (g)} = 31.46\text{BH (m)} \times \text{BW (kg)}^{0.5} + 1.43 \quad (R^2 = .83)$$

$$\text{Right lung (g)} = 35.30\text{BH (m)} \times \text{BW (kg)}^{0.5} + 1.53 \quad (R^2 = .83)$$

The four studies agree that lung weights in adults have a coefficient of variation of about 0.3 and that this variation is not predicted by age (above age 19), height, or weight. At most, less than 20% of variance can be explained by these factors (Whimster and MacFarlane, 1974).

The model proposed by Ogiu et al. (1997) is used for children and young adults, ages 0–18.

The approach used for adults is discussed in a later section of this report. The development of better models of lung weights in adults is an important area for future research.

Pancreas and Thyroid

The pancreas and thyroid were studied by Ogiu et al. (1997). The weights of the two organs were well predicted by height and weight in children and young adults but not adults. Ogiu et al. (1997) reported the following equation based on lung weight for children and young adults, aged 0 to 19.

Pancreas

Males:

$$\text{Pancreas weight (g)} = 7.46\text{BH (m)} \times \text{BW (kg)}^{0.5} - 0.79 \quad (R^2 = .92)$$

Females:

$$\text{Pancreas weight (g)} = 7.92\text{BH (m)} \times \text{BW (kg)}^{0.5} - 2.09 \quad (R^2 = .88)$$

Thyroid

Males:

$$\text{Thyroid weight (g)} = 1.17\text{BH (m)} \times \text{BW (kg)}^{0.5} - 0.29 \quad (R^2 = .71)$$

Females:

$$\text{Thyroid weight (g)} = 1.46\text{BH (m)} \times \text{BW (kg)}^{0.5} - 0.33 \quad (R^2 = .83)$$

The weights of these two organs are converted to volume by dividing the weight by the organ specific densities. The density used for the thyroid and pancreas is 1.04 kg/L.

The approach used to model the volumes of these organs in adults is discussed in the following section of this report. The development of better models of these organs in adults is an area for future research.

Organs Modeled on a Fraction of LBM

No models were identified for weight or volume of the following organs: organs of the gastrointestinal system (GI organs) for adults and children; (esophagus, stomach, small intestine; and large intestines), lungs for adults, pancreas for adults, or thyroid for adults.

The absence of models occurs because the organs have either not been studied or because the organs were found to be poorly predicted based on height, weight, and other anthropometry. Where these organs have been studied (the lung, pancreas, and thyroid), the technique used is the retrospective analyses of existing autopsy records. As such, they are limited to standard measurements of height, weight, age, and gender taken at the time of the autopsy. Measurements of organ size versus LBM have not been studied. This measure has the potential to be a better predictor than total weight since it does not reflect the highly variable adipose tissue compartment. In addition, LBM is the volume of the tissues where the majority of metabolism occurs (de Simone et al., 1997).

TABLE 6
Data on Reference Adults (ICRP, 2002)

	Weight (kg)		Ratios of organ weight to LBM	
	Male	Female	Male	Female
Total body weight	73	60		
Total nonessential fat	14.6	18		
LBM	58.4	42		
Lungs	1.2	0.8	0.021	0.019
GI organs	1.207	1.134	0.021	0.027
Pancreas	0.1	0.085	0.0017	0.0020
Thyroid	0.02	0.018	0.00034	0.00043

The approach used for the organs and organ systems just described is to assign a total volume for these organs based on a fraction of the LBM associated with the organ. This approach is not appropriate for organs that have relative weights that vary by age in ways that differ from increase in LBM (e.g., reproductive organs, thymus, or brain). In addition, the fraction is different for adults and children since the fraction of LBM that is skeletal muscle increases over childhood while the fraction represented by the viscera must decrease.

For adults the fractions of the LBM associated with the GI organs, pancreas, thyroid, and lungs, and are taken from ICRP (2002) (see Table 6). The total of the GI organs (esophagus, stomach, and intestines) are modeled as a single organ.

In the case of the GI organs the same approach found that the ratio for newborns and children aged 5 and 10 is also 0.021.

This predictions of the volumes of the lungs, pancreas and thyroid for ages 18 were compared to the predictions based on the models of children, see above. The two approaches predicted similar mean values and were highly correlated with R^2 values greater than .92 for all three organs.

Other Well-Perfused Organs Not Included in Project

There are a number of smaller organs that fall into the well-perfused tissue category. These include adrenals, thymus, breasts, gallbladder, reproductive organs, parathyroid, pineal gland, pituitary, and urogenital organs (other than kidney).

No models were identified for these organs or organ systems and they are not included in this project. Future work should seek to develop models for these organs since many of them are target organs of interest to PBPK modelers.

As Table 7 indicates, with the exception of the breasts in adult females, all of these organs/organ systems weigh less than 100 g. In adult males, these organs represent less than 5% of the total weight of the well-perfused tissues and less than 11% of the total weight of the well perfused tissues in females. Since many of the organs are reproductive, or related to sexual maturity, the percentages represented by these organs are smaller for children.

E. The Skeletal System (Bone Tissue and Yellow and Red Marrow)

From the perspective of PBPK modeling, the skeletal system is composed of three compartments; the bone tissue composed of hydroxyapatite crystals in a collagenous matrix, yellow marrow (fat), and red marrow (well-perfused tissue).[9] The bone tissue consists of the cortical and trabecular bone.[10] This compartment is regarded as being outside of the most PBPK models due to its very limited blood flow. The yellow and red marrows differ in their blood flows and are regarded as separate organs.

The skeletal volume is a function of genetic variation and has strong age and gender related differences in volume (ICRP, 1975). Growth of the skeleton is strongly influenced by hormonal changes. As a result, there is a large variation in

[9]The remaining components of the skeleton, skeletal cartilage and periarticular tissues, are included in the "other tissue category."

[10]The volume of the bone tissue follows the definition in ICRP (1995) and includes the volume of the lacunar–canalicular system.

TABLE 7
Total Mass of the Well-Perfused Tissues and Contributions From Specific Organs and Organ Systems for Adult Males and Females

Tissues in the well-perfused category	Average weight (g) (ICRP, 1975, 1995)		Included in the project	Percent of total mass of well-perfused tissues	
	Males	Females		Males (%)	Females (%)
Red marrow	1170	900	x	15.68	13.70
Adrenals (2)	14	13			
Brain	1400	1257	x	18.76	19.13
Gallbladder	10	8			
GI Tract	1200	927	x	16.08	14.11
Kidneys	310	271	x	4.15	4.12
Liver	1800	1575	x	24.12	23.97
Lung	1000	758	x	13.40	11.54
Pancreas	100	85	x	1.34	1.29
Parathyroid	0.12	0.14			
Pineal	0.18	0.14			
Pituitary	0.6	0.6			
Prostrate	0.13				
Salivary glands	85	64			
Spleen	180	154	x	2.41	2.34
Testes	35				
Thymus	20	19			
Thyroid	20	18	x	0.27	0.27
Bladder	45	34			
Breast	26	360			
Ovary		11			
Penis	47				
Uterus		80			
Uterine tube		10			
Vagina		25			
Total weight	7463.03	6569.88		96.21	90.49

the volume of this compartment across individuals. In this study, we have determined the total volume of the skeleton and then estimated the fraction of the total skeletal volume for each of the three subcompartments, bone tissue, red marrow, and yellow marrow.

Skeleton mass and volume can be measured directly using cadaveric studies, CT, MRI, neutron activation analysis, DPA, and DXA. The most frequent method is to use DXA and DPA to estimate the total body bone mineral (TBBM). DXA and DPA are based on the absorption of x- or gamma-rays by hydroxyapatite. In these studies, dry defatted bone is used as a calibration standard (Gotfredsen et al., 1987). Thus, TBBM can be viewed as the mass of mineral and protein content of the entire skeleton (bone tissue and the red and yellow marrows). Predictive equations for TBBM have been have been developed based on age, gender, height, weight, and independent measures of LBM.

Estimates of the volume of bone tissue and the red and yellow marrows can be derived from the weight fraction of the various components of bone, their densities,[11] and the predicted measurements of

[11] Many studies of bone composition using DXA and DPA measure areal bone density. Areal bone mineral density (BMD) is the mass of the bone mineral per unit area scanned (g/cm^2). Areal bone density is a common diagnostic measure produced using DXA and used in the diagnosis of osteoporosis. NHANES III includes measurements of BMD values for portions of the upper femur. Thus, BMD data on each individual in the NHANES III survey are available. Unfortunately, it is difficult to relate BMD to the true volumetric bone density. The thickness

TABLE 8
Weight Fraction of Mineral and Protein in Whole Bone by Age and Gender (ICRP, 1995)

Age/gender	Mineral	Protein	Total weight fraction
Infant (both sexes)	0.2	0.13	0.33
1 (Both sexes)	0.23	0.15	0.38
5 (Both sexes)	0.24	0.16	0.4
10 (Both sexes)	0.24	0.16	0.4
15 (Both sexes)	0.26	0.17	0.43
21 (Both sexes)	0.29	0.19	0.48
35 Male	0.29	0.19	0.48
40 Male	0.29	0.19	0.48
45 Male	0.28	0.19	0.47
50 Male	0.28	0.19	0.47
55 Male	0.27	0.18	0.45
60+ Male	0.27	0.18	0.45
35 Female	0.29	0.19	0.48
40 Female	0.28	0.19	0.47
45 Female	0.27	0.18	0.45
50 Female	0.26	0.17	0.43
55 Female	0.25	0.17	0.42
60+ Female	0.24	0.16	0.4

TBBM. The relationship between TBBM and skeletal mass is given by a simple equation:

$$\text{Skeletal mass (kg)} = \text{TBBM (kg)}/\text{WF}_{\text{TBBM}}$$

where WF_{TBBM} is the weight fraction of TBBM in the skeleton. ICRP (1995) reported a weight fraction of the mineral and protein components of bone in adults of 0.48.

The relationship does not hold for children or the elderly. Proesmans et al. (1994) reported a 59% increase in bone mineral density in children over the ages of 3 to 14. Gotfredsen et al. (1987) reported a 17% decline in women and a 7% decline in men over the ages of 30 to 60+. ICRP (1995) reported that the weight fraction of ash (mineral) in the skeleton at birth is 0.2 and increases to 0.27–0.31 in adults.

We have used the data on whole bone composition reported by ICRP (1995) (see Table 8). Using these data, the total mass of the skeleton can be determined for each age and gender.

Once the total mass of the skeleton is determined, the volume of the bone tissue and the red and yellow marrow can be determined using the following equations:

$$\text{Bone tissue volume (L)} = \text{skeletal mass (kg)} \times \text{WF}_{\text{Bone Tissue}}/\delta_{\text{Bone Tissue}}$$

$$\text{Red marrow volume (L)} = \text{skeletal mass (kg)} \times \text{WF}_{\text{Red Marrow}}/\delta_{\text{Red Marrow}}$$

$$\text{Yellow marrow volume (L)} = \text{skeletal mass (kg)} \times \text{WF}_{\text{Yellow Marrow}}/\delta_{\text{Yellow Marrow}}$$

where $\text{WF}_{\text{Bone Tissue}}$, $\text{WF}_{\text{Red Marrow}}$, and $\text{WF}_{\text{Yellow Marrow}}$ are the weight fractions of the bone tissue, red marrow and yellow marrow; and $\delta_{\text{Bone Tissue}}$, $\delta_{\text{Red Marrow}}$, and $\delta_{\text{Yellow Marrow}}$ are the densities of the bone tissue, red marrow, and yellow marrow.

Table 9 presents the weight fraction of the three skeletal components. The densities of red and yellow marrow are relatively independent of age and

of the bone that x-rays pass through for each pixel of a DXA scan varies from point to point. In addition, BMD measurements tend to be machine and reference population specific. No studies of the relationship of BMD to volumetric density were identified in the literature; therefore, the NHANES III BMD data could not be used in this project.

TABLE 9
Weight Fraction of Bone Tissue, Red Marrow and Yellow Marrow By Age and Gender (ICRP, 1995)

	<1 Year	1 Year	5 Years	10 Years	15 Years (Male)	15 Years (Female)	>18 Years (Male)	>18 Years (Female)
Bone	0.773	0.776	0.716	0.646	0.613	0.609	0.601	0.597
Red marrow	0.227	0.197	0.193	0.177	0.163	0.164	0.128	0.134
Yellow marrow	0.000	0.026	0.091	0.177	0.224	0.227	0.271	0.269

gender and have values of 1.03 and 0.98 kg/L. The density of wet bone tissue is age dependent and varies from 1.65 kg/L at birth to 1.85 kg/L at adulthood (ICRP, 1995).

Determination of TBBM in Adults, Children, and Infants

Adults (18+ Years)

One study of TBBM was identified for adults, Gotfredsen et al. (1987). Gotfredsen et al. (1987) studied TBBM in adults using dual photon absorptiometry (DPA) in 135 healthy adult woman and 101 healthy men. The measure of absorption and bone mineral mass was calibrated using dry defatted animal bones. The researchers found that TBBM slowly declines with age in females and to a lesser extent in males. TBBM was well predicted by age and LBM. Female levels were constant with age until menopause and then followed an exponential decline.

Gotfredsen et al. (1987) proposed that LBM may be used as a measure of TBBM (R^2 not reported) using the age-specific ratios given in Table 10.

Use of this model of TBBM requires an estimate of LBM in adults. As discussed in the section on adipose tissue volume, the model of LBM developed by Houtkooper et al. (1992) can be used.

Children (Ages 3–18)

Three studies of TBBM in children were identified Ogle et al. (1995), Proesmans et al. (1994), and Ellis and coworkers (Ellis, 1997; Ellis et al. 1997).

Ogle et al. (1995) reported a high correlation of total bone mineral content with LBM in 256 individuals (137 males and 128 females) with ages ranging from 4 to 26. The reported gender specific equations are:

Males:

$$\text{TBBM (g)} = 60.9\text{LBM (kg)} - 288.5$$

Females:

$$\text{TBBM (g)} = 75.5\text{LBM (kg)} - 516$$

This approach requires an estimate of the LBM. The model proposed by Houtkooper et al. (1992) requires a measure of bioimpedance. Since this measurement was not performed on children under the age of 12, models of TBBM that are based on LBM cannot be applied to children under the age of 12. Therefore, this model was not used.

Proesmans et al. (1994) examined TBBM in 97 healthy children aged 3–14 years using DPA. A good

TABLE 10
Ratio of Total Body Bone Mineral/LBM (Gotfredsen et al., 1987)

Gender	Age	TBBM (g)/LBM (g)
Male	21–30	0.058
Male	31–40	0.058
Male	41–50	0.058
Male	51–60	0.054
Male	>61	0.046
Female	21–30	0.05
Female	31–40	0.051
Female	41–50	0.051
Female	51–60	0.048
Female	>61	0.047

fit of TBBM in both genders was reported based on weight and height.

$$\text{TBBM (g)} = 7.4\text{BH (cm)} + 28.9\text{BW (kg)} - 789.6 \quad (R^2 = .93)$$

Ellis and coworkers (Ellis, 1997; Ellis et al., 1997) studied 313 female and 297 male children ages 3–18 and measured the mass of body fat, bone mineral content, and lean tissue mass measured using dual-energy x-ray absorptiometry (DXA). The results were regressed against age, weight, and height. This study examined three different ethnic populations (White, African American, and Hispanic) but reported no significant differences among the ethnic groups.

Males:

$$\text{TBBM (kg)} = 23.6\text{BW (kg)} + 7.75(\text{age}) - 416.5 \quad (R^2 = .86)$$

Females:

$$\text{TBBM (kg)} = 4.38\text{BW (kg)} + 18.6\text{BH (cm)} + 59.1(\text{age}) - 753 \quad (R^2 = .86)$$

Ellis (1997) also reported that TBBM was highly correlated to LBM and reported the following equations based on LBM:

Males:

$$\text{TBBM (g)} = 51.25\text{LBM (kg)} - 258.8$$

Females:

$$\text{TBBM (g)} = 66.25\text{LBM (kg)} - 379.5$$

Note that the LBM coefficients are quite similar in the Ogle et al. (1995), Ellis et al. (1997), and Gotfredsen et al. (1987) studies.

The skeletal volumes predicted by the Ellis et al. (1997) and Proesmans et al. (1994) studies are quite similar. The Ellis et al. (1997) model of TBBM tends to predict very low values of TBBM for certain NHANES III records. Because of this fact and the higher R^2 reported in the Proesmans et al. (1994) study, the Proesmans et al. (1994) model is used in this project. Because of the lack of children under the age of 3 in the Proesmans et al. (1994) study, the estimates of TBBM from these models are limited to children age 3 and above.

Young Children and Infants (Age <3 Years)

Koo et al. (2000) investigated TBBM in a population of 150 singleton infants, ages 25 days to 391 days (composed of roughly equal numbers of Whites and African Americans and equal numbers of male and female). Gender and race were found to be poor predictors of TBBM. A model of TBBM was developed based on weight, age (days), and length.

$$\text{TBBM (g)} = 77.24 + 24.94\text{BW (kg)} + 0.21\ \text{Age (days)} - 1.889\ \text{BH (cm)} \quad (R^2 = .976)$$

This model is relevant only for the age range of 0–1 year. The model developed for Proesman et al. (1994) is based on data on children age 3 and above. No models of TBBM were identified for children aged 1 and 2 years. Extrapolating the Koo et al. (1998) model to 3 years results in skeletal volumes that are substantially higher than those predicted by the Proesman et al. (1994) model. However, extrapolation of the Proesman model to ages below 3 years results in implausibly small estimates of skeletal volume (<0.2 L).

The approach adopted is to use the Koo et al. (1998) model to predict the skeletal volumes for ages 1 to 3. However, the value for the age term is capped at 1.1 years (the age of the oldest child in the Koo et al. (1998) study). When this is done, the Koo et al. (1998) model produces estimates of skeletal volume at age 3 that are similar to the predictions of the Proesman et al. (1994) model. However, the estimates of the skeletal volumes should be revisited in the future when studies of children ages 1–2 become available.

F. Total Compartment Volumes

In addition to the volumes of the individual organs and tissues, this project also developed estimates of the total volumes of the fat, poorly and well perfused compartments. The total volumes of the fat and poorly perfused compartments are defined as the simple sum of the volumes of the organs and tissues of those compartments. The total volume of the fat is the sum of the fatty or yellow marrow determined in section III,E and the adipose tissue determined in section III,B. The total volume of the poorly perfused tissue is the sum of the volumes

TABLE 11
Cumulative Fractions of Body Weight (Age ≥20)

Percentile	Adipose tissue	Blood	Skeletal muscle	Skin	Skeleton	All tissues
0.0	0.03	0.06	0.30	0.67	0.85	0.94
0.01	0.04	0.08	0.35	0.73	0.88	0.97
0.05	0.05	0.09	0.38	0.76	0.90	0.98
0.1	0.05	0.10	0.40	0.77	0.90	0.99
0.3	0.06	0.11	0.44	0.78	0.92	1.00
0.5	0.07	0.12	0.48	0.80	0.93	1.02
0.8	0.08	0.14	0.54	0.81	0.95	1.03
0.9	0.08	0.14	0.56	0.82	0.96	1.04
0.95	0.09	0.15	0.58	0.83	0.96	1.05
0.99	0.09	0.16	0.62	0.84	0.97	1.07
1	0.14	0.22	0.70	0.90	1.01	1.11

of the skeletal muscle, skin (dermis and epidermis), tongue, and heart determined in section III,C.

The total volume of the well-perfused tissues is determined in a similar manner but takes into account the fact that there are organs that are not addressed (see Table 7). To account for these missing volumes, the volume of the well-perfused compartment is estimated as the sum of the well perfused organs modeled in section III,D divided by an adjustment factor. The adjustment factor is defined as the fraction of the total volume of all the well-perfused tissues and organs included in this project. This value for this factor is .96 for adult males and children of both sexes. The value is .9 for adult females.

G. Mass Check

The volumes developed in this project are the product of more than 30 separate equations developed independently from diverse study populations. As a result, the values may over- or underestimate the total volume of the NHANES III population. It is possible to determine if this occurs and the magnitude of over- or underestimation by converting the volumes to their equivalent masses (using organ-specific densities), summing the weights, and comparing the summed weights to the reported body weights for each individual.

When making this comparison, three points should be taken into consideration. First, the reported organs do not include the weight of tissues in compartments that are not usually included in PBPK models. These include cartilage, periarticular tissues, stratum corneum, dense connective tissues, teeth, hair, nails, and contents of the bladder and GI organs.

Second, the reported body weight includes the weight of the individual's clothing during weighing.

Third, the model double counts the mass of a portion of the blood. The mass of blood in the entire body is reported as one parameter and the mass of the blood in the individual organs is reported as part of the weight of the individual organs.

The results of the mass check are presented in Table 11 (individuals over the age of 20) and Table 12 (individuals under the age of 20). These tables present the estimate of the weight in terms of the reported body weight. Each column is the distribution of the fraction of the body weights for the compartment/tissue in that columns and the prior columns. As Table 11 shows, the median value of the sum of weights for all estimated organs and tissues in adults is 99% of the reported body weight, and 98% of the records are within 97% and 107% of the reported body weights. As Table 12 shows, the median value of the sum of weights for all estimated organs and tissues in children is 95% of the reported body weight and 98% of the records are within 87% and 104% of the reported body weights.

IV. RESTING CARDIAC OUTPUT AND BREATHING RATES

A. Resting Cardiac Output (CO)

The level of the resting cardiac output (CO) is determined in two ways. First, models of CO based on NHANES anthropometry were identified

TABLE 12
Cumulative Fractions of Body Weight (Age <20)

Percentile	Adipose tissue	Blood	Skeletal muscle	Skin	Skeleton	All tissues
0.0	0.03	0.06	0.24	0.50	0.59	0.77
0.01	0.06	0.09	0.31	0.58	0.72	0.87
0.05	0.07	0.10	0.32	0.61	0.74	0.89
0.1	0.07	0.10	0.33	0.62	0.75	0.90
0.3	0.08	0.11	0.35	0.65	0.77	0.93
0.5	0.08	0.12	0.38	0.67	0.79	0.95
0.8	0.08	0.12	0.45	0.72	0.85	0.98
0.9	0.09	0.13	0.50	0.76	0.89	0.99
0.95	0.09	0.13	0.54	0.78	0.91	1.01
0.99	0.09	0.15	0.59	0.81	0.95	1.04
1	0.12	0.17	0.67	0.85	0.98	1.15

and used to predict the CO for each record. Second, estimates of organ-specific perfusion rates were identified in the literature and these perfusion rates were used to determine the blood flows for each of the compartments. These blood flows were summed to give an estimate of the CO.

Models of CO from Anthropometry

A number of studies have investigated the relationship between the anthropometry and CO in adults and children. The relationships, while statistically significant, were moderate or weak. Katori (1979) investigated CO in 124 healthy Japanese adults (ages 14–78) and 27 Japanese children (ages 4–14). The strongest relationship of CO for children (ages <14) was with height:

$$\text{CO (L/min)} = 21.008\text{BH (m)} - 22.508 \qquad (R^2 = .38)$$

In adults the strongest relationship was given by surface area:

$$\text{CO (L/min)} = 31.847[\text{surface area}(\text{m}^2)] - 45.704 \qquad (R^2 = .26)$$

No gender-related differences were reported and the inclusion of age did not improve the fit of the model.

In one study, de Simone et al. (1997) investigated CO in 970 normotensive children (ages 1 day to 18 years) and 544 adults (ages 18 to 85 years). CO was found to be best predicted by surface area:

Children:

$$\text{CO (ml/min)} = 3294[\text{surface area } (\text{m}^2)]^{0.53} \qquad (R^2 = .30)$$

Adults:

$$\text{CO (ml/min)} = 2421[\text{surface area } (\text{m}^2)^{1.15}] \qquad (R^2 = .25)$$

Cowles et al. (1971) reported the following equation proposed by Wade and Bishop (1962) for adults:

$$\text{CO (ml/min)} = 3500[\text{surface area } (\text{m}^2)] \qquad (R^2 \text{ not reported})$$

Collis et al. (2001) investigated a population of 2744 American Indians composed of older adults (45–74). FFM was found to be the most significant predictor of CO. However, the R^2 for the regression equations was low, 0.12 for males and 0.15 for females.

A comparison of the approaches demonstrates that the Katori (1979) model results in implausibly high value of resting CO (>15 L/m) and for some individuals predicts negative values. The models of Cowles et al. (1971) and de Simone et al. produced highly correlated results ($R^2 > .99$) for adults, with the de Simone model giving values that are 30% lower. The de Simone model is used in this project since the basis for the model is more clearly described in the literature.

TABLE 13
Organ-Specific Perfusion Rates (milliliters of blood/minute/milliliters of organ)

Organ	Cowles et al. (1971) Male and female	Fiserova-Bergerova and Hughes (1983) Male	KAPKR (Williams and Legett, 1989) Male	KAPKR (Williams and Legett, 1989) Female	Values used in this project Male	Values used in this project Female
Thyroid	5.00	3.57	—	—	5.00	5.00
Kidneys	3.96	3.96	3.68	3.22	3.68	3.22
Heart	0.806	0.81	0.73	0.96	0.73	0.96
Brain	0.529	0.53	0.51	0.52	0.51	0.52
Splanchnic tissues	0.038	—	—	—	—	—
Liver	—	0.58	0.84	1	0.84	1.00
Pancreas	—	—	0.6	0.61	0.60	0.61
Spleen	—	—	1	1.04	1.00	1.04
GI organs	—	0.37	0.75	0.78	0.75	0.78
Skin	0.057	0.09	0.12	0.15	0.12	0.15
Muscle	0.0212	0.05	0.03	0.03	0.03	0.03
Skeleton	—	—	0.03	0.03		
Red marrow	0.399	—	—	—	0.30	0.30
Yellow marrow	0.028	0.03	—	—	0.03	0.03
Bone tissue	—	0.01	—	—	—	—
Adipose tissue	0.0241	0.03	0.02	0.03	0.02	0.03

Modeling CO Using Organ- and Tissue-Specific Perfusion Rates

Under this approach, CO is defined as the sum of the blood flows for the bodies organs and tissues.

$$\text{CO (ml/min)} = \sum(\text{volume}_i \times \text{perfusion rate}_i)$$

where volume$_i$ is the volume of the ith tissue (ml) and perfusion rate$_i$ is the perfusion rate of the ith tissue (ml blood/min/ml tissue). Three sets of perfusion rates were identified in the published literature: Cowles et al. (1971), Fiserova-Bergerova and Hughes (1983), and University of Manchester Center for Applied Pharmacokinetics and Research (CAPKR) (Williams and Legett, 1989). Using these data, perfusion rates were assigned to each of the organs and tissue (see Table 13).

The blood flows for the fat, poorly perfused, and well-perfused compartments are determined by summing the predicted blood flows for each of the modeled blood flows of the tissues and organs that make up the compartments.

Comparison of the Two Methods

The two predictions of CO are very similar in children but differ in adults (see Table 14). The two sets of values are highly correlated in

TABLE 14
Relationship Between Anthropometric and Perfusion Rate-Based Estimates of Resting Cardiac Output (L/min)

	NHANES records (males and females)		
	All records	Age >18	Age <18
Median value (anthropometry) L/min	4.3	4.9	2.8
Median value (perfusion rate) L/min	6.3	6.8	2.4
Correlation between the two methods (R^2)	0.96	0.96	0.96
Ratio of average values	1.35	1.40	0.95

both age groups ($R^2 = .96$); however, the perfusion rate-based estimate of CO is 40% higher than the anthropometry-based estimate of CO in adults and 5% lower in children. The finding that the perfusion-based estimates are higher than anthropometry-based estimates in adults is surprising since the perfusion rate-based estimates of CO do not include the flows for the well-perfused organs that are missing volumes (Table 7). The anthropometry-based model predicts values are lower than the value used in PBPK models of average adults, 5.8 L/min (Anderson et al., 1987; Clewell et al., 1999) and the perfusion-based estimates are higher.

Because of the differences between the two estimates and the lack of a preferred approach, both estimates of the resting cardiac output are included in the individual's records.

B. Inhalation Rates

The average breathing rate for NHANES III records can be estimated using the equations provided by Layton (1993) and discussed in detail in the tables and equations given in the U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1997a). The estimate is based on average food consumption and reflects both the resting and active periods of the day.

$$\text{Daily average inhalation rate } (m^3/\text{day}) = \text{BMR (MJ/day)} \times \text{VQ} \times A \times \text{OU } (m^3O_2/\text{MJ})$$

where BMR is the basal metabolic rate (MJ/day), VQ is the ventilation equivalent and has a value of 27 (unit less), oxygen uptake/energy expended (OU) is the oxygen uptake per megajoule of energy expended and has a value of 0.05 (m^3O_2/MJ), and A is the ratio of the food-energy intake to BMR. Age-, gender-, and weight-specific values for A and BMR are taken from the *Exposure Factors Handbook*, Tables 5–12 and 5A-4 (U.S. EPA, 1997).

V. DEVELOPING SAMPLES FOR VARIOUS POPULATIONS

Once the models of the organ-specific volumes and flow, CO and breathing rates were established, they were used to create values for each of the NHANES III records. A sampling program was created called Physiological Parameters for PBPK Modeling (PPPM or P^3M). P^3M allows the user to specify the gender, age range, and race/ethnicity of the population of interest and request a specific number of records. The program then samples, with replacement, from the NHANES III records. Where records are requested for multiple ages, an equal number of records for each age are sampled. The sampled records are exported by the program to an output file that can be opened in either Excel or Access. If the number of records requested is large, the data set will contain multiple copies of the same record.

P^3M is a user-friendly model that is compatible with Windows 98, XP, and ME.[12] This program can be obtained by downloaded from www.thelifelinegroup.org or by contacting the lead author.

VI. RESULTS

The model P^3M was used to generate three data sets each with 2000 records. The first was for male and female children ages 4–6. The second for adult males ages 25 to 35. The third was for adult females ages 25 to 35. All ethnic groups were included. Table 15 presents the means, standard deviations, and coefficients of variance for the parameters for the three data sets.

When viewing these data it should be remembered that the estimated parameters (tissue volumes, blood flows, and others) are the product of regression equations that do not capture all of the variance. As indicated in the preceding sections, most of the regression equations have R^2 values greater than .7; however, this implies that the true variance may be more than 30% higher than the estimates given below. In addition, the reporting of the standard deviation and variance should not be taken as evidence that the shapes of the distributions are normal. As shown by Hattis et al. (2003), there is evidence that certain parameters are best described by multi-modal distributions.

The values of the parameters reflect the general pattern of increased volumes and flows with body weight. The coefficient of variation of the values is greatest for adipose tissue reflecting the role of the individual's behavior on that parameter.

Tables 16 and 17 present the mean estimates for volumes and flows predicted in this project and the values published by Fiserova-Bergerova and

[12]Windows is a registered trademark of Microsoft Corporation.

TABLE 15
Predicted Values of Physiological Parameters

	Children ages 4–6			Adult males (25–35)			Adult females (25–35)		
	Mean	Std. dev.	CV	Mean	Std. dev.	CV	Mean	Std. dev.	CV
Weight (kg)	19.28	3.68	0.19	83.12	17.94	0.22	68.91	17.74	0.26
Height (cm)	109.68	6.30	0.057	176.54	7.50	0.04	162.89	6.54	0.040
Hematocrit (unitless)	0.37	0.02	0.060	0.45	0.027	0.06	0.39	0.029	0.075
Resistance (ohm)	—	—	—	473.60	62.22	0.13	584.10	81.40	0.14
Total well perf. vol. (L)	3.26	0.45	0.14	8.18	1.09	0.13	6.85	1.02	0.15
Red marrow vol. (L)	0.43	0.11	0.25	1.59	0.28	0.17	1.05	0.20	0.19
Lungs vol. (L)	0.24	0.039	0.16	1.01	0.13	0.13	0.87	0.12	0.14
Brain vol. (L)	1.39	0.15	0.11	1.34	0.08	0.06	1.20	0.08	0.06
Kidneys vol. (L)	0.09	0.015	0.15	0.32	0.068	0.22	0.26	0.068	0.26
Liver vol. (L)	0.50	0.073	0.15	1.57	0.26	0.16	1.35	0.27	0.20
Pancreas vol. (L)	0.03	0.0050	0.15	0.10	0.0178	0.18	0.086	0.017	0.20
Spleen vol. (L)	0.07	0.010	0.15	0.22	0.037	0.17	0.19	0.038	0.20
GI organs vol. (L)	0.28	0.044	0.16	1.23	0.22	0.18	1.17	0.23	0.20
Blood vol. (L)	1.46	0.22	0.15	5.82	0.67	0.11	4.14	0.40	0.10
Plasma vol. (L)	0.97	0.15	0.15	3.46	0.42	0.12	2.68	0.28	0.11
Blood cell vol. (L)	0.49	0.082	0.17	2.36	0.31	0.13	1.46	0.18	0.12
Total poorly perf. vol. (L)	5.6	0.91	0.16	36	6.13	0.17	25	4.62	0.19
Dermis vol. (L)	0.52	0.059	0.11	3.71	0.43	0.12	3.2	0.43	0.13
Epidermis vol. (L)	0.06	0.0068	0.11	0.16	0.019	0.12	0.14	0.019	0.13
Skeletal muscle vol. (L)	4.9	0.83	0.17	32	5.6	0.18	21	4.13	0.20
Heart vol. (L)	0.11	0.015	0.14	0.36	0.051	0.14	0.30	0.042	0.14
Tongue vol. (L)	0.02	0.0044	0.19	0.10	0.021	0.22	0.082	0.021	0.26
Total fatty tissues vol. (L)	10.40	2.45	0.24	32.19	11.84	0.37	34.78	13.16	0.38
Adipose tissue vol. (L)	6.89	2.45	0.36	28.69	11.84	0.41	31.27	13.16	0.42
Yellow marrow vol. (L)	0.23	0.075	0.32	3.51	0.61	0.17	2.32	0.44	0.19
Bone tissue vol. (L)	1.00	0.24	0.24	4.12	0.72	0.17	2.73	0.52	0.19
Total well perf. bl. flow (L/min)	2.60	0.39	0.15	8.00	1.35	0.17	7.44	1.50	0.20
Red marrow bl. flow (L/min)	0.13	0.032	0.25	0.48	0.083	0.17	0.32	0.060	0.19
Brain bl. flow (L/min)	0.72	0.07	0.10	0.68	0.00	0.00	0.63	0.00	0.00
Kidneys bl. flow (L/min)	0.33	0.05	0.16	1.17	0.25	0.22	0.85	0.22	0.26
Liver bl. flow (L/min)	0.46	0.08	0.17	1.32	0.22	0.16	1.35	0.27	0.20
Pancreas bl. flow (L/min)	0.021	0.0031	0.15	0.060	0.011	0.18	0.05	0.010	0.20
Thyroid bl. flow (L/min)	0.026	0.0040	0.15	0.10	0.018	0.18	0.09	0.018	0.20
Spleen bl. flow (L/min)	0.070	0.011	0.15	0.22	0.04	0.17	0.20	0.040	0.20
GI organs bl. flow (L/min)	0.22	0.034	0.16	0.93	0.16	0.18	0.91	0.18	0.20
Total poorly perf. bl. flow (L/min)	2.69	0.54	0.20	3.79	0.59	0.15	3.77	0.57	0.15
Dermis bl. flow (L/min)	0.070	0.011	0.16	0.45	0.052	0.12	0.49	0.065	0.13
Epidermis bl. flow (L/min)	0.0081	0.0013	0.16	0.020	0.0023	0.12	0.02	0.0029	0.13
Skeletal muscle bl. flow (L/min)	0.15	0.025	0.17	0.95	0.17	0.18	0.63	0.12	0.20
Heart bl. flow (L/min)	0.84	0.11	0.14	0.73	0.00	0.00	0.96	0.00	0.00
Tongue bl. flow (L/min)	0.00067	0.00013	0.20	0.0030	0.00064	0.22	0.00	0.00063	0.26
Total fat bl. flow (L/min)	0.28	0.07	0.26	0.68	0.24	0.35	1.04	0.39	0.38
Adipose tissue bl. flow (L/min)	0.17	0.07	0.43	0.57	0.24	0.41	0.94	0.39	0.42
Yellow marrow bl. flow (L/min)	0.0070	0.0023	0.33	0.11	0.018	0.17	0.07	0.013	0.19
CO—anthropometry (L/min)	2.85	0.17	0.06	5.45	0.74	0.14	4.68	0.72	0.15
CO—perfusion rate (L/min)	2.60	0.39	0.15	8.00	1.35	0.17	7.44	1.50	0.20
Resting inhalation rate (m^3/day)	8.24	0.77	0.09	16.66	2.04	0.12	11.08	1.31	0.12

TABLE 16
Comparison of Predicted Values of Mean Organ and Tissue Volumes from P[3]M and Reference Values

	P[3]M			Fiserova-Bergerova and Hughes (1983)*	CAPKR		ICRP (2002)*		
	Children ages 4–6	Adult males (25–35)	Adult females (25–35)	Adult males	Adult males	Adult females	Child 5 years old	Adult males	Adult females
Weight (kg)	19	83	69	70	73	60	19	73	60
Red marrow vol. (L)	0.43	1.6	1.1	0.062			0.33	1.13	0.87
Lungs vol. (L)	0.24	1.0	0.87	0.58	0.47	0.37	0.55	1.73	1.35
Brain vol. (L)	1.4	1.3	1.2	1.4	1.4	1.2	1.20	1.39	1.25
Kidneys vol. (L)	0.09	0.32	0.26	0.29	0.31	0.28	0.11	0.30	0.26
Liver vol. (L)	0.50	1.6	1.4	0.58	1.8	1.4	0.55	1.73	1.35
Pancreas vol. (L)	0.03	0.10	0.09		0.1	0.085	0.03	0.10	0.08
Spleen vol. (L)	0.07	0.22	0.19	0.14	0.18	0.15	0.048	0.17	0.14
Thyroid vol. (L)	0.026	0.099	0.090	0.027			0.01	0.020	0.017
GI organs vol. (L)	0.28	1.2	1.2		1.2	1.1	0.29	1.16	1.09
Blood vol. (L)	1.5	5.8	4.1	5.3	5.6	4	1.42	5.40	4.08
Plasma vol. (L)	0.97	3.5	2.7		3.1	2.8			
Blood cell vol. (L)	0.49	2.4	1.5		2.5	1.2			
Total poorly perf. vol. (L)	5.6	36	25	33					
Dermis vol. (L)	0.52	3.7	3.2		2.5	1.8	0.51	2.9	2.0
Epidermis vol. (L)	0.060	0.16	0.14		0.1	0.09			
Skeletal muscle vol. (L)	4.9	32	21	30	30	18	5.4	28	17
Heart vol. (L)	0.11	0.36	0.30	0.29	0.33	0.27	0.082	0.32	0.24
Tongue vol. (L)	0.02	0.10	0.08					0.07	0.06
Total fatty tissues vol. (L)	10	32	35	11			4.0	19	21
Adipose tissue vol. (L)	7	29	31	8.7	13	18	3.8	16	20
Yellow Marrow vol. (L)	0.23	3.5	2.3	2.4			0.17	2.7	2.0
Bone tissue vol. (L)	1.00	4.1	2.7				0.76	3.0	2.2

*Volumes of the organs are determined by dividing by tissue density of 1.05 kg/L for nonfat tissues, 0.923 kg/L for fatty tissues, and 1.65 for children's bone and 1.85 for adult bone.

Hughes (1983), those developed by the University of Manchester Center for Applied Pharmacokinetics and Research (CAPKR), and the values for the ICRP Reference Man (ICRP, 2002).

The results of the model are similar to the previously reported values with a number of exceptions. The lung volumes are larger than the volume of the tissue reported by CAPKR and Fiserova-Bergerova and Hughes (1983). This occurred because of the inclusion of the volume of the blood contained in the lung. The volume of the adipose tissue is larger than the reference values. This is consistent with the reports of increased obesity in the United States. The greater body weight may also explain the larger estimates for the dermis and epidermis. The bases for differences in other parameters, such as thyroid, are less clear.

TABLE 17
Comparison of Predicted Values of Mean Organ and Tissue Blood Flows and Other Parameters from P³M and Reference Values

	P³M			Fiserova-Bergerova and Hughes (1983)*	CAPKR	
	Children ages 4–6	Adult males (25–35)	Adult females (25–35)	Adult males	Adult males	Adult females
Total well perf. bl. flow (L/min)	2.6	8	7.4	4.5		
Red marrow bl. flow (L/min)	0.13	0.48	0.32		0.3	0.26
Brain bl. flow (L/min)	0.72	0.68	0.63	0.8	0.7	0.62
Kidneys bl. flow (L/min)	0.33	1.2	0.85	1.2	1.1	0.88
Liver bl. flow (L/min)	0.46	1.3	1.4	1.5	1.5	1.4
Pancreas bl. flow (L/min)	0.021	0.06	0.053		0.06	0.052
Spleen bl. flow (L/min)	0.07	0.22	0.2	0.1	0.18	0.16
GI organs bl. flow (L/min)	0.22	0.93	0.91		0.9	0.88
Total poorly perf. bl. flow (L/min)	2.7	3.8	3.8	1.8		
Dermis bl. flow (L/min)	0.07	0.45	0.49		0.3	0.26
Skeletal muscle bl. flow (L/min)	0.15	0.95	0.63		1	0.6
Heart bl. flow (L/min)	0.089	0.26	0.28	0.24	0.24	0.26
Total fat bl. flow (L/min)	0.28	0.68	1	0.34		
Adipose tissue bl. flow (L/min)	0.17	0.57	0.94	0.27	0.3	0.44
Yellow marrow bl. flow (L/min)	0.007	0.11	0.07	0.07		
CO—anthropometry (L/min)	2.8	5.4	4.7	6.7	6	5.2
CO—perfusion rate (L/min)	2.6	8	7.4	6.7	6	5.2
Average inhalation rate (m^3/day)	8.2	17	11	11		

VII. DISCUSSION

A. The Project's Findings

This project sought to provide a method of capturing the correlation between the tissue and compartment volumes, blood flows, body weight, gender, and other demographic information. The project met with considerable success finding multiple studies relating anthropometry to the physiological parameters of interest. In general, the published models address the majority, and in many instances more than 80% of the variance of the tissue volumes in the test population. Where multiple models were identified, there was considerable agreement between the predicted volumes leading to an increased confidence that the regression models would be applicable to the NHANES III records.

The mean values of the volumes, flow, and other parameters were generally similar to previously reported reference values. Where differences were observed, they often could be explained by the increased weight and adiposity of the individuals in the NHANES III population as compared to the reference individuals.

The prediction of the organ-specific volumes was checked by converting the volumes to their corresponding masses, summing the estimates of mass, and compared the total to the individual's reported body weight. The estimates produced by the models were found to be consistent with the reported overall body weight with and excellent agreement in adults and a slightly poorer agreement in children. This different in the mass check is not surprising given the lower R^2 values in the models of adipose tissue and the lack of a validated model for ATFSM for children.

The predictions of the organ-specific flow rate were more difficult to check due to a limited ability to independently model CO from anthropometry. However, the sum of the organ-specific rates and the anthropometric-based estimates had excellent agreement in children. In adults, the anthropometric-based estimates of CO were smaller than the sum of the organ-specific blood flows by a consistent factor of about 30%. This may be

due to the specific model used in developing the anthropometric-based estimates.

These findings support the conclusion that the organ-specific volumes, while based on models that were developed independently and using diverse methods, product estimates that are internally consistent. The organ-specific flows were more difficult to evaluate because of the absence of an external check.

B. Future Work

Using P³M in PBPK Modeling

The outputs of P³M need to be applied in an actual PBPK model of interindividual variation to determine if the variation in internal doses or predicted levels in urine and blood match observations of interindividual variation.

The P³M outputs also provide an opportunity to model the impact of autocorrelation of PBPK parameters in specific models. This impact can be measured by comparing model runs of population variance determined by generating a P³M output file and:

1. Model the population of interest by pulling data from an individual record. This use captures correlations between uses.
2. Model the population by randomly and independently sampling the parameter values from any record.

A comparison of the results will provide a measure of the impact of including the correlation of parameters in the model.

Data Gaps in the Models of Physiological Parameters

The project identified a number of gaps in the published literature for anthropometry-based models of organ volumes and mass. Future work on modeling intra-individual variation in organ size should seek to address the following issues:

1. Better models of adult organ volumes. If they are not correlated with age, gender, height, or weight, are they correlated to LBM?
2. Models for the volumes of the breast, GI tract, and urogenital organs.
3. Better models of adipose tissue in children.
4. Better models of brain volume in adults and children.
5. Additional modeling of body composition in children ages 6 months to 3 years. Existing studies tend to focus on either newborns or children aged 3 and above, resulting in a data gap for this age range.
6. The relationship of CO to organ volumes needs to be better defined. What is the source of the remaining variance that is not predicted by age, height, LBM, and weight?

Future Modeling of Physiological Parameters

It is important to note how recent are the publications cited in this article. The majority of the publications are less than 5 years old. This reflects how rapidly the field of modeling organ weights and volumes is progressing. In addition, NHANES IV is currently underway. This survey includes whole-body DXA assessment that will report TBBM, adipose tissue, and LBM for each individual. These data will allow the replacement of estimates of these tissues with actual measurements. Because of the ongoing publications and the NHANES IV data, the estimates of the parameters developed in this project should be reevaluated in the near future. Finally, future work in this area should seek to obtain the actual data so the variation associated with the residuals can be captured in the model.

VIII. CONCLUSIONS

The P³M program represents a tool for modeling autocorrelation between parameters typically used in PBPK modeling. While there is room for future improvements of the tool, the database and the software provide a useful tool for modeling variation in physiological parameters across individuals of different ages, genders and ethnicities.

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