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PHYSIOLOGICAL PARAMETER VALUES FOR PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

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INTRODUCTION

Physiologically based pharmacokinetic (PBPK) models are being used increasingly by regulatory agencies to estimate the internal dose of toxic agents or their metabolites to target tissues. Using this technique, risk assessments for toxic substances can be based on estimates of the amount of the agent that reaches the target tissue, rather than on the applied dose.

In PBPK modeling, the pharmacokinetic behavior of a compound in the body—that is, its absorption, distribution, metabolism, and elimination—is represented by equations that attempt to quantitatively describe actual physiological processes. The parameters of these equations are key anatomical and physiological descriptors of the organism, such as organ volume, organ

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2. Abbreviations: BW, body weight; DS, physiological dead space; F344, Fischer 344 rats; IBAT, intrascapular brown adipose tissue; ICRP, International Commission on Radiological Protection; NCI, National Cancer Institute; NTP, National Toxicology Program; PBPK, pharmacokinetic; Q_A, alveolar ventilation rate; RSI, Risk Science Institute; TCE, trichloroethylene; U.S. EPA, U.S. Environmental Protection Agency; V_E, minute volume; V_T, tidal volume.

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perfusion rates, and breathing rates. Values for these parameters can be determined experimentally, external to the process of fitting the model to the data. The advantage of such an approach is that a given model structure can be used to describe different species, sexes, strains, and conditions through choice of an appropriate set of parameter values. Although models are invariably simplifications of complex processes, their performance, accuracy, and biological relevance are enhanced by accurate specification of parameter values. Accurate characterization of parameter values is especially important for those parameters that have the greatest effect on the predictive ability of the model.

The parameter values necessary for the development of PBPK models fall into four broad classes: (1) physiological and anatomical descriptors; (2) partition coefficients of the compound between various media; (3) descriptors of metabolic transformation pathways; and (4) when the assumption of diffusion-limited uptake is made, transport parameters. Of these classes, the last three are compound-specific and must be determined anew in each case; the physiological and anatomical descriptors, however, will be common to models for many different compounds. Therefore, it is advantageous to accumulate a base of knowledge about representative physiological parameter values in multiple species.

In the application of pharmacokinetic models in risk assessment, the differences in compound disposition between humans and experimental animals are of particular interest. Therefore, there is a need to establish appropriate physiological values for humans and for the more commonly used laboratory species. To address this need, representative values and biologically plausible ranges of these values are provided for a number of anatomical and physiological parameters in multiple species. These representative values are means (or other measures of central tendency) selected from a review of the literature for healthy, resting, young adults. As a result, these values can serve as reasonable, empirically based defaults that can be used in a PBPK model when case-specific data are unavailable. Clearly, it is preferable to determine physiological and anatomical values directly on the individuals under study, or, at least, on individuals known to be drawn from the same population and subjected to similar conditions.

Several compilations of organ volumes, blood flows, and alveolar ventilation rates are available to provide representative values for these parameters in a PBPK model. The document prepared for the U.S. Environmental Protection Agency (U.S. EPA) by Arms and Travis (1988) has long served as the primary source of physiological parameter values for PBPK models. More recently, Davies and Morris (1993) have prepared a compilation of representative physiological parameter values that can be used in PBPK models. Each of these documents provides "reference values" for the physiological parameters, values that were selected by these investigators after their review of the literature. Although these reference values for specific parameters provide modelers with input values for PBPK models, they do not indicate the biological and experimental variability associated with data. The absence of information provided by Davies and Morris (1993) on the variability associated with their reference values prompted by following comment by Sothern and Gruber (1994).

In their article presenting "acceptable" values..., Davies and Morris [1993] give a single mean reference value for each parameter which they derived from an extensive search of the literature. While these values may be useful for broad interspecies scaling, they represent a ballpark without revealing the dimensions of the playing field.

Representation of the variability associated with these parameters is becoming increasingly important with the use of distributional approaches, such as Monte Carlo analysis, in PBPK models.

This paper was prepared to expand and improve on the efforts of Arms and Travis (1988) and Davies and Morris (1993) by providing modelers with information on the variability associated with each parameter and on factors that may influence the values selected for each parameter. This document also expands on the earlier efforts of Arms and Travis (1988) and Davies and Morris (1993) by expanding the database from which representative parameter values were selected; ensuring that parameter values are selected only from studies that used resting, healthy, unanesthetized (for cardiac output values) adults; providing documentation of the criteria used to select the studies; and addressing gaps in the data for several physiological parameters. Also included in this paper are discussions of the potential problems associated with the use of default parameter values in PBPK models.

BODY WEIGHT AND ORGAN VOLUME

The compartments of a PBPK model correspond to specific organs and tissues in the body or to organs and tissues that are grouped according to characteristics such the relative proportion of the cardiac output that they receive (e.g., richly perfused tissues). The goal of this section is to provide investigators with representative mean values for the volume of the organs, tissues, and tissue groups that typically are represented in PBPK models and an indication of the range of mean values for these parameters identified in different studies. Organ volume values are provided for the adrenals, adipose tissue, bone, brain, gastrointestinal tract, heart, kidneys, liver, lung, muscle, pancreas, skin, spleen, and thyroid in four species. When available, values also are provided for the weight of different regions within these tissues (e.g., stomach and small and large intestines of the gastrointestinal tract). Physiologically based pharmacokinetic models often are developed to simulate the pharmacokinetic behavior of a compound in a group of experimental animals with known body weights. However, models also can be developed for animals of a specified reference weight, typically a 25-g mouse, a 250-g rat, or a 70-kg human. These values were proposed by Arms and Travis (1988) as reference body weights and since have been widely used in PBPK models. Prior to a discussion of organ volume values, the validity of the reference body weights proposed by Arms and Travis (1988) will be explored.

CRITERIA FOR DATA SELECTION AND REPRESENTATION OF THE DATA

Body and organ weight values are provided in this document for healthy, adult animals. In general, organ weight data were not used from mice less than 20 g or 7 weeks of age and rats less than 200 g or 9 weeks of age. Data were collected only for strains of mice and rats that are commonly used in research; organ weight data for other strains of mice and rats can be found in the extensive compilations of data prepared by Crispens (1975) and Frank (1976). Also, only those animals fed a conventional laboratory chow diet were used in this study. No data were collected from transgenic animals or animals selectively bred to express a certain trait (e.g., obesity), captured in the wild, kept under adverse environmental conditions, or exposed to drugs or toxic agents.

Data obtained on organ weights of B6C3F1 mice and Fischer 344 (F344) rats used as controls in 13-week studies conducted by the National Toxicology Program (NTP) are reported separately from data extracted from the open literature. Separate listing of these data provides investigators who are using these strains exclusively for pharmacokinetic or modeling purposes with access to a data set specific for these strains.

Two very comprehensive sources of organ weight data were not used to provide values for this report: (1) the encyclopedic collection of organ weight data for rats complied by Donaldson (1924) and (2) the paper by Crile and Quiring (1940) providing organ weight data on multiple species. A concern exists that organ weight values from these sources may not be representative of the organ weights in strains of animals currently used in research.

Laboratory animal breeders and contract laboratories are potentially useful sources of organ weight data. Data reported by Frank (1976) from these sources were used in this analysis, but the reader should be aware that these values were not reported in the peer-reviewed open literature.

With few exceptions, the values provided for the weight of human organs were taken from the International Commission on Radiological Protection (ICRP) Report of the Task Group on Reference Man (ICRP, 1975). Given the comprehensive nature of this work and its degree of acceptance in many fields no attempt was made to refine or expand these values. The intent of this document is to provide investigators with physiological parameter values for the species that are used most commonly in pharmacokinetic studies (mouse, rat, dog, and human). When the data were available, equations are provided in the text to allow investigators to estimate age- and body-weight-related changes in organ weight within a species.

The physiological parameter values provided in the tables in the body of the document are means of the mean values reported in individual studies. The standard derivation values are standard deviations of the reported means. This approach was necessary because values for individual animals rarely were reported in the literature. Although representation of the data in this way may be useful as a measure of central tendency, it does not fully represent the variability of the data for individuals within a species. Instead, the standard deviations reported in this paper are measures of the variation among the different studies. This variability may be due to sampling error; interlaboratory variation; and, notably for some parameters (e.g., adipose tissue weight), differences in the techniques used to obtain the data. As a result, these standard deviations reflect uncertainty more than biological variability.

Mean values for organ weight, represented as a fraction of the body weight, were derived only from those studies that provided explicit body weight data or that presented the data as percent body weight. Relative organ weight values were not derived when only a range of body weights was provided in the study. Also, default organ weight estimates used in PBPK models were not used to derive the mean values reported in this paper. Only those studies that reported values obtained experimentally were used as sources of data.

In most cases, the values provided in this paper reflect the weight of organs that are drained of blood. Notable exceptions are the data on mouse organ weight obtained from the Durbin et al. (1992), where an effort was made to retain the blood in the tissues. As will be discussed in some detail in the section on adipose tissue, the weight of the adipose tissue reflects the weight of dissectible tissue only. Gastrointestinal tissue weights do not include the contents of the gut. The weight of the "bone" in rodents is, in some cases, the wet weight of the entire skeleton. When data were provided in a study for only one-half of a paired organ (e.g., kidney), the assumption was made that the weight of both halves was equal to twice the weight of the organ from one side.

BODY WEIGHT

Whenever possible, the actual weight of the animals undergoing the pharmacokinetic study should be used when developing a PBPK model to describe the pharmacokinetic behavior of a compound or drug. However, default or reference body weight values may be necessary for certain applications, such as scaling pharmacokinetic data across species for a body weight "standard".

The reference body weight values selected by Arms and Travis (1988) for mice and rats were derived largely from the standard body weights recommended by the U.S. EPA (1980) for these species. Reference body weights of 30 and 350 g are recommended in the U.S. EPA (1980) document for mice and rats, respectively, because they are intended to approximate the terminal weight for these species. However, Arms and Travis (1988) recommended reference body weights of 25 and 250 g be used for mice and rats, respectively, because they felt that animals typically are used in pharmacokinetic studies before they reach terminal body weight. In contrast, Arms and Travis (1988) recommend 70 kg as the reference weight for humans, a value that approximates the terminal body weight in human males.

Male B6C3F1 mice and F344 rats that weigh 25 and 250 g, respectively, are only about 9–10 weeks of age, an age at which these animals are undergoing rapid growth. There are several concerns with the selection of reference body weights that occur in animals in a rapid-growth phase. First, animals remain at this weight for only a short period; therefore, the proposed reference weights are not representative of the weight of the animals for the majority of their lifespans. Second, organ weights are represented in this document as a fraction of the body weight. As long as the organ weight/body weight ratio remains the same across all body weight values, then the selection of any body weight as the reference weight may be valid. Although the organ weight/body weight ratio remains constant for most organs across body weights, there are notable exceptions, particularly the volume fraction of fat. As will be discussed in the section on adipose

tissue, the dissectible fat weight is about 9% of the body weight in a 250-g male F344 rat and about 16% of the body weight in a 450-g rat. Because a male F344 rat weighs about 450 g for most for its life, it would be inappropriate to derive a representative value for volume fraction of fat in this species based on the reference body weight proposed by Arms and Travis (1988). Finally, an inconsistency exists when body weight values for mice and rats in a rapid-growth phase are used to develop a PBPK model that will be scaled up to adult, 70-kg humans.

Body Weight in Mice

Altman and Dittmer (1972) and Frank (1976) have compiled body weight values for a number of strains of mice. Terminal body weight values reported by these investigators range from 28–40 g in male mice and about 28–37 g in female mice, depending on the strain.

Data on age-related changes in body weight are compiled routinely for control animals used in carcinogenesis bioassays conducted or sponsored by NTP or the National Cancer Institute (NCI). These compilations serve as useful and comprehensive sources of data on age-related changes in body weight for strains of mice and rats that often are used in PBPK modeling efforts.

Cameron et al. (1985) described age-related changes in body weight among B6C3F1 mice used as controls in carcinogenesis bioassays conducted or sponsored by NCI between 1968 and 1981. Data collected on these animals indicate that male mice gain approximately 1g/week of body weight from the time they are put on test (6 weeks of age) to about 20 weeks. The mice then gain weight more gradually until a maximum is reached about Week 80. A gradual weight loss is observed in male mice from Week 80 to Week 110. A somewhat different growth pattern was observed for female mice. The initial growth phase is not as rapid and a weight loss late in life was not observed. In fact, untreated female mice weighed 1.3 g more than their male counterparts at Week 110.

Presumably, age-associated body weight data were used by Cameron et al. (1985) to derive the mean values without regard to the year in which the bioassay was conducted. However, Rao et al. (1990a) observed that the maximum mean body weight of B6C3F1 mice used in NCI or NTP bioassays decreased over a 9-year period from 1973–1981. For example, the maximum mean body weight of male mice used as controls in bioassays initiated in 1973 was 45.4 g, whereas the maximum mean body weight of male mice used as controls in bioassays started in 1981 was 41.9 g. A similar but less dramatic trend was seen in the body weight of female mice.

To provide an indication of the weight of mice used in more contemporary studies, the body weight data reported by NTP for mice used in the 2-year bioassay of mercuric chloride (NTP, 1993a) were used to establish the relationship between age and body weight in B6C3F1 mice at different growth stages. From these data, it appears that male mice typically go through four growth phases during their lives. A rapid growth phase occurs from birth to about 19 weeks of age; this is followed by a period of more gradual growth from 19 to about 67 weeks of age. Body weight seems to plateau at around 40 g in male mice from 67–91 weeks of age, followed by a gradual decline in body weight in animals from 91–109 weeks of age. A similar pattern is seen in female mice; however, the final stage of age-related loss of body weight is less dramatic, with

body weight plateauing at around 35 g for the remainder of the lifespan. Table 1 provides regression equations for estimating the body weight of male and female B6C3F1 mice of various ages. General use of these relationships requires the assumption that the growth patterns displayed by the mice used in this particular NTP bioassay study are representative of their strain and species.

The relationships shown in Table 1 are consistent with the observation that male B6C3F1 mice weighing 25 g are only about 9 weeks of age. Therefore, this reference value is not representative of the body weight of an adult animal.

TABLE 1. Age-Related Growth in B6C3F1 Mice

Age (Weeks)	Male	Female
7–19	0.68(age) + 18.98 r = 0.97	
7–18		0.50(age) + 15.61 r = 0.94
20–67	0.18(age) + 28.04 r = 0.98	
19–63		0.25(age) + 19.51 r = 0.99
68–91	Plateau around 40 g	
64–109		Plateau around 35 g
92–109	-0.24(age) + 61.78 r = -0.65	

Body Weight in Rats

Terminal body weight in rats ranges from about 335 g to over 500 g in male rats and about 220 g to over 300 g in female rats, depending on the strain (Altman and Dittmer, 1972; Frank, 1976).

Unlike the time-related decreases in maximum mean body weight observed in B6C3F1 mice used in NCI or NTP bioassays, Rao et al. (1990b) noted a marked increase in the mean body weight of male and female F344 rats used in NCI and NTP bioassays from 1971–1983 (Table 2).

Cameron et al. (1985) reported that the body weight of male F344 rats reached a maximum of about 428 g at 76 weeks. However, according to Rao et al. (1990b), the mean maximum body weight of male F344 rats put on test in 1983 was 477 g. This value is consistent with the maximum body weight of male F344 rats used in the recent NTP (1993a) bioassay of mercuric chloride. Body weights from control male and female rats in this study were used to derive the regression equations shown in Table 3.

Male F344 rats weighing 250 g are only about 10 weeks of age and are in a rapid phase of growth. The terminal weight of these animals, about 450–475 g, is maintained for most of the second year of life. The terminal weight of male Sprague-Dawley rats can exceed 500 g (Gur and Waner, 1993).

TABLE 2. Time-Related Changes in Body Weight in Untreated Male and Female F344 Rats Used in NCI and NTP Bioassays (Rao et al., 1990b)

	Body Weight (g)	
Year	Male	Female
1971	408	307
1972	422	310
1973	441	313
1974	444	315
1975	466	318
1976	433	316
1977	447	321
1978	441	308
1979	452	319
1980	470	335
1981	477	347
1982	484	359
1983	477	346

TABLE 3. Age-Related Growth in F344 Rats

Age (Weeks)	Male	Female
7–19	16.20(age) + 86.80 r = 0.97	6.60(age) + 94.0 r = 0.94
20–34		Plateau around 225 g
20–55	2.59(age) + 330.00 r = 0.99	
35–91		2.07(age) + 152.93 r = 0.99
56–91	Plateau around 475 g	
92–109	-2.38(age) + 691.7 r = -0.94	Plateau around 330 g

Body Weight in Dogs

Body weight in dogs is highly strain-dependent and can range from around 1 kg to over 100 kg. However, the beagle commonly is used when dogs are required in preclinical toxicity and pharmacokinetic studies. Andersen (1970) conducted a survey of caretakers in 18 commercial or institutional beagle colonies and found that male beagles typically are used for experimental purposes when they weigh about 23 lbs (10.5 kg); female beagles typically are used when they weigh about 20 lbs (9.9 kg). In the same volume, Andersen and Goldman (1970) provide data on age-related changes in body weight in male and female beagles. In female beagles, body weight seems to plateau at around 7–9 kg in the first or second years of life and around 9–11 kg from Years 2–7. One group of animals a little over 3 years of age weighed about 15.5 kg.

Body Weight in Humans

The ICRP (1975) has recommended a reference human body weight of 70 kg for males and 58 kg for females. Although there is widespread acceptance of these values as reference body weights for male and female humans, they were derived primarily from only two studies (Stoudt et al., 1960, 1965). Furthermore, subjects selected for these studies represent only one race and geographic area. Therefore, these values should be used with some caution as reference body weights for humans.

Designation of reference body weights does not provide information on the variability associated with body weight values. Stoudt et al. (1960) reported that the mean body weight for males was 71.7 kg, with a standard deviation of 10 kg, and was 56.7 kg for females, with a standard deviation of 8.6 kg.

In summary, the reference body weights proposed by Arms and Travis (1988) for mice and rats may be representative of the weight of the animals typically used in pharmacokinetic studies but are markedly lower than body weights attained by these animals for a majority of their lifespan. Use of these reference weights in a PBPK model could result in an underestimate of the volume of the fat compartment in adult mice and rats. Equations are provided for estimating age-related changes in body weight in F344 rats and B6C3F1 mice. Although reference values are not provided in this document, it appears that representative body weights for adult male and female B6C3F1 mice are about 35 and 40 g, respectively. Representative body weights for adult female and male F344 rats are about 330 and 450–475 g, respectively. Body weight values in beagle dogs used for experimental purposes range from about 9–16 kg. Regarding human body weight values, it is important to recognize that the reference body weights for humans derived by the ICRP (1975) and adopted by Arms and Travis (1988) are representative only for one race of humans in one geographical area.

ORGAN WEIGHT

Values for the volume (or weight) fraction of organs and tissues typically represented in PBPK models are provided in Tables 4–7 for mice, rats, dogs, and humans, respectively. The mean values reported in Tables 4–6 were derived from experimentally derived mean values reported in the literature.

Organ weight values have been reported by NTP since 1991 for control and treated in animals 13-week and 2-year studies. Typically, data are reported on the weight of the brain, heart, right kidney, liver, lung, and thymus in animals undergoing 13-week studies and on the weight of the brain, right kidney, and liver at a 15-month time interval in the 2-year bioassay. Mean organ weight values were derived for B6C3F1 mice and F344 rats from the organ weight data reported in 10 randomly selected bioassays for control animals in 13-week exposure studies. These values are summarized in Table 8. There appears to be relatively little difference in body weight-normalized values for organ weight among different strains of rats used in NTP studies (Table 9).

TABLE 4. Relative Organ Weight (Percent Body Weight) in Mice

Organ	Mean ± Standard Deviation	Range	Number	
			Studies	Animals
Adipose Tissue	See text	See text		
Adrenals	0.048		[a]	**5**
Bone	10.73 ± 0.53	10.16–11.20	3	**30**
Brain	1.65 ± 0.26	1.35–2.03	4	**419**
Gastrointestinal Tract				
Stomach	0.60		**1**	**5**
Small Intestine	2.53		**1**	**5**
Large Intestine	1.09		1	**3**
Heart	0.50 ± 0.07	0.40–0.60	4	**46**
Kidneys	1.67 ± 0.17	1.35–1.88	7	**84**
Liver	5.49 ± 1.32	4.19–7.98	7	**84**
Lungs	0.73 ± 0.08	0.66–0.86	5	**35**
Muscle	38.40 ± 1.81	35.77–39.90	4	**40**
Pancreas	See text	See text		
Skin	16.53 ± 3.39	12.86–20.80	5	**45**
Spleen	0.35 ± 0.16	0.16–0.70	5	**60**
Thyroid	No data	No data		

[a]Dowell et al. (1992)

TABLE 5. Relative Organ Weight (Percent Body Weight) in Rats

Organ	Mean ± Standard Deviation	Range	Number	
			Studies	Animals
Adipose Tissue	See text	See text		
Adrenals	0.019 ± 0.007	0.010–0.031	**7**	1017
Bone	See text	See text		
Brain	0.57 ± 0.14	0.38–0.83	**9**	**548**
Gastrointestinal Tract				
Stomach	0.46 ± 0.06	0.40–0.60	**4**	46
Small Intestine	1.40 ± 0.39	0.99–1.93	**4**	46
Large Intestine	0.84 ± 0.04	0.80–0.89	**4**	46
Heart	0.33 ± 0.04	0.27–0.40	**9**	**632**
Kidneys	0.73 ± 0.11	0.49–0.91	**12**	1091
Liver	3.66 ± 0.65	2.14–5.16	**15**	2230
Lungs	0.50 ± 0.09	0.37–0.61	**7**	**173**
Muscle	40.43 ± 7.17	35.36–45.50	**2**	**30**
Pancreas	0.32 ± 0.07	0.24–0.39	**3**	**34**
Skin	19.03 ± 2.62	15.80–23.60	**3**	**138**
Spleen	0.20 ± 0.05	0.13–0.34	**5**	**582**
Thyroid	0.005 ± 0.002	0.002–0.009	8	215

TABLE 6. Relative Organ Weight (Percent Body Weight) in Dogs

	Mean ± Standard Deviation	Range	Number	
			Studies	Animals
Adipose Tissue				
Adrenals	0.009 ± 0.004	0.004–0.014	4	64
Bone	8.10		1	8
Brain	0.78 ± 0.16	0.43–0.86	4	230
Gastrointestinal Tract				
Stomach	0.79 ± 0.15	0.65–0.94	4	37
Small Intestine	2.22 ± 0.68	1.61–2.84	4	37
Large Intestine	0.67 ± 0.03	0.65–0.69	2	37
Heart	0.78 ± 0.06	0.68–0.85	6	206
Kidneys	0.55 ± 0.07	0.47–0.70	6	206
Liver	3.29 ± 0.24	2.94–3.66	6	206
Lungs	0.82 ± 0.13	0.62–1.07	9	339
Muscle	45.65 ± 5.54	35.20–53.50	2	24
Pancreas	0.23 ± 0.06	0.19–0.30	3	14
Skin	See text	See text		
Spleen	0.27 ± 0.06	0.21–0.39	6	182
Thyroid	0.008 ± 0.0005	0.0074–0.0081	2	10

Adipose Tissue

Prior to discussing values for this parameter, it is important first to define what constitutes the fat compartment in a PBPK model. In their review of PBPK modeling principles, Krishnan and Andersen (1994) have noted that "fat depots such as perirenal, epididymal, and omental fat as well as the adipose component of many other tissues are grouped and represented as a single 'fat' compartment." However, values selected for this parameter in rodent PBPK models largely come from studies in which the fat was carefully dissected from the animal (e.g., Caster et al., 1956; Decad et al., 1981; Gasiewicz et al., 1983; Banks et al., 1990; Delp et al., 1991). Consequently, the fat compartment in most rodent PBPK models primarily represents dissectible fat in fat depots and, depending on how the dissection was done, the fat that is present interstitially in muscle (but not the adipose component of other tissues). There are two reasons why the weight of the adipose component of other component tissues usually is not included in the fat compartment: (1) the adipose would already be accounted for in the total weight of those organs, and (2) any storage role for these lipids would be accounted for in the partition coefficient for these tissues. Therefore, for the purposes of this document, the weight of the adipose tissue in mice, rats, dogs, and humans is intended to represent the weight of dissectible fat, not the total fat content of those species.

Values for the fat content of humans is rarely derived through dissection; rather, techniques such as *in vivo* neutron activation analysis, whole body counting for total body potassium, tritiated water dilution for total body water, bioelectric impedance, underwater weighing, and skin-fold anthropometry are commonly used to estimate total body fat. However, values reported in this section were obtained from the limited studies of human cadaver dissection.

TABLE 7. Relative Organ Weight (Percent Body Weight) for Reference Man (ICRP, 1975)

Organ	Reference Weight
Adipose Tissue[a]	21.42
Adrenals	0.02
Bone[b]	14.29
Brain	2.00
Gastrointestinal Tract[c]	1.71
Stomach	0.21
Small Intestine	0.91
Large Intestine	0.53
Heart	0.47
Kidneys	0.44
Liver	2.57
Lungs[d]	0.76
Muscle	40.00
Pancreas	0.14
Skin	3.71
Spleen	0.26
Thyroid	0.03

[a]Subcutaneous, separable yellow marrow, interstitial.
[b]Bone and marrow.
[c]Except esophagus.
[d]Without blood.

TABLE 8. Relative Organ Weight (Percent Body Weight) of Control B6C3F1 Mice and F344 Rats Used in 13-Week NTP Studies[a]

	B6C3F1 Mice		F344 Rats	
Organ	Male	Female	Male	Female
Adrenals	0.02	0.04	0.01	0.03
Brain	1.49	1.98	0.56	0.90
Heart	0.53	0.53	0.30	0.34
Kidneys	1.75	1.52	0.67	0.69
Liver	4.62	4.73	3.49	3.22
Lungs	0.70	0.83	0.45	0.55
Thymus	0.12	0.22	0.09	0.13
Body Weight	30.57	23.91	341.90	195.60

[a]Values are means of mean organ weight values reported in 10 randomly selected 13-week NTP studies.

TABLE 9. Relative Organ Weight (Percent Body Weight) of Three Strains of Rats Used as Controls in a 13-Week NTP Study

	F344		Sprague-Dawley		Osborne-Mendel	
Organ	Male	Female	Male	Female	Male	Female
Brain	0.54	0.93	0.47	0.73	0.50	0.71
Heart	0.29	0.33	0.41	0.40	0.37	0.37
Kidneys	0.68	0.76	0.84	0.76	0.74	0.66
Liver	4.29	3.53	4.11	4.12	3.92	3.79
Lung	0.48	0.62	0.55	0.71	0.45	0.56
Thymus	0.08	0.13	0.11	0.14	0.08	0.11
Body Weight (g)	363	194	449	271	421	274

Table 10 summarizes data on the dissectible fat content of nine strains of mice used in research. Values for dissectible fat content range from 5–14% and are highly strain and age dependent. For example, the mean fat content of DBA strain mice is 12.2%, compared to a mean fat content of 6.8% in C57BL strain mice (with body weights ≤ 33 g).

In heavier mice, fat constitutes a greater percentage of body weight. Birnbaum (1993) has shown that 18-month-old C57BL/6N mice, weighing 37.5 g, have a fat content of 14%, whereas 3-month-old mice of the same strain, weighing 30.1 g, have only about half as much fat (7.4%). This does not appear simply to be an age-related effect because since 28-month-old animals of the same strain, weighing 33 g, had a fat content of 7.6%.

West et al. (1992) have conducted an extensive investigation of the fat content of various strains of mice. Values are provided in this paper for the weight of various adipose tissue depots (e.g., epididymal, retroperitoneal, inguinal, mesenteric, and interscapular). Although these data may be useful for investigators who require data on the weight of individual fat depots, it is not clear that the sum of the depot weights represents the weight of all of the dissectible fat in these mice. For example, the sum of the tissue weights from these depots, as reported by West et al. (1992), equals 2.02 and 4.26% of the body weight in C57BL/6J and DBA/2J mice, respectively, compared to values about three times greater for these strains reported by Decad et al. (1981) and Gasiewicz et al. (1983). The weight of various adipose tissue depots in mice also has been reported by Atal et al. (1994) and Rebuffe-Scrive et al. (1993).

Values reported by Caster et al. (1956), Lutz et al. (1977), and Delp et al. (1991) for fat content of the rat have been used widely for this parameter in PBPK models. In these studies, fat content was determined by careful dissection, removal, and weighing of all visible adipose tissue. The values for fat content reported in these studies range from 5.5–7.0% for male Sprague-Dawley rats.

TABLE 10. Fat Content of Mice

Strain	Sex	Body Weight	Tissue Weight (Percent Body Weight)	Reference
C57BL/6J	Male	23.1	5.9	Gasiewicz et al. (1983)
C57BL/6J	Male	26.0	7.5	Decad et al. (1981)
C57BL/6N	Male	25.2	5.8	Birnbaum (1993)
C57BL/6N	Male	33.0	7.6	Birnbaum (1993)
C57BL/6N	Male	30.1	7.4	Birnbaum (1993)
C57BL/6N	Male	37.5	14.0	Birnbaum (1993)
DBA/2J	Male	23.9	11.5	Gasiewicz et al. (1983)
DBA/2J	Male	25.1	12.9	Decad et al. (1981)
B6D2	Male	24.3	5.0	Gasiewicz et al. (1981)

Bailey et al. (1980) have conducted a thorough study of body weight-related changes in the weight of individual fat depots in male Sprague-Dawley rats and have derived intraspecies allometric equations to describe these relationships (Table 11).

Data on age- and body weight-associated changes in the weight of intrascapular brown adipose tissue (IBAT) in male Sprague-Dawley rats were reported by Sbarbati et al. (1991). Based on these data, the following relationship can be derived to estimate the weight of this fat depot as a function of body weight:

IBAT Weight (g) - 0.00094 (BW) + 0.12, r = 0.96,

where BW equals body weight in grams.

Body weight-related changes in the combined weight of the fat depots in male Sprague-Dawley rats, as reported by Bailey et al. (1980) are shown in Table 12. These values are fairly consistent with those obtained by Delp et al. (1991) for the weight of all dissectible fat.

Assuming the sum of the fat depot weights in the Bailey et al. (1980) study closely approximates the total weight of dissectible fat, the following relationship can be used to estimate the proportion of the body weight in male Sprague-Dawley rats that represents dissectible fat:

Adipose Tissue (% BW) = 0.0199 (BW) + 1.664, r = 0.99,

where BW equals body weight in grams.

TABLE 11. Intraspecies Allometric Equations To Describe the Relationship Between Body Weight and the Size of Various Fats Depots in Male Sprague-Dawley Rats (Bailey et al., 1980)

Fat Depot	Equation[a]	r
Axillary	$y = 0.83\ BW^{1.55}$	0.945
Buttock	$y = 0.16\ BW^{1.68}$	0.961
Epididymal	$y = 0.012\ BW^{2.16}$	0.981
Inguinal	$y = 0.009\ BW^{2.29}$	0.951
Mesenteric	$y = 0.97\ BW^{1.40}$	0.937
Perirenal	$y = 0.00062\ BW^{2.70}$	0.976

[a]y = log tissue weight (mg), BW = log body weight (g).

TABLE 12. Body Weight-Related Changes in the Total Fat Depot Weight in the Male Sprague-Dawley Rats (Bailey et al., 1980)

Body Weight (g)	Total Fat (g)	Depot Weight (Percent Body Weight)
152.2	7.016	4.61
254.5	18.354	7.21
337.6	27.072	8.02
443.1	44.410	10.02
497.1	59.785	12.03

Extensive use of the rat as an animal model in nutrition and endocrinology research has lead to the publication of a large body of literature containing values for the fat content of various strains of rats. Typically, chemical extraction methods are used in these studies to determine the total amount of fat in the body. Use of chemical extraction or other methods to determine total body fat content often yields values that are as much as two to three times higher than those obtained though dissection. Therefore, modelers requiring these data should keep in mind how values for fat content were obtained before using these values in a PBPK model. However, chemical extraction methods also can be used to assess the accuracy of dissection methods to determine fat weight. For example, using direct dissection, Manning et al. (1991) found the body fat of male Sprague-Dawley rats to be 7.36% of the total body weight. Chemical extraction of the carcass, minus the visceral organs, yielded a similar value (6.9%) for this parameter.

To accurately describe age-related changes in the pharmacokinetic behavior of 2,3,7,8-tetrachlorodibenzo-p-dioxin in F344 rats, Birnbaum and colleagues (Banks et al., 1990; Anderson et al., 1993) obtained data on the fat content of F344 rats from age 3–120 weeks (Table 13). Based on these data, the following relationship can be derived to estimate fat content from body weight in male F344 rats:

Fat Content (% BW) = 0.035 (BW) + 0.205, r = 0.98,

where BW equals body weight in grams. This equation has recently been used to estimate the fat content of male F344 rats in the PBPK models developed by Kedderis et al. (1993) and Evans et al. (1994).

As shown in Table 13, age-related differences in the fat content of male F344 rats have been reported in at least two other studies. Although comparisons at the same time points are not possible, the fat content values reported by Carter et al. (1991) for carcass without visceral organs are comparable to those reported by Banks et al. (1990) and Anderson et al. (1993). Close correspondence of the values obtained by dissection (Banks et al., 1990; Anderson et al., 1993) and chemical extraction of the carcass (Carter et al., 1991) suggest that careful dissection can yield accurate values for the fat content of the animal, minus the visceral organs, as also shown in the Manning et al. (1991) study. Rikans et al. (1993) reported obtained values for fat content of male F344 rats using a dual-energy X-ray absorptiometry technique. These values are somewhat higher than those reported by Banks et al. (1990), Anderson et al. (1993), or Carter et al. (1991), perhaps, in part, because this technique quantifies all of the lipid in the body.

TABLE 13. Fat Content of Male F344 Rats

Week	Study			
	Anderson et al. (1993)	Banks et al. (1990)	Carter et al. (1991)	Rikans et al. (1993)
3	4.0 ± 0.7			
5	4.3 ± 0.2			
8	9.6 ± 0.3			
10		10.6 ± 0.7		
13			**10.0**	
21				21 ± 1
36		15.6 ± 0.7		
52			**13.8**	
56				29 ± 1
64		16.0 ± 2.1		
86		18.2 ± 2.2		
100			**15.1**	
117				17 ± 1
120		13.0 ± 3.3		

Wilkinson and McEwan (1991) used an ultrasound technique to estimate the thickness of the subcutaneous layer of fat in dogs at different body sites and correlated subcutaneous fat thickness to total body fat. Using this technique, they found fat constitutes about 38.2% of the body weight in beagles; however, this value seems to be too high for beagles used for experimental purposes.

Studies of fat content in humans number in the hundreds, if not thousands. However, relatively few studies have employed dissection to obtain these values. Clarys et al. (1984) summarized the results of all of the studies they identified in the literature in which human fat content values were obtained through dissection. Values for fat content in adult males 30–60 years of age (mean age = 42.4 years) range from 5.2–21.6% of the total body weight (mean fat content = 13.6 ± 5.3%, number = 7). Only two values were provided in this summary for adult females, one of which was a 67-year-old woman who died from carcinoma. Therefore, these data were not used in this analysis.

In addition, Clarys et al. (1984) determined the fat content of 25 adult cadavers using dissection. However, the mean ages of males and females in this study were 72 and 80 years, respectively. Because fat content increases in humans with increasing age (Deurenberg et al., 1991), the values obtained by Clarys et al. (1984) are not representative of young adult humans. The ICRP (1975) offered the following default values for weight of adipose tissue in a 70-kg reference man and a 58-kg reference woman (Table 14).

TABLE 14. Adipose Tissue Distribution in Humans as Reported by ICRP (1975)

	Relative Adipose Tissue Weight (Percent Body Weight)	
Site	Male (70 kg)	Female (58 kg)
Subcutaneous	10.7	22.4
Separable	7.1	6.9
Yellow Marrow	2.1	2.2
Interstitial	1.4	1.2
TOTAL	21.3	32.7

The total fat mass corresponds to 21.3% of the body weight in males and 32.7% of the body weight in females.

If estimates of fat content in humans are encountered in the literature, modelers should be aware that these estimates can vary widely depending on the techniques used to obtain the estimates. For example, estimates of fat content in males can vary from about 15–16%, as measured using bioelectrical impedance, to a value about twice as high in the same subjects, when estimated based on total body potassium (Wang et al., 1993a). Therefore, variability in reported fat content values in humans is due, in part, to the experimental technique used to obtain these values.

To improve the fit of PBPK model-derived simulations to experimental data, it may be necessary to include more than one fat compartment in the model. Fiserova-Bergerova (1992) provides an example of how two fat compartments were included in a PBPK model of anesthetic agents in humans. Consistent with the reference values provided by the ICRP (1975), Fiserova-Bergerova (1992) assumed that 60% of the body fat of a reference man is subcutaneous fat, and 35% of the fat is found in internal fat depots; the remaining 5% is assumed to be interstitial fat and is not explicitly represented in the model.

Adrenal Glands

The adrenals rarely are represented as a separate compartment in PBPK models. Nevertheless, the weight of this organ often is determined in control and treated animals in toxicity studies. As a result, data are readily available on the weight of this organ in experimental animals.

The adrenals constitute approximately 0.02% of the body weight in male B6C3F1 mice at the end of 13-week studies conducted by NTP and 0.04% of the body weight of female mice used in these studies. These estimates are consistent with the data reported by Dowell et al. (1992) for female C57BL mice. However, the data compiled by Frank (1976) on the weight of the adrenals in 20 strains of mice suggest that the mean weight of this organ in male mice is on the order of 0.01 and 0.02% of the body weight for male and female mice, respectively.

Based on data from six studies and over 1000 animals, the mean relative weight of the adrenals in rats is approximately 0.02% of the body weight. The adrenals of male F344 rats used as controls in 13-week NTP studies constituted about 0.01% of the body weight; the relative weight of the adrenals in female rats was about 0.03% of the body weight.

The relative weight of the adrenals ranges from about 0.004–0.14% of the body weight in dogs, with a mean weight of about 0.01%.

In humans, adrenal weight remains fairly constant throughout adult life, weighing about 13 g in males and 12 g in females, or about 0.02% of the body weight (ICRP, 1975).

Bone

The fraction of the body weight composed of bone in mice is fairly consistent in the three studies identified that report these data. Baxter et al. (1994) found that bone comprises 10.16% of the body weight in female Nu/Nu mice, Bourne et al. (1992), reported a value of 10.83% of the body weight in female Balb/c mice, and Durbin et al. (1992) determined that the skeleton comprised 11.20% of the body weight of female Swiss Webster mice.

Values for relative bone weight in rats reported in most studies range from 5–7% of the body weight. Caster et al. (1956) determined that the fresh weight of the skeleton constituted 5.96% of the body weight in rats. Donaldson (1924) has compiled an extensive collection of data on body weight- and age-related changes in bone weight in Albino rats. These data suggest the skeleton of a 250-g rat constitutes about 6% of the body weight, whereas the skeleton of a 450-g rat constitutes about 5% of the body weight. MacPherson and Tothill (1978) determined fat-free

bone weight to be 4.77 ± 0.17% of the body weight of male rats. Prior to developing a PBPK model for bone-seeking elements in the growing rat, O'Flaherty (1991a) characterized age-related changes in bone weight and volume in rats. From O'Flaherty's review of the literature, values of 7.3 g/100 g body weight and 4.9 mL/100 g body weight were selected as the mass and volume, respectively, of the skeleton (minus cartilage) in a mature small animal skeleton. In contrast to these values that range from about 5–7% of the body weight, Delp et al. (1991) reported that the mass of bone in rats with a mean weight of 366 g was 53.9 g, or about 14.7% of the body weight. The discrepancy between values for bone weight reported by most investigators and those obtained by Delp et al. (1991) may be due, in part, to residual tissue present on the bones in the Delp et al. (1991) study. For example, cartilage was included with many of the bones dissected from the rat, especially the ribs. Also, small amounts of residual muscle and connective tissue remained even after scraping. Because such marked differences exist among values for this parameter identified by different investigators, no mean value across studies was derived for Table 5.

Few studies have been published that report total bone weight in dogs. The mean relative bone weight in mongrel dogs with a mean body weight of 21 kg is 8.1% of the body weight (Quillen and Reid, 1988).

The entire skeleton of a reference adult male human makes up 14.3% of the body weight (ICRP, 1975). This value is essentially identical to that reported by Clarys et al. (1984) for dissected cadavers. Bone comprises 50% of the weight of the skeleton (or 7.1% of the body weight) in humans; 80% of the bone mass is cortical bone, and 20% is trabecular bone. The remainder of the skeleton is composed of red marrow (hematopoietic tissue), yellow marrow (fatty tissue), cartilage, and periarticular tissue. O'Flaherty (1991a) identified the proportion of the mature skeleton (minus cartilage) in a 350-g male rat that would be represented by cortical bone, trabecular bone, red marrow, and yellow marrow. These estimates are shown in Table 15, with similar estimates for the composition of bone in mice and humans from Durbin et al. (1992) and ICRP (1975), respectively.

TABLE 15. Composition of the Skeleton (as Percent of Body Weight)

	Mouse[a]	Rat[b]	Human[c]
Skeleton	11.2	7.3	14.3
Bone	5.4	5.0	7.1
Cortical	4.0	4.0	5.7
Trabecular	1.4	1.0	1.4
Red Marrow		2.1	2.1
Yellow Marrow	5.8[d]	0.2	2.1
Cartilage			1.6
Periarticular Tissue			1.3

[a]Durbin et al. (1992).
[b]O'Flaherty (1991a).
[c]ICRP (1975).
[d]Bone soft tissue, mostly marrow, but also may include some connective tissue and adherent muscle.

O'Flaherty (1991a,b) has derived intraspecies allometric equations to predict skeletal weight, marrow weight, and marrow-free bone weight in rats and humans as a function of age (Table 16).

TABLE 16. Body-Weight-Dependent Changes in Bone Weight in Rats and Humans (O'Flaherty, 1991a,b)

	Rat[a]	Human[b]
Skeletal Weight (g) =	$0.0801\ (BW)^{0.983}$	$58\ (BW)^{1.21}$
Marrow Weight (g) =	$0.0469\ (BW)^{0.866}$	$7.02\ (BW)^{1.46}$
Marrow-Free Bone Weight (g) =	$0.0257\ (BW)^{1.10}$	$29\ (BW)^{1.21}$

[a]BW = body weight in grams.
[b]BW = body weight in kilograms, marrow-free bone weight in humans includes marrow-free and cartilage-free bone weight.

Brain

The brain constitutes about 1.7% of the body weight in mice, 0.6% in rats, 0.8% in dogs, and 2.0% in humans. When expressed on a body weight-normalized basis, a difference in brain weight also exists between male and female rodents (Table 8), principally because of the relatively larger mass of male animals.

The brain has been represented as a single compartment in a number of PBPK models of compounds with neurotoxic or therapeutic effects on the central nervous system. However, parallel increasing knowledge of the site specificity of drug or neurotoxicant action in the brain, more sophisticated PBPK models are being developed that represent different regions of the brain in the models. Therefore, knowledge of the relative weight of the brain regions in different species is important for PBPK models that represent these regions. Table 17 provides information on the relative weight of the cerebrum, cerebellum, and brain stem in rats and humans.

TABLE 17. Relative Weight of Brain Regions in Rats and Humans

	Percent of Total Brain Weight	
Region	Rat[a]	Human[b]
Cerebrum	51.6	85–88
Cerebellum	14.3	10–12
Midbrain	15.2	
Olfactory Lobe	2.8	
Brain Stem	16.1	1.9–2.3
Medulla	11.5	
Pons	4.6	

[a]Delp et al. (1991).
[b]ICRP (1975).

Gastrointestinal Tract

Explicit representation of the gastrointestinal tract in a PBPK model may be necessary when the modeled compound is administered orally (Clewell and Jarnot, 1994), when enterohepatic recirculation or biliary clearance occurs (e.g., Engasser et al., 1981; King et al., 1983), when the gastrointestinal tract is a target tissue of toxicity, or when gut metabolism is represented in the model (e.g., Frederick et al., 1992).

Without contents, the gastrointestinal tract (stomach, small intestine, and large intestine) constitutes about 2 to 4% of the body weight in mice, rats, dogs, and humans. Somewhat higher values have been reported in two mouse studies (Bourne et al., 1992; Baxter et al., 1994), but the weight of the gastrointestinal tract reported in these studies includes the contents. Values for the relative weight of the different subdivisions of the gastrointestinal tract in rats, dogs, and humans are provided in Table 18.

Heart

As shown in Tables 4 through 7, the weight of the heart is fairly constant across species and constitutes approximately 0.50% of the body weight in mice, 0.13% of the body weight in rats, 0.78% of the body weight in dogs, and 0.44% of the body weight in humans.

Kidneys

The kidneys constitute about 1.67% of the body weight in mice, 0.73% in rats, 0.55% in dogs, and 0.44% in humans. The volumetric composition of the human and dog kidney is on the order of 70% cortex, 25% medulla, and 5% collecting system (ICRP, 1975).

Liver

The relative weight of the liver is fairly constant across species. For example, to develop an allometric scaling equation for this parameter, Boxenbaum (1980) used relative liver weight values that ranged from 1.06% in cattle to 5.06% in the mouse. The mean relative liver weights for the species addressed in this paper are as follows: mouse, 5.5%; rat, 3.4%; dog, 3.3%; and humans 2.6%.

The mean weight of the liver in mice derived from the data reported in seven studies is about 5.5% of the body weight. The mean values from these studies range from 4.2–8.0%. Values for individual liver weights in some studies spanned approximately the same range. The data reported by Ruebner et al. (1984) suggest that strain-related differences do not exist in relative liver weight in mice. The geometric means of liver weight/body weight ratios reported in C57BL/6, C3H/He, and B6C3F1 strains of mice were 5.7, 5.5, and 5.6%, respectively.

Body weight-normalized values for liver weight in mice appear to decrease slightly as the animal ages. DeMarte and Enesco (1986) found that the liver constitutes about 5.7% of the body weight in 8-week-old male Swiss albino mice. This value fell to about 4.6–4.9% in mice aged 12–36 weeks and to about 4.2% in mice 52–78 weeks old.

TABLE 18. Relative Weight (Percent Body Weight) of the Gastrointestinal Tract Segments in Mice, Rats, Dogs, and Humans

	Mouse	Rat				Dog				Human
Segment	Stott et al. (1983)	Caster et al. (1956)	Delp et al. (1991)	Peters and Boyd (1966)	Stott et al. (1983)	Andersen (1970)	Andersen (1970)	Goodhead (1969)	Quillen and Reid (1988)	ICRP (1975)
Stomach	0.60	0.50	0.40	0.52	0.40	0.94	0.91	0.65	0.69	0.21
Forestomach	0.16			0.13	0.13					
Glandular Stomach	0.44			0.39	0.27					
Small Intestine	2.53	1.93	1.39	0.99	1.27	2.77	2.84	1.61	1.65	0.91
Duodeneum			0.15					0.25	0.19	
Jejunum and Ileum			1.24					1.36	1.46	
Large Intestine	1.09	0.89	0.80	0.86	0.82	0.69	0.65			0.53
Cecum	0.30		0.35	0.32	0.33					
Colon			0.44	0.54				0.23	0.47	
Gastrointestinal Tract Total	4.22	3.32	2.59	2.37	2.49	4.40	4.40			1.65

The mean value reported in Table 4 for this parameter is identical to the reference value selected by Arms and Travis (1988) for liver volume in mice. To develop interspecies scaling relationships for liver weight, Boxenbaum (1980) used a value of 5.06% of the body weight as the relative liver weight in mice. However, the reference value selected by Davies and Morris (1993) for this parameter, 8.75%, is significantly higher than the mean values that have been reported in the literature. In fact, this proposed reference value overestimates mean values for relative liver weight in 20-week-old mice (Table 8) by about twofold.

Relative liver weight in rats ranges from about 2.1% of the body weight, as reported by Kozma et al. (1969) for male Long-Evans rats, to 5.2% of the body weight, as reported by Frank (1976) for male Sprague-Dawley rats. The mean value for relative liver weight for the rat across 15 studies is 3.7%, a value similar to that reported by Delp et al. (1991) for male Sprague-Dawley rats and to the mean value derived from rat liver weight data reported in 10 randomly selected 13-week studies conducted by the NTP (Table 8).

Based on the data reported by Coniglio et al. (1979), the following equation can be derived to estimate the absolute weight of the liver of male F344 rats as a function of age:

$$\text{Log Liver Weight (g)} = \text{Log Age (months)} \times 0.1482 + 0.9468;\ r = 0.999.$$

The liver constitutes approximately 3.3% of the body weight in dogs. Mean values for this parameter identified in the literature range from 2.9–3.7%. Davies and Morris (1993) selected a reference value of 3.2% from their review of the literature, and Boxenbaum (1980) used a value of 2.9% of the body weight for allometric scaling.

In humans, the median liver weight in males and females aged 20–29 is 1820 and 1440 g, respectively (ICRP, 1975), or about 2.6% of the body weight. A comparable liver volume was reported by Swift et al. (1978) for persons in the same age group. In this study, individuals with healthy, nonpalpable livers had a liver volume that was 1.8% of the body weight, as measured by ultrasound.

Although liver weight remains relatively unchanged throughout most of adulthood, it is reduced by about 25% in persons over the age of 65 years when compared to 40-year-old individuals. A fairly poor correlation is obtained when body weight is plotted against liver volume in females ($r = 0.64$), but this correlation improves somewhat for males ($r = 0.71$).

Both Arms and Travis (1988) and Davies and Morris (1993) selected 2.5% as the reference value for this parameter in humans. Boxenbaum (1980) used 2.42% as the relative liver weight in humans for allometric scaling of this parameter.

As discussed above, advanced age is associated with a decline in liver volume. The reduced capacity of the liver to clear substrates like antipyrine is due, in part, to age-related reduction in liver volume, hepatic blood flow, and, to some degree, the intrinsic metabolic capacity of the liver (Woodhouse and Wynne, 1992).

A number of compounds are known to produce hepatomegaly in humans and experimental animals (Plaa, 1991). In some cases, liver volume can increase by twofold in rodents exposed to hepatotoxic compounds. For example, the relative liver weight in Swiss Webster mice exposed to 10 000 parts per million of oxazepam in a 14-week study conducted by the NTP (1993b) was 10% of the body weight, compared to 5% of the body weight in control animals.

Depending on the pathological process leading to liver enlargement, increased liver volume may be associated with an increase, a decrease, or no change in the hepatic clearance of xenobiotic compounds (Sotaniemi et al., 1992). Induction of metabolic enzymes along with liver enlargement will result in an increase of metabolic capacity *in vitro* and may produce increased hepatic clearance *in vivo*. Fatty infiltration is a common cause of liver enlargement in humans. Patients with a fatty liver will have reduced hepatic capacity when metabolic activity is normalized for liver weight, but the metabolic capacity of the whole liver will be unchanged. Fibrotic changes in the liver (e.g., cirrhosis) result in increased liver volume but decreased metabolic capacity. When liver volume is increased because of the presence of tumors, the metabolic capacity of the unaffected tissues typically remains the same. Therefore, liver volume may increase in animals and humans as a result of pathological processes. Hence, it may be necessary to represent these changes in a PBPK model. However, changes in liver volume do not always result in an increase in the metabolic capacity of the liver, and changes to the intrinsic metabolic capacity of the liver should be accounted for as well.

Lungs

The lungs constitute from 0.5–0.8% of the body weight in mice, rats, dogs, and humans. Because the lung is a vascular tissue, some percentage of the lung weight will consist of residual blood, even in reasonably well-drained tissues.

Muscle

Skeletal muscle constitutes, by far, the largest single tissue in the body on the basis of weight or volume. Muscle mass represents about 40% of the body weight in mice and rats and 45% of the body weight in dogs. Skeletal muscle constitutes about 29 and 40% of the mass of adult female and male humans, respectively. Investigators requiring data on the weight of specific muscles in the rat are encouraged to access the extensive data set published by Delp et al. (1991).

Pancreas

The weight of the pancreas constitutes about 0.32% of the body weight in rats, 0.69% of the body weight in dogs, and 0.14% of the body weight in humans. Few data are available on the weight of the pancreas in mice. Data tabulated by Crispens (1975) suggest that the pancreas makes up 0.5–0.7% of the body weight in two strains of obese New Zealand mice, but the relevance of these data for strains of mice used more commonly in pharmacokinetic studies is unknown.

Skin

Representation of the skin in PBPK models is important when the skin and skin-associated structures (hair) serve as a route of absorption (e.g., McDougal, 1991) or elimination (e.g., Farris et al., 1993).

Reported values for the weight of the skin of mice, rats, and dogs vary somewhat, largely because of differences in the tissues that are included with the skin. For example, the weight of the "pelt" in mice reported by Durbin et al. (1992) includes the weight of the subcutaneous fat, ears, and, presumably, hair. Although the skin weight reported by Friedman (1955) for mice also includes some subcutaneous fat, the value for this parameter on a body weight-normalized basis is much lower than those reported by Durbin et al. (1992) and Stott et al. (1983). The mean value for relative skin weight in mice, obtained from data reported in five studies, is 16.5% of the body weight.

Values for the weight of the skin in rats range from 15.8–23.6% of the body weight, with a mean across five studies of 19.0%. The PBPK model developed by Farris et al. (1993) to describe the pharmacokinetic behavior of methyl mercury in rats is unique in its explicit representation of a hair compartment. This compartment was necessary in this model to account for the loss of methyl mercury via shed hair and the oral uptake of the compound via ingestion of hair during grooming. In their model, hair constitutes 1.5 and 2.0% of the body weight of male F344 rats weighing 307 and 548 g, respectively.

Some discrepancy exists among values identified for the weight of skin in dogs. Warner and McFarland (1970) reported that the integument constitutes around 16% of the body weight in beagles. This value, which includes the weight of the nose, foot pads, and nails, is similar to the values reported for other species. However, Quillen and Reid (1988) found that the mean weight of the skin in eight mongrel dogs with a mean body weight of 21.1 kg was 1.911 kg, or about 9.1% of the body weight. Although it is not surprising that this value is less than that reported by Warner and McFarland (1970) because the latter does not include the weight of structures such as foot pads and nails, it is not possible to identify a representative value for this parameter in dogs without additional data.

The skin constitutes about 3.1–3.7% of the body weight in reference woman and man, respectively (ICRP, 1975). The dermis makes up 95–96% of the total skin weight in humans and the epidermis makes up the remainder.

In addition to total skin weight, values for the thickness of the skin or skin regions may be required for PBPK models with a dermal input function. Data on the thickness of the stratum corneum and other skin layers in the rat and human are provided by Bronaugh et al. (1983) and Scheuplein and Blank (1971), respectively, and are discussed in the U.S. EPA (1992) document on dermal exposure assessment. McDougal (1991) and Singh and Roberts (1993) have demonstrated how these data can be used in a dermal PBPK model.

Spleen and Thyroid

Although they represent a small proportion of the total body weight, the spleen and thyroid can be important target organs of toxicity. Mean values for the weight of these tissues in mice, rats, dogs, and humans can be found in Tables 4–7.

USE OF ORGAN WEIGHT VALUES IN PBPK MODELS

Use of the organ weight data provided in Tables 4–7 in a PBPK model requires that the weight estimates be converted to units of volume. In addition, the values need to be scaled to the body weight of the animals under study, tissue mass balance should be accounted for in the model, and the anatomical and physiological heterogeneity of the organs may need to be represented.

Mass-to-Volume Conversion

With few exceptions, the values provided previously represent the mass of the organs. However, PBPK model compartments are defined by their volume rather than their mass. Because the density of most visceral organs approximates 1.00 (most have densities that range from 1.02–1.06), a mass-to-volume conversion usually is ignored. However, the density of some tissues, such as bone, differs sufficiently from 1.00 to warrant consideration of a mass-to-volume conversion. For example, the density of marrow-free bone is 1.92 g/cm^3. Although the weight of this tissue in a mature small mammal skeleton is 5.00 g/100 g body weight, the volume is 2.60 cm^3/100 g body weight (O'Flaherty, 1991a). The only other tissues that may require a mass-to-volume conversion to more accurately reflect their volume in the model are adipose tissue and the stratum corneum of the skin, with densities of 0.916 and 1.50 cm^3/100 g body weight, respectively.

Investigators who wish to make more precise mass-to-volume conversions can use the specific gravity values reported in ICRP (1975) for human tissue (Table 19). Presumably, the density of mouse, rat, and dog organs is sufficiently similar to allow for the use of these values for other species.

Selecting Organ Weight Values for Animals Within a Species

Unlike previous compilations of organ weight data (e.g., Arms and Travis, 1988; Davies and Morris, 1993), the mean organ weight values presented in this document were not adjusted to provide representative values for mice, rats, dogs, and humans of a "standard" body weight. Because the mean organ weight values provided in Tables 4–7 were derived from adult animals whose body weight fell within the range of values that would be considered normal, the use of relative organ weight values expressed as the percent of body weight should be valid for estimating the organ weights for animals with the same body weight range within a species, if organ weight increases at the same rate as body weight. In cases were organ weight may increase at a disproportionately greater rate than body weight (e.g., adipose tissue), intraspecies allometric equations are provided (if data are available). However, it has been a common practice in PBPK modeling to use interspecies allometric equations to estimate organ weights for animals of different weight within a species. Because the relative organ weight values provided in Tables 4–7 are species specific, one might expect that they would predict organ weight for animals within a species with greater accuracy than interspecies allometric equations developed using data from multiple species. This assumption was tested using the rat organ weight data obtained in the studies conducted by Delp et al. (1991) and Farris et al. (1993). The results of this exercise are shown in Table 20.

TABLE 19. Organ Density in Humans (ICRP, 1975)

Tissue	Specific Gravity
Adipose Tissue	0.916
Adrenals	1.016–1.033
Bone	
Cortical	**1.99**
Trabecular	**1.92**
Red Marrow	1.028
Yellow Marrow	0.783
Brain	1.030–1.041
Gastrointestinal Tract	
Stomach	1.048–1.052
Small Intestine	1.041–1.047
Large Intestine	1.042
Heart	1.030
Kidneys	1.050
Liver	
Lungs	1.045–1.056
Muscle	1.041
Pancreas	1.040–1.050
Skin	
Stratum Corneum	1.50
Epidermis	1.10–1.19
Dermis	1.116
Hypodermis	0.971
Spleen	1.054
Thyroid	1.036–1.066

Although the interspecies allometric equations have been derived using data from animals that range in size from the shrew to the elephant, the equations generally were able to estimate the mean organ weight values obtained in the Delp et al. (1991) study within approximately an order of two. However, in every case, the relationships shown in Table 5 were able to more closely estimate the organ weight values obtained in the Delp et al. (1991) study. This result is not surprising because these relationships are specific to the rat, for which the Delp et al. (1991) data were among those used to derive the relationships provided in Table 5.

Similar results were obtained when this assumption was tested with the organ weight data of Farris et al. (1993), with two notable exceptions. The interspecies allometric equations predicted more closely the mean weight of the skin and liver in rats weighing around 300 g in the Farris et al. (1993) study. The results of this exercise suggest that it is valid to use the relationships provided in Table 5 to provide organ weight estimates for rats of different weights. However, in some cases, interspecies allometric relationships can provide a reasonable estimate of organ weight, at least in male Sprague-Dawley rats.

TABLE 20. Ability of Intraspecies and Interspecies Scaling Relationships to Predict Organ Weight Values in Male Sprague-Dawley Rats

	Organ Weight (g)		
		Predicted Using:	
Organ	Measured[a]	Table 5	Interspecies Equations[b]
Brain			
Delp et al. (1991)[c]	2.20	**2.12**	4.47–7.17
Farris et al. (1993)[d]	1.83	**1.78**	3.92–6.28
Farris et al. (1993)[e]	2.02	**2.92**	5.63–9.13
Gastrointestinal Tract			
Delp et al. (1991)	**9.50**	**10.87**	**28.77**
Farris et al. (1993)	9.49	**9.12**	24.40
Farris et al. (1993)	13.53	14.93	**38.77**
Skin			
Delp et al. (1991)	69.80	69.65	53.93
Farris et al. (1993)	48.54	58.46	45.72
Farris et al. (1993)	87.29	95.67	72.73
Liver			
Delp et al. (1991)	12.42	12.48	13.93–15.76
Farris et al. (1993)	13.42	10.47	11.96–13.58
Farris et al. (1993)	17.17	17.14	18.36–20.64

[a]Mean.
[b]Provided in Table 36.
[c]366 g body weight.
[d]307.21 g body weight.
[e]502.75 g body weight.

Tissue Mass Balance

The information Table 21 demonstrates that a tissue mass balance can be maintained using the values provided in Tables 4–7. Because these values are means derived from multiple studies, it is not surprising that the totals for each species do not equal exactly 100%. Nevertheless, this exercise does indicate that the values provided in Tables 4–7 provide a reasonable starting point for the selection of representative organ weight (volume) values for use in PBPK models. Since many PB-PK models contain only a few compartments (fat, rapidly perfused, slow perfused, and liver), often the total volume accounted for is only about 90% (Allen and Fisher, 1993; Reitz et al., 1996).

Investigators who include terms to account for age-related changes in organ growth in their models should keep tissue mass balance considerations in mind, especially for compartments (e.g., adipose tissue) that increase in size at a rate greater than that of other tissues.

TABLE 21. Tissue Mass Balance

Tissue	Mice	Rats	Dogs	Humans
Adipose	~7.0	~7.0	~15.0	21.4
Bone	10.7	**7.3**	8.1	14.3
Brain	1.7	**0.6**	0.8	2.0
Gastrointestinal Tract	4.2	**2.7**	3.7	1.7
Heart	0.5	**0.3**	0.8	0.5
Kidneys	1.7	**0.7**	0.5	0.4
Liver	5.5	**3.4**	3.3	2.6
Lungs	0.7	**0.5**	0.8	0.8
Muscle	38.4	**40.4**	45.7	40.0
Skin	16.5	**19.0**	9.1	3.7
Gastrointestinal Tract Contents	5.7	**~5.0**	4.3	1.4
Blood	**4.9**	**7.4**	8.2	7.9
Rest of Body	2.5	**5.7**	**0**	3.3
TOTAL	100.0	100.0	100.5	100.0

Anatomical and Physiological Heterogeneity

Use of the data in Tables 4–7 to derive a value for the volume of a particular organ implies that this organ is anatomically and physiologically homogeneous. This assumption is sufficient for most PBPK applications; however, it may be important to represent the heterogeneity of the organ in the model. An attempt has been made previously to identify values for the weight of anatomically or physiologically distinct regions of organs and tissues. For example, data have been provided for the weight of different regions of the adipose (brown versus white; subcutaneous versus internal), bone (cortical versus trabecular and marrow versus marrow-free), brain (cerebrum, cerebellum, and brain stem), and gastrointestinal tract (forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, and colon). This level of detail is not necessary for every PBPK model, but may be required for the process being modeled. For example, Frederick et al. (1992) included a detailed description of the gastrointestinal tract in their PBPK model of orally administered ethyl acrylate to account for uptake and metabolism of the compound in different regions of the gastrointestinal tract. Data on the weight of the gastrointestinal tract necessary to develop their model are found in Table 18. Because of the rapid rate at which ethyl acrylate is metabolized in the liver, these investigators also chose to represent the metabolic heterogeneity of the liver in their model.

The respiratory tract is represented in many PBPK models as a simple lung compartment. However, models recently have been developed to account for regional distribution, metabolism, and uptake of compounds in the respiratory tract. The data provided in this paper are insufficient to provide values required for the detailed representation of the respiratory tract found in these models; however, investigators requiring these data may find the review prepared by Medinsky et al. (1993) of recent efforts in this field to be useful.

CARDIAC OUTPUT AND REGIONAL BLOOD FLOW

In classical pharmacokinetic models, movement of a compound across a membrane is represented either by mass terms and kinetic rate constants or by concentration terms and transfer constants. However, in flow-limited PBPK models, the transfer constant is equivalent to the blood flow to the tissue (O'Flaherty, 1987). Consequently, values are needed in flow-limited PBPK models for cardiac output and for regional distribution of cardiac output to the organs. Values for these parameters are provided in this section for mice, rats, dogs, and humans.

CRITERIA FOR DATA SELECTION AND REPRESENTATION OF THE DATA

Because cardiac output regional blood flow distribution is influenced dramatically by a number of factors, such as the degree of consciousness or level of physical exertion, inclusion criteria were established to attempt to ensure that the blood flow data provided in this paper are representative of flow patterns in "normal" subjects. The exclusion of studies, such as those of anesthetized animals, represents a departure from the approach used in previous compilations of blood flow data (e.g., ICRP, 1975; Arms and Travis, 1988; Williams and Leggett, 1989; Davies and Morris, 1993).

Regional blood flow data in experimental animals were obtained only from studies that used the radiolabeled microsphere technique. This technique was originally reported by Rudolph and Heymann (1967) and has become the method of choice for measuring the distribution of blood flow among and within organs in animals (Hoffman et al., 1977). This is not to imply, however, that the technique is without limitations. On the contrary, great care must be used to ensure accurate results. For example, aggregation of the microspheres, inadequate mixing of the microspheres with the blood, "streaming" of microspheres past small arteries, tissue samples containing less than 400 microspheres, and flow impairment following infusion of too many spheres can lead to inaccuracies in flow determination (Hoffman et al., 1977; Austin et al., 1989; Zwissler et al., 1991). Technical strategies have been developed to overcome each of these difficulties, and methods to verify accuracy are routinely used by investigators (Austin et al., 1989; Hof et al., 1980; Laughlin et al., 1982; Zwissler et al., 1991). The overwhelming advantage of microspheres is that they can be used to measure simultaneously the cardiac output and the blood flow distribution among and within organs throughout the entire body. In addition, use of the microsphere technique does not induce surgical trauma to organs and vascular beds of interest, as frequently occurs with flow probes.

Previous estimates of regional blood flow distribution in the mouse have been based largely on the studies conducted by Wetterlin et al. (1977), Stott et al. (1983), and Quintana et al. (1979). However, these studies were not included in this analysis because the mice were anesthetized and because of technical problems experienced by these investigators. As pointed out by Barbee et al. (1992) and Wang et al. (1993b), these problems included inadequate mixing of microspheres, the development of catheter-induced outflow obstructions, and potential cardiac dysfunction from direct injection of microspheres through the ventricular wall.

Only two studies (Barbee et al., 1992; Wang et al., 1993b) have been found that report regional blood flow distribution in conscious mice. Blood flow in the study of Wang et al. (1993b) was measured while the mice were restrained. Physical restraint also has the potential to greatly alter blood flow distribution. However, flow data from this study were included in this paper because of the close agreement between flows reported in this study and those reported by Barbee et al. (1992).

Regional blood flow values for the rat in many PBPK models are based on the results of Malik et al. (1976), Sasaki and Wagner (1971), and Tsuchiya et al. (1978), as summarized by Arms and Travis (1988). These studies were included in this analysis, along with the studies of Carmichael et al. (1988), Delp et al. (1991), and Nishiyama et al. (1976). Eight additional studies were used to provide a more comprehensive blood flow database (in milliliters per minute per 100 g tissue) for rats.

Studies of canine blood flow have tended to focus on a particular organ or organ system; therefore, most studies report flow to only a few tissues. A notable exception is the study published by Quillen and Reid (1988), which, in addition to reporting regional blood flow distribution, reports cardiac output and blood flow as a percent of cardiac output for conscious dogs at rest.

Williams and Leggett (1989) recently have published a comprehensive review of regional blood flow values in humans. These authors have compiled human data from studies using various techniques to measure tissue perfusion. Where blood flow values were not available for humans in the literature, representative flow values from animal studies are given (Williams and Leggett, 1989). A few of the human studies referenced by Williams and Leggett (1989) used techniques, such as Xenon clearance, to measure blood flow that are now known to yield erroneous results. However, the reference values suggested by Williams and Leggett (1989) for regional blood flow in humans are consistent with those recommended by Rowell (1993). Therefore, human tissue perfusion rates (listed in Table 26) are based primarily on those previously published by Williams and Leggett (1989).

Representation of blood flow in units normalized for tissue weight, and shown in Tables 22–26, can result in significant errors if default reference weights are used instead of the tissue-specific weight values reported in the same paper as the flow values. As a result, weight-normalized flow values were used only when the data were reported as such in the original paper or when tissue weights were reported in the paper (or could be deduced from other data in the same paper). Similarly, data in units of percent cardiac output were used only when the data were presented that way or when data on cardiac output were reported in the same paper.

CARDIAC OUTPUT

Mean cardiac output values for unanesthetized mice, rats, dogs, and humans are shown in Table 22.

TABLE 22. Cardiac Output (Milliliters per Minute) in Unanesthetized Mice, Rats, Dogs, and Humans

Species	Cardiac Output		Number	
	Mean ± Standard Deviation	Range	Studies	Animals
Mouse	13.98 ± 2.85	12–16	2[a,b]	16
Rat	110.4 ± 15.60	84–134	5[c-g]	92
Dog	2936[h]	1300–3000[i]	1[h]	8
Human	5200[j]	4600–4600[k]		

[a]Barbee et al. (1992).
[b]Wang et al. (1993b).
[c]Coleman (1974).
[d]Delp et al. (1991).
[e]Hachamovitch et al. (1989).
[f]Jansky and Hart (1968).
[g]Tsuchiya et al. (1978).
[h]Quillen and Reid (1988).
[i]Detweiler et al. (1970).
[j]Astrand (1983).
[k]Arms and Travis (1988).

TABLE 23. Regional Blood Flow Distribution Mean Percent Cardiac Output

Tissue	Mouse[a]	Rat[b]	Dog[c]	Human[d]
Adipose		7.0		5.2
Adrenals		0.3	0.2	
Bone		12.2		4.2
Brain	3.3	2.0	2.0	11.4
Heart	6.6	5.1	4.6	4.0
Kidneys	9.1	14.1	17.3	17.5
Liver (Total)	16.1	18.3	29.7	22.7
Hepatic Artery	2.0	2.1	4.6	
Portal Vein	14.1	15.3	25.1	18.1
Lung	0.5	2.1	8.8	
Muscle	15.9	27.8	21.7	19.1
Skin	5.8	5.8	6.0	5.8
Thyroid				1.6

[a]Data from Barbee et al. (1992) and Wang et al. (1993b).
[b]Data from Delp et al. (1991), Malik et al. (1976), Nishiyama et al. (1976), Sasaki and Wagner (1971), and Tsuchiya et al. (1978).
[c]Data from Quillen and Reid (1988).
[d]Provisional measure of central tendency from Williams and Leggett (1989).

Only two studies (Barbee et al., 1992; Wang et al., 1993b) were identified in the literature that reported cardiac output measurements in unanesthetized mice. Values ranged from about 12 mL/min in the Wang et al. (1993b) study to 16 mL/min in the Barbee et al. (1992) study. Each of these studies employed the microsphere method to measure cardiac output in male C3H mice.

TABLE 24. Regional Blood Flow Distribution in Mice

Tissue	Blood Flow Rate (mL/min/100g) Mean (Standard Deviation)	Range	Number of Studies	Blood Flow Distribution (Percent Cardiac Output) Mean (Standard Deviation)	Range	Number of Studies
Adipose						
Adrenals						
Bone						
Brain	85 ± 1	84–85	2[e,f]	3.3 ± 0.3	3.1–3.5	2[e,f]
Heart	781 ± 18	768–793	2[e,f]	6.6 ± 0.9	5.9–7.2	2[e,f]
Kidneys	439 ± 23	422–495	2[e,f]	9.1 ± 2.9	7.0–11.1	2[e,f]
Liver (Total)[a]	131			16.2		2[e,f]
Hepatic Artery[b]	20		1f	2.0		1[f]
Portal Vein[c]	111 ± 9	104–117	2[e,f]	14.1	13.9–14.2	2[e,f]
Lung[d]	35		1[f]	0.5		1[f]
Muscle	24 ± 6	20–28	2[e,f]	15.9 ± 5.2	12.2–19.6	2[e,f]
Skin	18 ± 12	9–26	2[e,f]	5.8 ± 3.5	3.3–8.3	2[e,f]

[a]Hepatic artery and portal vein.
[b]Principally through the hepatic artery.
[c]Sum of flows through the splanchnic organs.
[d]Bronchial flow.
[e]Barbee et al. (1992).
[f]Wang et al. (1993b).

TABLE 25. Regional Blood Flow Distribution in Rats

Tissue	Blood Flow Rate (mL/min/100g) Mean (± SE)	Range	Number of Studies	Blood Flow Distribution (Percent Cardiac Output) Mean (± SE)	Range	Number of Studies
Adipose	33 ± 5	18–48	6[e,f,g,j,k,o]	7.0		1[g]
Adrenals	429 ± 90	246–772	6[f-h,m-o]	0.3 ± 0.1	0.2–0.3	2[g,n]
Bone	24 ± 3	20–28	3[g,j,m]	12.2		1[g]
Brain	110 ± 13	45–134	7[e-g,j,n-p]	2.0 ± 0.3	1.5–2.6	4[g,n,p,q]
Heart	530 ± 46	405–717	8[f-i,l,n-p]	4.9 ± 0.1	4.5–5.1	5[g,l,n,p,q]
Kidneys	632 ± 44	422–826	11[e-h,j-p]	14.1 ± 1.9	9.5–19.0	5[g,l,n,p,q]
Liver (Total)[a]				17.4	13.1–22.1	5[g,l,n,p,q]
Hepatic Artery[b]	23 ± 44	9–48	10[f-l,n-p]	2.4	0.8–5.8	5[g,l,n,p,q]
Portal Vein[c]	108 ± 17	67–162	5[g,j,l,n,p]	15.1	11.1 - 17.8	5[g,l,n,p,q]
Lung[d]	127 ± 46	38–147	6[g,h,l,n-p]	2.1 ± 0.4	1.1–3.0	5[g,l,n,p,q]
Muscle	29 ± 4	15–47	8[e-h,j,k,m,o]	27.8		1[g]
Skin	13 ± 4	6–22	5[e,g,h,j,p]	5.8		1[g]

[a]Hepatic artery and portal vein.
[b]Principally through the hepatic artery.
[c]Sum of flows through splanchnic organs.
[d]Bronchial flow.
[e]Armstrong and Laughlin (1984).
[f]Bergø et al. (1989).
[g]Delp et al. (1991).
[h]Flaim et al. (1990).
[i]Hachamovitch et al. (1989).
[j]Kuwahira et al. (1993).
[k]Laughlin and Armstrong (1982).
[l]Malik et al. (1976).
[m]McDonald et al. (1992).
[n]Nishiyama et al. (1976).
[o]Risberg et al. (1987).
[p]Sasaki and Wagner (1971).
[q]Tsuchiya et al. (1978).

TABLE 26. Regional Blood Flow Distribution in Dogs

Tissue	Blood Flow Rate (mL/min/100 g)			Blood Flow Distribution (Percent Cardiac Output)		
	Mean (± SE)	Range	Number of Studies	Mean (± SE)	Range	Number of Studies
Adipose	14 ± 1	13–14	2[i,j]			
Adrenals	311 ± 143	171–543	3[e,f,m]	0.2		1[m]
Bone	13 ± 1	12–13	2[i,m]			
Brain	65 ± 4	59–76	5[f,g,j,k,m]	2.0		1[m]
Heart	79 ± 6	57–105	7[f-j,m,n]	4.6		1[m]
Kidneys	406 ± 37	307–509	5[f,j,k,m,n]	17.3		1[m]
Liver (Total)[a]				29.7		1[m]
Hepatic Artery[b]	21 ± 3	12–30	5[f,g,j,k,m]	4.6		1[m]
Portal Vein[c]	52 ± 4	42–58	4[f,j,k,m]	25.1		1[m]
Lung[d]	79 ± 43	36–122	2[j,m]	8.8		1[m]
Muscle	11 ± 2	6–18	6[f,g,i,j,l,m]	21.7		1[m]
Skin	9 ± 1	8–13	5[f,i-k,m]	6.0		1[m]

[a]Hepatic artery and portal vein.
[b]Principally through the hepatic artery.
[c]Sum of flows through splanchnic organs.
[d]Bronchial flow.
[e]Faraci et al. (1989).
[f]Fixler et al. (1976).
[g]Haberer et al. (1993).
[h]Hintze et al. (1990).
[i]Liard (1986).
[j]Liard (1988).
[k]Musch et al. (1987).
[l]Pendergast et al. (1985).
[m]Quillen and Reid (1988).
[n]von Ritter et al. (1988).

The mean value for cardiac output in unanesthetized mice listed in Table 22 is slightly lower than the reference value selected by Arms and Travis (1988) (17 mL/min), but quite a bit higher than the value selected by Davies and Morris (1993) as a default value for this parameter. The reference value selected by Arms and Travis (1988) was derived as follows. First, the heart rate in unanesthetized mice reported by Blizard and Welty (1971) was multiplied by the average stroke volume reported by Wetterlin and Pettersson (1979) in anesthetized mice to derive a cardiac output estimate. Then, assuming cardiac output is related to the 0.75 power of body weight, they developed the following allometric equation to estimate cardiac output in a standard 25-g mouse:

$$\text{Cardiac Output (L/min)} = 0.275\ (\text{BW})^{0.75},$$

where BW equals body weight in kilograms. Although this approach yields a value similar to those derived experimentally, it seems preferable to use a data-based approach free of assumptions about cross-species scaling patterns to derive estimates for this parameter.

The mean cardiac output value for unanesthetized rats, 110.4 mL/min, was derived from the results reported in five studies: (1) Coleman (1974), (2) Delp et al. (1991), (3) Hachamovitch et al. (1989), (4) Jansky and Hart (1968), and (5) Tsuchiya et al. (1978). Although the results reported by Carmichael et al. (1988) were used to derive regional blood flow estimates, the absolute cardiac output value reported in this study was about half of that reported by other investigators. Therefore, these data were not used to derive the mean absolute cardiac output value for rats. In addition, data on the cardiac output of spontaneously hypertensive rats in the Tsuchiya et al. (1978) study were not used in this analysis.

The default value for cardiac output in rats was developed by Arms and Travis (1988) in much the same way as the mouse value was derived, except only data from unanesthetized rats was used, and a geometric mean of the ratios of cardiac output/body weight$^{0.75}$ values from these studies was used to derive the value for the intercept. The resulting equation,

Cardiac Output (L/min) = 0.235 BW (kg)$^{0.75}$,

yields a value of 83 mL/min for a 250 g-rat and 118 mL/min for a 400-g rat. This range encompasses the mean cardiac output value for rats (weighted mean body weight = 396 g) reported in Table 22.

Detweiler et al. (1970) report that cardiac output values in unanesthetized beagles weighing 8–12 kg range from 1300–3000 mL/min; dogs under anesthesia have cardiac output values ranging from 900–2700 mL/min. Because mean values were not reported by Detweiler et al. (1970), these data were not used to develop Table 22. However, these values are consistent with those identified in the literature for anesthetized and unanesthetized dogs. For example, using the microsphere technique, Quillen and Reid (1988) determined the mean cardiac output of unanesthetized male and female mongrel dogs (mean weight 21 kg) to be 2936 mL/min. Goodhead (1969) and In-Nami et al. (1974) report cardiac output values of 2421 and 2140 mL/min, respectively, in anesthetized dogs.

Cardiac output has been well characterized in humans; consequently, it is impractical to provide a comprehensive listing of all of the values that have been reported in the literature. As summarized by Arms and Travis (1988), mean cardiac output values identified in the literature for unanesthetized humans range from about 4.6–6.5 L/min. The work conducted by Astrand (1983) is highly respected, and, as a result, cardiac output parameter values in human PBPK models (e.g., Dankovic and Bailer, 1994) have been derived from this work. Astrand (1983) reports a cardiac output value of 5.2 L/min in resting individuals. During light work (33.67 W of exercise), cardiac output increases to 8.36 L/min. Slightly more strenuous exercise (50 W) requires a cardiac output of 9.9 L/min. Very strenuous exercise is associated with cardiac output values of up to 30 L/min in humans.

Cardiac output remains constant at about 6.5 L/min in males aged 20–35 years, then begins a gradual decline. Based on the data obtained by Brandfondbrenner et al. (1955), the following equation can be derived to estimate cardiac output as a function of age in males:

Cardiac Output (L/min) = -6.846 log age (years) + 16.775; r = -0.98.

REGIONAL BLOOD FLOW

Table 23 provides mean blood flow values for major organ systems in the mouse, rat, dog, and human. The statistical variability and uncertainty associated with these estimates is described more fully for each species in Tables 24–27.

TABLE 27. Regional Blood Flow Distribution (Percent Cardiac Output) in Humans (from Williams and Leggett, 1989)

	Reference Value[a]				
Tissue	Male	Female	PCMT[b]	Range[c]	n[d]
Adipose	5.0	8.5	5.2	3.7–11.8	11
Adrenals[e]	0.3	0.3			
Bone	5.0	5.0	4.2	2.5–4.7	5
Brain	12.0	12.0	11.4	8.6–20.4	39
Heart	4.0	5.0	4.0	3.0–8.0	19
Kidneys	19.0	17.0	17.5	12.2–22.9	85
Liver (Total)	25.0	27.0	22.7	11.0–34.2	56
Hepatic Artery					
Portal Vein[f]	19.0	21.0	18.1	12.4–28.0	26
Lung[g]	2.5	2.5			
Muscle	17.0	12.0	19.1	5.7–42.2	54
Skin	5.0	5.0	5.8	3.3–8.6	10
Thyroid	1.5	1.5	1.6	1.9–2.2	2

[a]Value determined by the authors to be most representative for this parameter. May be based on animal or human data.
[b]Provisional measure of central tendency, the median of five measures of central tendency.
[c]For human studies only.
[d]Number of human studies.
[e]Based on animal studies.
[f]Sum of blood flows to stomach, esophagus, small intestine, large intestine, spleen, and pancreas.
[g]Bronchial flow.

Some of the values presented in Tables 23–27, notably the blood flow distribution to the liver in rodents, differ from values that have been used widely in PBPK models. These differences are due, in part, to the earlier use of blood flow values derived from studies using anesthetized animals in the models.

Adipose Tissue

Despite the importance of adipose tissue as a pharmacokinetic compartment, there are relatively few studies available on which to base estimates of blood flow to this tissue. The limited number of studies that are available suggest that the values selected by Arms and Travis (1988) for rats and humans are reasonable. No data were identified on regional blood flow to adipose tissue in mice.

Adipose is a physiologically heterogeneous tissue consisting of "white fat" in the hypodermis and around the abdominal organs and "brown fat" in the interscapular hypodermis and in the perirenal and axillary regions. This tissue is physiologically heterogeneous both in terms of function (white fat is assumed to take up excess energy, whereas brown fat plays a role in consuming excess energy) and blood flow.

When normalized for tissue weight, brown fat receives considerably more blood flow in rats than does white fat. For example, Kajita et al. (1994) found that white fat in rats received a blood flow of 5 mL/min/100 g, whereas brown fat received about 36 mL/min/100 g. Similar results were observed by Jansky and Hart (1968) However, because white fat represents a greater proportion of body weight than brown fat, it receives a greater percentage of the cardiac output. In contrast, no significant difference was reported by Bulow and Madsen (1978) between blood flow to abdominal and perirenal fat in humans (1.4 mL/min/100 g for abdominal fat vs 2.3 mL/min/100 g for perirenal fat).

Expressed in milliliters per minute per 100 g, humans and rats receive about the same blood flow to the white adipose tissue. Values range from about 1.4–8.3 mL/min/100 g of tissue. These values are consistent with those reported previously by Mapleson (1963) and Cowles et al. (1971) for humans. Based on the value reported in Table 27, and the default adipose weight of 12 500 g in males and 17 500 g in females, about 3–11% of the cardiac output is distributed to the adipose tissue in humans. Based on the blood flow values reported by Delp et al. (1991) for adipose tissue in the epididymal, inguinal, and abdominal regions and on the total weight of dissectible fat, about 7% of the cardiac output is distributed to adipose tissues in the rat.

Fiserova-Bergerova (1992) included two adipose tissue compartments in a PBPK model of anesthetic agents in humans. Blood flow to the inner adipose tissue compartment was set at 0.66 L/min, a value equivalent to about 11% of the cardiac output. A value of 0.19 L/min was used for blood flow to the subcutaneous adipose tissue. This value was not determined experimentally; instead, it was derived from the difference between the cardiac output and the sum of the perfusion rates to the other tissues.

Adrenal Glands

Normalized for tissue mass, the adrenal cortex is among the most richly perfused tissues in the body. For example, Delp et al. (1991) found that the mean blood flow to the adrenal cortex of unanesthetized rats was about 863 mL/min/100 g tissue (blood flow to the medulla was 43 mL/min/100 g tissue). To provide a blood flow estimate that is representative of the entire tissue, a weight-averaged estimate of 429 mL/min/100 g tissue was derived for rats and reported in Table 25. However, this value does not reflect the marked hemodynamic heterogeneity of this organ.

Although the adrenal tissues are well perfused, they account for only a small percentage of the total cardiac output (< 1% in rats) because of the small size of this organ. Therefore, unless the adrenal is determined to be a target tissue, omission of this tissue in a well-perfused compartment will not introduce significant error into estimates of regional blood flow distribution.

No data were found in the literature regarding blood flow distribution to the adrenals in unanesthetized mice or humans. The reference value of 200 mL/min/100 g provided by Williams and Leggett (1988) for this parameter in humans was derived from animal data.

Bone

Accurate estimates of blood flow to the bone are essential for PBPK models of bone-seeking elements. As mentioned above, bone perfusion has been estimated to be approximately 3% of cardiac output in anesthetized rats (O'Flaherty, 1991a,b) and approximately 12% in conscious rats (Delp et al., 1991). No studies have been found that report skeletal blood flow in conscious mice or bone perfusion rate in conscious dogs as a portion of cardiac output.

The PBPK models of compounds that are toxic to the hematopoietic system require a separate compartment to describe the pharmacokinetic behavior of the compound or its metabolites in the bone marrow. Various estimates of bone marrow blood flow have been used in PBPK models. Experimentally derived values for this parameter correspond well to blood flow estimates used in recent PBPK models that contain a bone or bone marrow compartment. For example, in their recent PBPK model of chloropentafluorobenzene, Clewell and Jarnot (1994) assumed that 11% of the cardiac output was distributed to the bone marrow in mice, rats, monkeys, and humans. This value corresponds well to the values reported by Kahn et al. (1994).

As with muscle, blood flow to bone demonstrates a marked heterogeneity (e.g., Delp et al., 1991). This heterogeneity should be kept in mind when selecting a representative value for this parameter.

Brain

A marked species difference exists in regional blood flow to the brain. In mice, rats, and dogs, about 2–3% of the cardiac output is distributed to the brain. In contrast, the human brain receives about 11–12% of the cardiac output.

Interest in developing pharmacological agents to improve cerebral circulation after occlusion or stenosis of cerebral vessels has resulted in the recent publication of a number of studies in which blood flow to the human brain has been measured. The results of these studies confirm earlier estimates of regional blood flow to the brain.

Data on blood flow to different regions of the brain may be necessary for complex PBPK models that incorporate this level of detail. Investigators requiring such data are referred to Delp et al. (1991) for such values in the rat.

Gastrointestinal Tract

All of the blood reaching the liver via the portal vein is derived from splanchnic circulation, including blood flow from the stomach, small intestine, large intestine, pancreas, and spleen. In the unanesthetized rat, the gastrointestinal tract receives about 14% of the cardiac output (Delp et al., 1991). Values for the blood flow to different regions of the gastrointestinal tract in the rat have been reported by Delp et al. (1991).

Heart

Blood flow rates to the myocardium are remarkably constant across species: mice, rats, dogs, and humans each receive about 4–7% of the cardiac output to the heart.

Delp et al. (1991) have shown that interregional differences exist in blood flow to the heart in rats, with the ventricles receiving about twice the flow rate as the atria. Similar heterogeneity of flow in the myocardium also has been observed in miniature swine (Laughlin et al., 1988).

Kidneys

Renal blood flow rates are fairly constant across species, both when expressed per unit mass (406–632 mL/min/100 g) or as the relative portion of cardiac output (13.5–17.5%). This apparent consistency exists across species in spite of the relatively wide range of values for renal blood flow within each species.

Liver

Studies on unanesthetized animals suggest that blood flow to the liver constitutes approximately 16% of the cardiac output in mice, 18% of the cardiac output in rats, 30% of the cardiac output in dogs, and 23% of the cardiac output in humans. The mean value for humans derived from these studies is comparable to the reference value suggested by Arms and Travis (1988); however, the mean value for blood flow to the liver of mice and rats is considerably lower. In fact, the reference value suggested by Arms and Travis (1988) for blood flow to the liver in rodents (25%) does not even fall within the range of mean values identified for this parameter in mice and rats.

As discussed briefly above, the difference between the mean values for liver blood flow in rodents presented in Tables 23–27 and the reference values selected by Arms and Travis (1988) for this parameter is due primarily to the investigators' reliance on studies of anesthetized animals, but also, in part, to their imprecision in selecting a representative value from the existing data. For example, the reference value selected by Arms and Travis (1988) for blood flow to liver in rats is based primarily on the results of the studies conducted by Tsuchiya et al. (1978) and Malik et al. (1976), who reported values for total liver blood flow of about 17 and 20%, respectively. Nevertheless, Arms and Travis (1988) selected a reference default value of 25% for this parameter, a value that has been used extensively in PBPK models. Because the metabolism of highly cleared compounds in the liver is blood-flow limited, values for hepatic blood flow should be characterized accurately.

As discussed more fully in the next section, blood flow rate through some organs such as the liver is highly variable over short time intervals and can be markedly influenced by factors such as anesthesia, posture, food intake, and exercise. Longer term changes in hepatic blood flow rate can be caused by the presence of disease (e.g., cirrhosis or tumors) or be a function of the aging process. These changes may need to be accounted for in a PBPK model.

Lung

In PBPK models with a lung compartment, it is assumed that all of the cardiac output goes through the lung. However, the values presented in Tables 23–27 for the lung compartment represent blood flow to the bronchial region.

Muscle

Muscle blood flows (in milliliters per minute per 100 g) in the mouse and rat are approximately twofold greater than that in the dog and five- to six-fold greater than that in man. However, the relative portion of cardiac output going to skeletal muscle is surprisingly similar across species.

Mean resting muscle blood flows in Tables 23–27 do not reflect the heterogeneity of blood flow to this tissue. For example, resting blood flow in the rat can range from 8 mL/min/100 g in the abdominal muscles to 121 mL/min/100 g in the vastus intermedius muscle of the thigh, more than an order of magnitude difference (Delp et al., 1991). This heterogeneity of flow distribution primarily reflects differences in the activities of the various muscles when the animal is at rest. The muscles receiving the highest flows, such as vastus intermedius, soleus, and triceps brachii muscles, are antigravity muscles that are active in maintaining posture. When the animals are anesthetized (Laughlin et al., 1982) or no longer weight-bearing (McDonald et al., 1992), blood flow to these antigravity muscles decreases to less than 10 mL/min/100 g. Conversely, when the animals begin to move about in their enclosure, flows to various muscles increase significantly. This heterogeneity of flow to muscle makes it important for investigators measuring muscle perfusion to thoroughly sample this tissue and for modelers to use values that are representative of the entire mass of skeletal muscle.

As one might expect, physical activity is the single greatest determinant of muscle blood flow. From a modeling perspective, this is important because any compound that influences the activity of an organism will alter the blood flow to muscle. In addition, if occupational exposure to a certain compound were being modeled and the occupation involved physical exertion, then muscle and other tissue perfusion parameters would be different from those at rest. Such changes were incorporated into the PBPK model of methylene chloride developed by Dankovic and Bailer (1994) that simulated the pharmacokinetic behavior of this compound in humans at work and at rest.

Skin

The PBPK models of dermal absorption require a separate compartment for the skin. However, caution should be exercised in selecting a default value for blood flow to the skin, because of the marked variability of dermal blood flow rate at different anatomical sites. For example, Monteiro-Riviere et al. (1990) found that cutaneous blood flow rates in the mouse varied from 1.41 mL/min/100 g when measured in skin on the ear to 36.85 mL/min/100 g when measured in skin on the ventral abdomen.

Dermal blood flow data also were obtained by Monteiro-Riviere et al. (1990) at four other sites in eight other species, including the species that are the focus of this paper. As a result, the work conducted by Monteiro-Riviere and colleagues (1990) may serve as a valuable source of dermal blood flow data for modelers requiring such data. However, these values were obtained using anesthetized animals and, therefore, are presented separately in Table 28.

TABLE 28. Region-Specific Blood Flow Measurements (Milliliters per Minute per 100 g) in Mice, Rats, and Dogs (Monteiro-Riviere et al., 1990)

Site	Mouse	Rat	Dog
Buttocks	3.88 ± 0.92	4.20 ± 1.05	2.21 ± 0.67
Ear	1.41 ± 0.48	9.13 ± 4.97	5.21 ± 1.53
Humeroscapular Area	10.10 ± 3.51	6.22 ± 1.47	5.52 ± 1.31
Thoracolumbar Area	20.56 ± 4.69	9.56 ± 2.17	1.94 ± 0.27
Ventral Abdomen	36.85 ± 8.14	11.35 ± 5.53	8.78 ± 1.40

There also appears to be some diurnal variation in blood flow to the skin in humans. Houben et al. (1994) reported that forearm blood flow, which is principally a measure of blood flow to the skin, increased in humans from 2.8 mL/min/100 g in the morning to 4.3 mL/min/100 g in the afternoon. Delp et al. (1991) have reported a similar pattern in blood flow to hind-limb skin of the rat.

After dermal application, lipophilic compounds can penetrate through the epidermis and dermis and migrate into deep tissues underlying the skin before being taken up into the systemic circulation. Representation of this process in a PBPK model requires that blood flow values be obtained for both dermal and underlying subcutaneous tissues. The values recently were obtained by Singh and Roberts (1993) in the anesthetized rat and incorporated into their model. Using the microsphere technique, they found that blood flow to the skin measured 5.18 mL/min/100 g tissue, a value somewhat less than the mean value provided in Table 25, but within the range of values reported by Monteiro-Riviere et al. (1990) for anesthetized rats.

FACTORS THAT INFLUENCE TISSUE PERFUSION

Although there are some factors that can alter organ volume values within an individual, these changes are, in general, less dramatic than the changes that can occur in regional blood flow in an individual. Also, regional blood flow values can change dramatically in a relatively short period of time. As a result, it is important for modelers to be aware of the factors that have the greatest influence on the values that may be selected for blood flow parameters in the model. In this section, the potential effects of disease, anesthesia, physical activity, food intake, posture, age, and gender on regional blood flow are discussed.

Disease

The parameter values provided in this paper are intended to be representative of values for healthy subjects. However, most PBPK models describe the pharmacokinetic behavior of environmental compounds with known or potential toxicity or carcinogenic activity or of therapeutic agents used in treatment of disease. Some of the disease states that may be either caused or treated by the compound may involve changes in overall or regional hemodynamics. Therefore, it may be necessary to represent changes in blood flow rate in the model that parallel blood flow rate changes occurring due to pathological processes in the exposed individuals.

Certain disease states are known to alter regional blood flow rates. Among the most important pathological alterations to keep in mind for the development of PBPK models are hepatic diseases that affect blood flow through the liver. Notable among these is cirrhosis, a disease that can produce a marked decrease in hepatic blood flow, with a resulting decrease in the hepatic elimination with highly cleared compounds (Bauer et al., 1994).

Hepatotoxic compounds can produce alterations in liver blood flow as one of their effects on the liver. For example, carbon tetrachloride, a compound whose pharmacokinetic behavior has been described in at least five PBPK models, exerts a vasoconstrictor effect on hepatic vessels, thereby altering blood flow patterns in the liver. Other compounds, such as beryllium and dimethylnitrosamine, produce hepatocellular necrosis, which subsequently can affect liver blood flow rates (Plaa, 1991).

Much of the recent interest in PBPK modeling stems from the application of this technique to assess human health risk posed by exposure to compounds that have been demonstrated to have carcinogenic effects in experimental animal species. Implicit in this approach is the assumption that the presence of tumors in experimental animals has no effect on physiological parameter values used in the models. However, Carter et al. (1994) and others have identified hemodynamic changes that occur in the livers of animals with intrahepatic tumors. Blood flow alterations also are observed in experimental animals with some types of tumors (Hemingway et al., 1993). Therefore, if PBPK-based simulations of the pharmacokinetic behavior of rodent carcinogens are carried out for long time courses, it may be necessary to account for tumor-associated changes in blood flow in tumor-bearing tissues.

Anesthesia

Anesthesia has a profound effect on tissue perfusion, particularly that of cardiac and skeletal muscle and splanchnic and hepatic tissues. As a result, default values for these parameters in PBPK models of compounds that are not expected to exert an anesthetic effect should be based only on studies that used unanesthetized animals. Conversely, PBPK models of clinical anesthetic agents or environmental pollutants that exert an anesthetic effect should account for the potential effect of the anesthetic agent on tissue blood flow.

Administration of anesthetic agents can result in increases or decreases in tissue blood flow. For example, in mice, anesthesia (Avertin: 2.5% 2,2,2-tribromoethyl and tertiary amyl alcohol, Sanofi Winthrop, Gentilly, France) increased blood flow to the liver via the portal vein by 33% and decreased skeletal muscle perfusion by 42%, when expressed as percent cardiac output (Barbee et al., 1992). In rats, inhalation anesthesia has been shown to reduce skeletal muscle blood flow by 79% (Laughlin et al.,1982) and hepatic flow by approximately 50% (Stanek et al., 1988), when flow is expressed in milliliters per minute per unit mass. However, rat liver perfusion also has been shown to increase with phenobarbital anesthesia (Sasaki and Wagner, 1971).

Perfusion of other tissues essential for PBPK models also may be influenced by anesthetics. For example, in the models of lead disposition in the rat and human, O'Flaherty (1991a,b) set bone blood flow equal to 3% of the cardiac output. This estimate, based on data reported by Tothill

and McCormick (1976) and Schoutens et al. (1979) for blood flow to different regions of the mature rat skeleton, is significantly different from that reported by Delp et al. (1991), who indicated that 12.2% of the cardiac output is distributed to the skeleton in the rat. Although each of these studies measured blood flow using the microsphere technique, Tothill and McCormick (1976) and Schoutens et al. (1979) used anesthetized animals, whereas Delp et al. (1991) used conscious rats. Whether the difference in bone perfusion reported in these studies is due to the use of anesthetics is unknown, but reports of bone blood flow (in milliliters per minute per 100 g) in other studies using conscious rats (Table 24) are consistent with the notion that skeletal perfusion is higher in the absence of anesthetics.

Anesthesia appears to have little effect on blood flow to the brain, unlike that to many other tissues. For example, Barbee et al. (1992) found no difference in relative blood flow to the brain of conscious mice and mice anesthetized with Avertin. Similarly, phenobarbital had little effect on cerebral blood flow in rats (Goldman and Sapirstein, 1973). However, narcotizing doses of thiopental have been shown to increase, decrease, or have no effect on cerebral blood flow in cats (see Goldman and Sapirstein, 1973, for discussion of these studies).

In addition to anesthetic agents, a number of drugs (e.g., beta-adrenergic blockers such as propranolol [Shepherd et al., 1985; Laughlin and Armstrong, 1987; Zoller et al., 1993] and calcium channel blockers such as nifedipine [Reiss et al., 1991]) produce changes in tissue blood flow rates. The influence of pharmacological agents is not limited to cardiac and skeletal muscle and splanchnic, hepatic, or bone tissue. For example, certain drugs (e.g., benidipine hydrogen chloride) also have been shown to increase blood flow to adipose tissue, principally to brown fat (Jansky and Hart, 1968; Kajita et al., 1994).

Other compounds for which PBPK models have been constructed may have direct or indirect vasoactive effects, resulting in alterations in tissue perfusion. One such compound is trichloroethylene (TCE). In the study conducted by Cowan et al. (1991), patients exposed to TCE experienced a mean 32% reduction in hepatic blood flow; some individuals in the study experienced close to a 70% reduction in hepatic blood flow after exposure to TCE. This report is interesting because it points out the potential problems associated with the use of default values for flow parameters in a PBPK model. However, the importance of representing altered hepatic blood flow in specific PBPK models for TCE obviously depends on whether this effect occurs at environmentally or occupationally relevant exposure levels of TCE, whether the altered blood flow effects the pharmacokinetic behavior of the compound, and whether other drugs given with TCE in the Cowan et al. (1991) study could have contributed to this effect.

The vasoactive influence of every compound is unique, as demonstrated by the fact that alterations in tissue blood flow induced by similar compounds, such as inhalation anesthetics, are not homogeneous. It should be noted that pharmacological agents also can affect cardiac output. Therefore, in a PBPK model, it is important to know how to represent these changes (i.e., either as an alteration in cardiac output, with a constant proportion of the cardiac output going to the various tissues, or as a selective change in tissue blood flow). The lack of a consistent pattern between tissue blood flow responses and exposure to pharmacological agents suggests that values

for this parameter ideally should be obtained through experimental determination of blood flow distribution patterns during exposure to the agent whose pharmacokinetic behavior is being modeled. The importance of accurately characterizing blood flow distribution is underscored by the sensitivity of a number of PBPK models for this parameter (such as in models of compounds that exhibit flow-limited hepatic clearance). The sometimes dramatic effect that anesthetic agents can have on blood flow distribution also underscores the importance of basing default or reference values for this parameter on blood flow studies of unanesthetized animals.

Physical Activity

Physical activity, whether through circadian variations in activity or exercise, results in profound changes in cardiac output and the distribution of cardiac output. In rats, for example, cardiac output changes by approximately 30% through the diurnal cycle (Smith et al., 1987). This change in cardiac output primarily reflects diurnal changes in behavior; cardiac output is highest when rats are engaged in foraging, grooming, and exploratory activities, and it is lowest when rats are inactive and sleeping (Smith et al., 1987; Delp et al., 1991). The increase in cardiac output resulting from feeding and locomotory activities is directed primarily to skeletal muscle, splanchnic tissue and fat pads (Delp et al., 1991). Humans exhibit similar circadian changes in tissue perfusion. For example, Lemmer and Nold (1991) have shown that hepatic blood flow in humans varies about 25% over the course of the day. Circadian variation in hepatic blood flow may be responsible for time-dependent variations observed in the pharmacokinetics of several drugs. Therefore, accurate prediction of blood or tissue levels of highly cleared compounds with a short elimination half-life may require incorporation of circadian variability of tissue blood flow estimates into the PBPK model.

Exercise represents one of the greatest stresses that can be placed on the cardiovascular system, resulting in dramatic, intensity-dependent increases in cardiac output and alterations in blood flow distribution (Rowell, 1993). Tables 23–26 depict tissue blood flows in mice, rats, and dogs at rest. When animals are conditioned to exercise, the mere anticipation of an upcoming bout of exercise results in increases in heart rate and blood pressure and possible elevations in muscle blood flow (Bolme and Novotny, 1969; Armstrong et al., 1989). At the commencement of low-intensity walking, skeletal muscle blood flow increases 83% in rats (Laughlin and Armstrong, 1982) and 173% in miniature pigs (Armstrong et al., 1987). This increase in flow to the skeletal muscle is a result of both an increase in cardiac output and a redistribution of flow away from other tissues, including the kidneys, splanchnic tissue, spleen, and fat. In the rat, slow treadmill walking results in 52, 85, and 91% decreases in blood flow to the kidneys, spleen, and fat, respectively (Laughlin and Armstrong, 1982). As exercise intensity increases, the cardiac and skeletal muscles receive greater absolute flows and a greater portion of cardiac output. For example, blood flow to the red portion of gastrocnemius muscle in rats increases from 54 mL/min/100 g at rest to 317 mL/min/100 g during high-intensity treadmill running (Laughlin and Armstrong, 1982). Similarly, flow to the deep gluteal muscle in miniature swine increases from 22 mL/min/100 g at rest to 202 mL/min/100 g during high-intensity treadmill running (Armstrong et al., 1987). Cardiac muscle blood flow increases from 107 mL/min/100 g at rest to 648 mL/min/100 g during exercise in miniature pigs (Armstrong et al., 1987). In addition to the increases in muscle blood flow, there are corresponding decreases in blood flow to many other tissues. Blood

flow to the kidneys, splanchnic tissue, spleen, and fat is 80–95% lower during intense exercise than at rest (Laughlin and Armstrong, 1982; Armstrong et al., 1987). In general, exercise, even at very low intensities, results in increases in blood flow to cardiac and skeletal muscle, lungs, and adrenal glands, remains unchanged to the brain, and decreases to most other tissues (Laughlin and Armstrong, 1982; Armstrong et al., 1987). These patterns of blood flow distribution during exercise also are evident in dogs (Musch et al., 1987) and humans (Rowell, 1993).

Food Intake

Food ingestion can influence blood flow to tissues involved in digestion and nutrient absorption through elevations in basal metabolic rate. As indicated above, when rats are actively engaged in foraging and eating, blood flow is elevated to skeletal muscle and visceral tissues (Delp et al., 1991). However, this phenomenon is not limited to rats, but also is true for mice, dogs, and humans as well. For example, Okazaki et al. (1986) found that human portal vein blood flow increased from 644–1470 mL/min following food consumption, a 130% increase. Postprandial increases in portal blood flow have obvious implications for the hepatic elimination of highly cleared compounds in the liver and also contribute to the biological variability of this parameter within a species. They also may need to be considered when the pharmacokinetic behavior of compounds administered in the feed or by gavage is modeled. Animals in the studies from which blood flow values in Tables 23–27 were compiled were presumable postabsorptive, although, in most studies, there was no apparent attempt to control this variable.

Posture

Posture also can have a significant effect on tissue blood flow rates. The blood flows presented in Tables 23–27 are for mice, rats, dogs, and humans in a resting state. However, there is considerable variation in the meaning of "resting state". Rest could be while the animals are lying down, quietly standing, or moving about in their enclosures. The variations in rest may be illustrated best by differences in resting activities during the diurnal cycle and the consequent differences in tissue perfusion (Delp et al., 1991). In compiling these data, there was no attempt made to standardize the resting state of the animals, because the majority of the studies did not define the behavioral characteristics of the resting animals. When several flow measurements were made at various times during the diurnal cycle, the blood flow values were averaged.

Postural differences in blood flow are also evident in humans. For example, Brown et al. (1989) reported that the mean blood flow rate in the portal vein in humans was reduced by 26% from the supine to the standing position (864 vs 662 mL/min). However, these changes parallel those in cardiac output that occur when going from a supine to a standing position. Therefore, absolute liver blood flow decreases when going from the supine to standing position, but relative hepatic flow, expressed as a percent of cardiac output, does not change.

Human skeletal muscle blood flow also may be influenced strongly by posture. For example, when individuals are recumbent, few muscles are needed to actively maintain posture. However, during sitting or standing, skeletal muscles must become more active to provide postural support. This difference in posture may explain, in part, the range of values reported for human muscle blood flow. In the majority of studies in which muscle blood flow has been measured, the subjects

were in a reclining position, resulting in flows of approximately 4 mL/min/100 g (e.g., Snell et al., 1987; Hartling et al., 1989). However, in studies measuring muscle blood flow while subjects are seated, flows range from 9–16 mL/min/100 g (Savard et al., 1987; Richter et al., 1988; Rolett et al., 1990).

Age

The mean parameter values provided in Tables 23–27 are intended to be representative for young adult members of the species. However, it may be necessary to incorporate age-related changes into a PBPK model for compounds with a long half-life or when the pharmacokinetic behavior of a compound at specific life stages (e.g., neonatal, elderly) is modeled. Furthermore, incorporation of age-related changes into a PBPK model may be important when the model is used to estimate the lifetime average daily dose of a compound or it's metabolites for risk assessment purposes.

Age-related changes in tissue perfusion have been demonstrated in several tissues. For example, age-related reductions in hepatic blood flow have been well characterized in humans (Woodhouse and Wynne, 1992; Wynne et al., 1990) and, to a lesser extent, in rats (Yates and Hiley, 1978). In general, it appears that liver blood flow decreases approximately 1%/year in humans after 40 to 50 years of age. These changes can have a dramatic effect on the pharmacokinetic behavior of highly cleared drugs in elderly populations. Fewer studies have been conducted of age-related changes in hepatic blood flow in experimental animals. Yates and Hiley (1978) reported that the distribution of the cardiac output in the hepatosplanchnic region fell from 21.1% in young rats (3–4 months old) to 11.4% in "middle-aged" rats (11–12 months old). However, blood flow measurements in this study were conducted in rats anesthetized with ketamine. The potential therefore exists that the difference in hepatic blood flow between young and middle-aged rats could represent a differential effect of the anesthetic agent, rather than simply an age-related difference in flow. In addition to hepatic tissue, blood flow to other rat visceral tissues, such as the kidneys and small intestines (Hoffman et al., 1982) and spleen (Tuma et al., 1985; Tuma et al., 1986; McDonald et al., 1989) has been reported to be lower in senescent rats.

Changes in body composition, which occur with advancing age, also could have a major impact on the relative distribution of cardiac output. For example, with increasing age during adulthood, humans experience an increase in relative body fat (Wessel et al., 1963; Myhre and Kessler, 1966) and a concomitant decrease in muscle mass (Tzankoff and Norris, 1977; Borkan et al., 1983). These age-related changes in body composition likely will influence the relative portion of cardiac output going to these tissues.

Because the results of PBPK models are used in risk assessment to interpret the results of chronic bioassays in experimental animal species, it seems appropriate to more accurately characterize age-related changes in anatomical and physiological hemodynamic parameters in mice and rats and, when appropriate, to incorporate these changes into PBPK models.

Gender

Mean blood flow values in Tables 23–27 are derived almost exclusively from male animals; the one exception is a canine study (Quillen and Reid, 1988) that used both male and female dogs. In general, there is a paucity of data comparing male and female tissue blood flows. It is likely that blood flow rates to reproductive tissues will differ, either when flow is expressed per unit mass or as a percent of cardiac output. There is also evidence that blood flow to other tissues may vary between males and females. For example, it has been reported that perfusion of human brain (Perlmutter et al., 1987) and myocardial (Rowe et al., 1959; Weinberg et al., 1964) tissue differs between males and females. In addition, gender-related variations in body composition could result in differences in the relative distribution of cardiac output among the various organs. For example, the gastrointestinal tract and adipose tissue of females may represent a larger portion of total body mass than in males (ICRP, 1975). This being the case, it is not unreasonable to assume that these tissues in females may receive a greater portion of cardiac output than in males.

USE OF CARDIAC OUTPUT AND REGIONAL BLOOD FLOW VALUES IN PBPK MODELS

In this section, methods for estimating cardiac output values for individuals of different body weight within a species are examined, and the need for maintaining equivalence between the sum of regional blood flows and cardiac output in PBPK models is emphasized.

Selecting Cardiac Output Values for Animals Within a Species

In their landmark paper, Andersen et al. (1987) used the following allometric scaling relationship to derive cardiac output values in their methylene chloride PBPK model for rats, hamsters, and humans:

$$\text{Cardiac Output (L/h)} = 15\ (\text{BW})^{0.74},$$

where BW equals body weight in kilograms. Subsequent PBPK models (e.g., Fisher et al., 1989; Kedderis et al., 1993; Evans et al., 1994) have used either this equation or a slight variation of this relationship to estimate cardiac output for rats.

Based on the cardiac output data reported by Delp et al. (1991), Dallas et al. (1994) developed the following relationship to generate cardiac output values for rats in their PBPK model of tetrachloroethylene:

$$\text{Cardiac Output (mL/min)} = 1.54\ (\text{mL/min/g})\ \text{BW}\ (\text{g})^{0.75}.$$

General use of this equation requires the assumption that cardiac output remains relatively constant over the range of body weights typically encountered for young adult rats used in pharmacokinetic studies. The data reported by Hachamovitch et al. (1989) suggest that cardiac output changes very little in male F344 rats over much of their lifetime. For example, cardiac output increased from 84 mL/min in 290-g, 4-month-old rats to 98 mL/min in 363-g, 12-month-old rats, and it remained at about that level in 20-month-old rats weighing 400 g. Assuming a similar pattern

exists for male Sprague-Dawley rats, the equation used by Dallas et al. (1994) to derive cardiac output values for rats is probably valid for use in estimating the cardiac output of adult male Sprague-Dawley rats of other body weights.

Comparison of estimated and predicted values of cardiac output in rats, as shown in Table 29, suggests that the widely used equations developed by Andersen et al. (1987) and Arms and Travis (1988) are appropriate for estimating cardiac output in unanesthetized rats. As expected, the relationship derived by Dallas et al. (1994) closely predicts the mean cardiac output reported by Delp et al. (1991) and only slightly overpredicts the mean cardiac output for rats derived from five studies.

TABLE 29. Predictive Ability of Various Allometric Scaling Equations Used to Estimate Cardiac Output Values for the Rat in PBPK Models

	Cardiac Output (mL/min)[a]	
Reference	Estimated	Measured
Andersen et al. (1987)	117.6	
Arms and Travis (1988)	110.6	
Dallas et al. (1994)	128.9	
Mean from Table 22		110.4
Delp et al. (1991)		131.0

[a]Estimated for a 366-g rat, the mean body weight of rats used in the Delp et al. (1991) study.

In contrast, the equations developed by Andersen et al. (1987) markedly overpredict the mean cardiac output value in unanesthetized mice derived from the results reported in the literature. The equation proposed by Andersen et al. (1987),

$$\text{Cardiac Output (L/h)} = 28\ BW^{0.74},$$

where BW equals body weight in kilograms, yields a value of 29.3 mL/min for a 25-g mouse.

In comparison, the mean cardiac output derived from results reported by Barbee et al. (1992) and Wang et al. (1993b) for unanesthetized mice with a mean body weight of 23–30 g is around 14 mL/min (Table 22). However, the equation derived by Arms and Travis (1988),

$$\text{Cardiac Output (L/h)} = 16.5\ BW^{0.75},$$

where BW equals body weight in kilograms, yields a value (17.3 mL/min) very similar to that found in the literature.

The following equation, derived by Dallas et al. (1994) to predict cardiac output in the dog was developed using the data obtained from Detweiler et al. (1970):

Cardiac Output (mL/min) = 1.05 (mL/min/g) BW $(g)^{0.75}$.

However, use of this equation to predict cardiac output in a 10-kg dog (the presumed weight of dogs in their model) yields a value of 1050 mL/min, a value that falls outside of the range of values reported by Detweiler et al. (1970) (cited as Andersen [1970] in their paper) for cardiac output in unanesthetized dogs. Use of this equation to predict the cardiac output of dogs weighing 21-kg yields a value of 1831 mL/min, a value that is around 60% lower than that determined experimentally in 21-kg dogs by Quillen and Reid (1988). Therefore, this equation should be used with some caution.

Summation of Regional Blood Flows

In parameterizing a PBPK model, it is crucial that the sum of the regional blood flows exactly equal 100% of the cardiac output. Failure to do so results in a flow imbalance in the model that typically leads to severe inaccuracy and model failure.

However, in Tables 23–27, the sum of mean tissue flows is less than 100% of cardiac output for mice (57.3%), rats (93.5%), dogs (90.3%), and humans (91.5%). There are several reasons why summed tissue flow rates from these tables do not equal cardiac output. First, representative flows from normal unanesthetized animals could not be found in the literature for certain tissues (e.g., adipose and bone tissues in mice and dogs). The gaps in the available blood flow data make it impossible to account for all of the cardiac output in these animals. Second, rarely did any study report cardiac output and blood flow to most tissues. (One exception is the study by Delp et al. (1991); these investigators used a direct measure of cardiac output and the sum of individual tissue blood flows to assess cardiac output in the rat. There was close agreement in the cardiac output values derived using these two methods.) In the absence of studies reporting total tissue perfusion rates, data were compiled from investigations in which blood flow to several individual tissues was measured. Although this approach establishes a representative mean or measure of central tendency for tissue blood flows, it does not mathematically yield individual perfusion rates that, when summed, equal 100% of the cardiac output; this is due to the interstudy variability of tissue perfusion rates. Finally, and most importantly, Tables 23–27 are not exhaustive in that they do not include all tissues in the body (e.g., reproductive tissues, eyes, bladder). Thus, summed tissue flows from these tables would not be expected to equal 100%.

Although the regional blood flow values provided in Tables 24–27 for rats, dogs, and humans do not yield 100% when summed, they should provide modelers with useful guidance in deciding how cardiac output should be apportioned among compartments, and may be good sources of data for blood flow to specific organs represented in the model. However, because data are unavailable for regional blood flow to many tissues in the mouse, the values provided in Table 23 cannot be used by themselves to develop cardiac output distribution estimates for a mouse PBPK model.

BLOOD VOLUME

Inherent in many recent PBPK models is the assumption that uptake of a compound into storage tissues is perfusion limited (i.e., diffusion across the tissue membranes occurs rapidly relative to blood flow). As a result, one can assume that the concentration of the compound is in equilibrium between the tissue and the blood in the tissue. Therefore, there is no need to represent the tissue and blood components of a storage compartment separately when the assumption of perfusion-limited uptake is made. In contrast, when diffusion occurs less rapidly than blood flow, then uptake is said to be diffusion limited. Diffusion-limited uptake may occur for compounds that are highly bound to plasma proteins or other blood components or when the compounds have a high molecular weight or are charged. When diffusion-limited uptake occurs in a storage compartment, it is necessary to write separate mass balance equations to describe the behavior of the compound in the tissue and in the blood in the tissue. Therefore, data on the volume of blood in the compartment are required when it is necessary to represent diffusion-limited uptake in a compartment.

Data on the residual volume of blood in each organ also are required when it is necessary to correct tissue:blood partition coefficient values used in the model for the volume of residual blood in the organ. Tissue:blood partition coefficient values are determined in one of two ways: (1) by dosing the animal, removing and homogenizing the tissues of interest, and determining the concentration of the compound in the blood and homogenized tissues or (2), for volatile compounds, by determining the partitioning behavior of the compound between homogenized tissues and blood *in vitro*, using the vial equilibration method. In both approaches, homogenized tissues are used. However, residual blood in the homogenized tissue has the potential to introduce error into the determination of the partition coefficient. The extent of error is dependent on the amount of blood that remains in the tissue and the extent to which the compound binds to blood components. Khor and Mayersohn (1991a,b) have demonstrated how tissue:blood partition coefficient values can be corrected for the amount of residual blood in the tissue. Implementation of this approach requires data on the volume of residual blood in each organ.

The compartments of a PBPK model are connected via a representation of the circulatory system. Although arterial and venous blood compartments are included explicitly in many PBPK models, others use an algebraic simplification of the mass balance differential equation for the blood compartment under the assumption of steady state. Representation of the mass balance equations in this way creates a "bloodless" PBPK model because the volume of blood in the animal is not explicitly accounted for. However, when it is necessary to obtain estimates of the amount of chemical in the blood with the model or when the compound being modeled either binds extensively to blood elements or is metabolized in the blood, it is necessary to include a parameter in the model to represent blood volume in the major arteries and veins.

CRITERIA FOR DATA SELECTION AND REPRESENTATION OF THE DATA

Measurement of residual blood volume in experimental animals usually involves injection of radiolabeled erythrocytes or plasma proteins into the animals and measurement of the radiolabel in excised tissues. All of the blood volume values presented in Table 30 for experimental animals were obtained using this approach. The use of blood volume values from excised tissue in a PBPK model requires the assumption that blood volume in excised tissue is the same as blood volume in the living state. However, the method used to sacrifice the animal may effect organ blood volume (e.g., immersion in liquid nitrogen may cause rapid hypothermia-induced shifts in blood volume). Also, differences in organ blood volume between the living and the excised state may be caused by the dissection techniques used by the investigators. Accidental or deliberate draining of blood from the organ during dissection and removal of the organ from the body would result in an underestimate of the amount of "equilibrium" blood in the tissue of the intact animal. In general, the studies used to provide the data represented in Table 30 involved excision and homogenization of tissues without attempts to drain blood from the organ. In some cases, (e.g., Kaliss and Pressman, 1950) attempts were made to preserve the blood volume of the tissues by ligation of vessels prior to excision of the organ.

Although most blood volume measurements in laboratory animals have been made using the same technique, a number of different techniques have been used to measure organ-specific blood volume in humans. Leggett and Williams (1991) have discussed the merits and limitations of these techniques in their review of the literature. In general, any study in humans that was deemed appropriate for inclusion in the Leggett and Williams (1991) paper also was considered for this analysis. In organs for which blood volume data were lacking in humans, Leggett and Williams (1991) derived reference values based on the results of animal studies. However, the results of animal studies were not used as a surrogate for human data in this paper.

BLOOD VOLUME DATA

Mean values and ranges are provided for the residual blood volume in various tissues of the mouse, rat, dog, and human in Table 30.

The values presented in Table 30 are volume fractions for that organ or tissue, in other words, the volume of residual blood in the organ relative to the volume of the organ. These values are not representations of the fraction of the total blood volume that resides in that tissue.

As shown in Table 30, bone, heart, kidneys, liver, lung, and spleen are among the more vascular tissues, whereas adipose, brain, muscle, and skin have a relatively small proportion of their volume taken up by blood.

In general, there is relatively good agreement across species in the volume fraction of blood in less vascular tissues. For example, it appears that from 1–5% of the volume of muscle tissue in mice, rats, and humans is occupied by blood. A larger variability exists within and across species in the volume of blood of the more vascular tissues. Although this variation may reflect true species or strain differences in the blood volume of these organs, it is more likely caused by differences in technique or interlaboratory variability.

TABLE 30. Volume Fraction of Blood in Organs and Tissues

	Mouse			Rat			Dog		Human		
	Mean	Range	Number Studies	Mean	Range	Number Studies	Mean	Number Studies	Mean	Range	Number Studies
Adrenal	0.03		1	0.24		1					
Adipose			1						0.02 ± 0.01	0.02–0.03	3
Bone	0.11		1	0.04					0.04		1
Brain	0.03		1	0.03	0.02–0.04	3	0.01	1	0.04 ± 0.01	0.03–0.10	15
Heart				0.26		1	0.07		1		
Kidney	0.24	0.12–0.34	3	0.16	0.11–0.27	3	0.08	1	0.36 ± 0.01	0.22–0.50	4
Liver	0.31	0.23–0.36	3	0.21	0.12–0.27	3	0.15	1	0.11		1
Lung	0.50	0.40–0.62	3	0.36	0.26–0.52	3	0.30	1			
Muscle	0.04	0.03–0.05	2	0.04	0.01–0.09	3	0.01		0.01		1
Skin	0.03		1	0.02		1			0.08		1
Spleen	0.17	0.17–0.19	3	0.22	0.17–0.28	3	0.51	1			
Thyroid				0.18		1					

Important differences exist in values for blood volume of the liver and kidneys in rats. For example, Triplett et al. (1985) found that about 24% of the volume of the rat kidneys was occupied by blood, whereas Khor and Mayersohn (1991b) estimated the volume fraction of blood in the kidneys to be about 11%. A similar trend was seen in values reported for the volume fraction of blood in the rat liver; Triplett et al. (1985) reported a value of about 25%, and Khor and Mayersohn (1991b) found this value to be about 12%. The difference in values reported in each of these studies may be due to the different strains used (Triplett et al. [1985] used Sprague-Dawley rats, and Khor and Mayersohn [1991b] used F344 rats) or differences in experimental techniques, or it simply may reflect the biological variability of this parameter. A wide variation in values for the liver and kidneys blood volume in the rat also is reported in the earlier literature. For example, the rat liver blood volume values reported by Caster et al. (1956), Everett et al. (1956), and Lewis et al. (1952) are 10, 27, and 18%, respectively, and their values for blood volume of the rat kidneys are 9, 13, and 28%, respectively.

Blood volume in most organs in humans has been characterized fairly well. For example, at least 15 studies of cerebral blood volume in humans have been published. If studies based on the indicator-dilution methods are disregarded, data indicate that the volume fraction of blood in the brain is 0.03–0.05. In contrast, there are no good estimates of the volume fraction of blood in the human liver. The reference value proposed by Leggett and Williams (1991) for blood volume in the human liver is based on an estimate taken from the review published by Greenway and Stark (1971), whose estimate is based on data from dogs.

The early PBPK models developed by Bischoff and colleagues (e.g., Bischoff and Brown, 1966) included detailed representations of the capillary blood volume, interstitial volume, and intercellular volume for each compartment in the model. Based on data available at that time, Dr. Bischoff assumed that capillary blood occupied about 6% of the liver volume, 9% of the lung volume, and 13% of the kidneys volume of a hypothetical "minimammal". These estimates are consistent with the low end of values that have been reported in the literature; however, they are intended to represent capillary blood volume, not the blood in the larger vessels present in the tissue. Greenway and Stark (1971) have suggested that 44% of the blood in the liver resides in the large vessels (e.g., hepatic artery, portal vein) and the remainder resides in the small vessels. Therefore, the assumption that 6% of the hepatic volume is occupied by blood seems like a reasonable one. Similar, but slightly lower values were used in the PBPK model for 2,3,7,8-tetrabromodibenzo-*p*-dioxin developed by Kedderis et al. (1993). For example, these investigators assumed that blood occupied only 5% of the liver, slowly perfused tissues, and fat, whereas only 1% of the volume of the richly perfused tissue and skin compartments was occupied by blood. These values are consistent with those presented in Table 30 for slowly perfused tissues but may underestimate the amount of blood in more vascular tissues.

Because excision and homogenization of tissues will include the blood from large as well as small vessels, the values used in Table 30 may be appropriate when correcting tissue:blood partition coefficients for the presence of residual blood. However, selection of values for organ-specific capillary blood volume in a model should take into account that the values presented in Table 30 presumably represent blood in large and small vessels of the organ.

The PBPK models with explicit compartments for the arterial and venous vessels require data on the blood volume that resides in those vessels. Standard textbooks of physiology apportion blood volume in the body as follows: veins, 64% (39% in large veins and 25% in small veins); arteries, 15% (8% in large arteries, 5% in small arteries, and 2% in arterioles); and capillaries, 5%. The ICRP (1975) document recommends the following distribution of blood volume be used for reference man and woman: arterial system, 19%; venous system, 61%; pulmonary circulation, 10%; and heart cavities, 10%. Lumping the blood in the heart and pulmonary circulation with the arterial blood yields values similar to those used in PBPK models developed by Igari et al. (1983) for arterial and venous blood volume. The values proposed by Leggett and Williams (1991) and Mapleson (1963) suggest a 25:75 division of blood volume between arterial and venous circulations.

FACTORS THAT INFLUENCE ORGAN-SPECIFIC BLOOD VOLUME

The two factors that have the greatest influence on blood volume in different compartments are posture and exercise. Going from a sitting to a standing position results in a shift of about 15% of the total blood volume from the upper body (intrathoracic and splanchnic regions) to the lower body (legs and pelvic area). From a modeling perspective, the factor that has the most effect on blood volume distribution is exercise. Summarizing data from several sources, Leggett and Williams (1991) note that blood volume can drop by 15% in the liver and 35% in the splanchnic region in exercising humans. In contrast, the blood volume in the lungs may increase by 30%.

Limited data are available on age-related changes in blood volume. Leenders et al. (1990) have found that cerebral blood volume decreased about 0.5%/year in humans aged 22–82 years. These changes may be important to consider for specific research in cerebrovascular hemodynamics, but probably have little impact on values that would be used in PBPK models.

ALVEOLAR VENTILATION

The PBPK models of agents that are either absorbed or eliminated by the respiratory tract require a lung compartment with parameters to represent these processes in the model. Values for these parameters often are taken from compendia such as the Arms and Travis (1988) document. Given the widespread use of this document as a source of respiratory parameter values in PBPK models, it is important to examine the accuracy of these values. Perhaps more important is the need to examine the validity of "standard" values used in PBPK models of agents that have the potential to affect the respiratory dynamics of animals and humans.

The pulmonary uptake of a volatile compound can be determined from data on the pulmonary blood flow rate, the blood:air partition coefficient, the concentration of the compound in the inhaled air, and the alveolar ventilation rate (Q_A). The Q_A can be defined as

$$Q_A = f \times (V_T - DS),$$

where f is the respiratory frequency, V_T is the tidal volume, and DS is the physiological dead space. Alternately, QA can be derived as

$$Q_A = V_E - (f \times DS),$$

where V_E is minute volume, which is equal to $f \times V_T$.

CRITERIA FOR DATA SELECTION

Values selected for this analysis were derived from studies using unanesthetized, healthy, resting, adult animals breathing room air. Because tracheotomy has been shown to effect tidal volume and respiratory frequency in animals, data from animals that had undergone this procedure were not used.

Alveolar ventilation rates, per se, rarely are reported in the literature for experimental animals. However, values for this parameter can be derived using the equations shown above. To derive reference alveolar ventilation values, Arms and Travis (1988) assumed that 33% of the tidal volume represents physiological dead space. Therefore, alveolar ventilation is assumed to be equal to 0.67 V_E in resting animals.

ALVEOLAR VENTILATION DATA

Alveolar ventilation is among the best characterized of the physiological parameters required for PBPK modeling. As a result, mean values can be derived for this parameter in mice, rats, dogs, and humans.

Mice

Compared to other species, few studies have been conducted to determine respiratory parameters in unanesthetized mice. Perhaps, this is because of the technical difficulties associated with the small size of these animals.

Mean values for alveolar ventilation in unanesthetized mice range from 83.0–145.1 mL/min/100 g. The mean alveolar ventilation rate for mice provided in Table 31, assuming $Q_A = 0.67\ V_E$, is 116.5 mL/min/100 g body weight. This value is slightly higher than the reference value of 100 mL/min/100 g selected by Arms and Travis (1988) for this parameter, largely due to inclusion of data from the more recent study by Vijayaraghavan et al. (1993).

TABLE 31. Alveolar Ventilation at Rest (Milliliters per Minute per 100g Body Weight)

Species	Mean	Range	Number of Studies
Mouse	116.5	83.0–145.1	5
Rat	52.9	31.5–137.6	**23**
Dog	23.1		**1**
Human	5.0	3.5–7.7	–

Rats

The values for respiratory parameters in unanesthetized rats were derived from 23 studies. The mean alveolar ventilation values (assuming $Q_A = 0.67\ V_E$) in rats range from 31.5–137.62 mL/min/100 g body weight, with a mean across all studies of 52.88 mL/min/100 g. This value differs somewhat from the reference value suggested by Arms and Travis (1988) for this parameter (46.8 mL/min/100 g body weight or 117 mL/min for a standard 250-g rat).

Values for weight-normalized minute volumes in unanesthetized rats are provided by Arms and Travis (1988) in their Table 4-23. According to the table header, minute volumes are represented in L per minute per kilogram; however, the first value in the table is represented in milliliters per minute per kilogram. Correct representation of the value from Blume and Zollner (1943) as 1.467, instead of 0.001 L/min/kg, would raise their mean estimate somewhat. Also, there are two other errors in their Table 4-23 that would result in a lower estimate of mean V_E. Values from Bartlett and Tenney (1970) and Olson and Dempsey (1978) were listed incorrectly in the table as 0.142 and 0.326 L/min/kg, respectively. The correct values are 0.381 and 0.528 L/min/kg for these studies, resulting in a higher estimate of the mean across all studies. Four of the mean V_E values used by Arms and Travis (1988) in their analysis are based on the study of Leong et al. (1964). One of the V_E values was obtained from animals weighing 52.3 g. The V_E is proportionally greater in smaller animals when the values are normalized for body weight. As a result, one might argue that V_E values from a 50-g rat may not be representative of those from a "standard" 250-g rat. Therefore, this value was not used to derive the mean value provided in Table 31. Finally, the overall mean estimate for alveolar ventilation provided in Table 31 for rats was derived from the means of 23 studies. Arms and Travis (1988) considered 13 studies in their derivation of the reference value for this parameter.

Dogs

Surprisingly few studies of alveolar ventilation rates measured in unanesthetized dogs were identified in the literature. Park et al. (1970) reported a mean V_E of 34.5 mL/min/100 g body weight in 20 beagles of both sexes. Assuming a dead space of 33%, the alveolar ventilation in the animals is expected to be 23.1 mL/min/100 g body weight.

Humans

Data on respiratory dynamics in humans have been collected for many years, have been summarized in compendia such as that compiled by Altman and Dittmer (1971). These authors have estimated the V_E expected for a reference man (20 years old, weighing 70 kg, with a surface area of 1.8 m^2) and woman (20 years old, weighing 55 kg, with a surface area of 1.52 m^2) using the results of individual studies. Estimates of V_E range from 4.38–8.44 L/min (five studies) for a reference woman and 5.28–11.43 L/min (six studies) for a reference man. For reference woman and man, the mean estimated V_E are 5.3 and 7.5 L/min, respectively. The values selected by ICRP (1975) for the V_E for reference woman and man are 6.0 and 7.5 L/min, respectively. The results of studies published since the Altman and Dittmer (1971) and ICRP (1975) documents (e.g., Brobeck, 1979; Frostell et al., 1983) are consistent with the reference values proposed for minute ventilation in humans.

Similar to V_E, numerous studies have been conducted to estimate dead space volume in humans. Altman and Dittmer (1971) have summarized the results of 16 of these studies and estimated dead space volume for a reference man and woman. The estimated values range from 17.6–39.4% of the tidal volume, with a mean estimate of 33%. This is identical to the value selected by Arms and Travis (1988) and supports the use of 0.67 V_E to estimate Q_A in humans.

FACTORS THAT INFLUENCE ALVEOLAR VENTILATION

Before the alveolar ventilation rates presented in Table 31 are used as default values in a PBPK model, the following issues should be considered.

Effect of the Compound Being Modeled on Respiratory Dynamics

Implicit in the use of default alveolar ventilation values in a PBPK model of unanesthetized animals breathing uncontaminated air is the assumption that exposure to the compound being modeled has no effect on respiratory dynamics. However, inhaled compounds can have very characteristic effects on breathing patterns. For example, exposure to respiratory irritants typically results in a reduction in breathing rate. Compounds that act as bronchoconstrictors reduce V_E by reducing the tidal volume. Pulmonary irritants alter expiratory breathing patterns (Vijayaraghavan et al., 1993). Anesthetic agents also affect respiratory dynamics. Vinegar et al. (1979) showed that both tidal volume and respiratory rate were reduced in mice after intravenous administration of pentobarbital. Based on the relationships described in the equations shown above, a corresponding reduction in V_E and Q_A is expected in animals anesthetized with pentobarbital.

Inhalation of anesthetics is known to reduce tidal volume and increase respiratory rate (Lockhart et al., 1991). The result is a depression of minute ventilation because the increase in respiratory rate cannot compensate for the decrease in tidal volume.

Despite the potential effect of inhaled compounds on respiratory dynamics, many PBPK models of volatile compounds use default values for Q_A, with little consideration of the potential error this may introduce into model-derived simulations. Johanson and Filser (1992) have demonstrated that use of the default values for Q_A proposed by Arms and Travis (1988) for mice and rats results in an overestimate of the clearance uptake measured using the closed-chamber gas uptake method. They found that experimentally determined clearance uptake values were about 60% of the values determined when the default reference values were used. Successful estimation of the experimentally derived clearance uptake values generally required the use of Q_A from about 30–80 mL/min for rats and about 5–14 mL/min for mice. Johanson and Filser (1992) offer three reasons for the necessity to use Q_A values that are about 60% lower than those proposed by Arms and Travis (1988) to successfully estimate experimentally derived clearance uptake values for animals in gas uptake studies. First, they point out that volatile compounds may act as respiratory irritants, which, as mentioned above, can reduce respiratory rate. Second, a wash-in/wash-out effect could be occurring where the volatile compound is absorbed onto the respiratory airways during inhalation and then desorbed during exhalation, resulting in reduced pulmonary uptake. Although alveolar ventilation may not be affected by the compound per se, a lower value for Q_A would enable clearance uptake from the chamber to be modeled more accurately. A third possibility,

but one that Johanson and Filser (1992) consider remote, is the potential for volatile compounds to exert an anesthetic effect on the animals in the closed chamber, thereby affecting respiratory dynamics.

Regardless of the reason (direct effect on respiration or correction for a wash-in/wash-out effect), use of Q_A values that are 60% lower than those proposed by Arms and Travis (1988) may be necessary to accurately estimate clearance uptake of a number of volatile compounds in closed-chamber gas uptake studies. These lower Q_A values have been used successfully by Johanson and Filser (1993) and Csanady et al. (1994) in PBPK models of butadiene and styrene, respectively. It is interesting to note that the alveolar ventilation rates derived by Medinsky et al. (1994) from a best-fit to the data in a PBPK model for butadiene are 17.1 and 70.8 mL/min for a 25-g mouse and a 250-g rat, respectively. These values are about 68 and 61% lower than the reference values for this parameter suggested by Arms and Travis (1988). Nevertheless, many investigators have had success fitting closed-chamber data using alveolar ventilation values similar to those proposed by Arms and Travis (1988). For example, based on their experience, Clewell (1994) and colleagues found that the "best" values for alveolar ventilation were around 115 mL/min/100 g for the mouse and 35–50 mL/min/100 g for the rat.

Because PBPK models of inhaled compounds with high blood solubility are sensitive to values of Q_A, and because these same compounds have the potential to alter respiratory dynamics, it is prudent to measure values for this parameter during exposures of animals or humans to these compounds (or at least to be aware of the effect that volatile compounds can have on respiration and to adjust the parameter values accordingly). Use of default values for Q_A in PBPK models of some inhaled compounds may result in overestimates of inhaled dose.

Effect of Physical Activity

Alveolar ventilation is one of the parameters in a PBPK model that responds most dramatically to exercise and physical work. The values provided in Table 32 are derived from the V_E data reported in the ICRP (1975) document for male and female humans at rest and performing light, moderate, and strenuous work.

TABLE 32. Alveolar Ventilation (Liters per Minute) During Exercise in Humans[a]

Activity	Male	Female
Resting	5	5
Light Activity	20	14
Heavy Work	35	20
Maximal Work	90	70

[a]Based on minute volume values reported in ICRP (1975) and assumptions that dead space equals 0.33 tidal volume at rest and 0.20 tidal volume during physical activity.

Extensive studies of the effect of exercise on respiratory dynamics also have been conducted by Balke and reported in Altman and Dittmer (1971). For sedentary and reasonably active individuals, the V_E during moderate exercise (heart rate = 120) ranges from about 23–30 L/min. During strenuous exercise (heart rate = 150), V_E tends to range from about 35–65 L/min, and maximal exercise (heart rate = 180+) results in V_E ranging from 50–100 L/min. Values for V_E at rest and during exercise are increased markedly in highly trained individuals.

Physiological dead space decreases during physical work and exercise. As summarized in Altman and Dittmer (1971), dead space volume in humans ranges from about 10–30% during exercise. If it is assumed that a dead space volume of 20% is representative of values that may be obtained in exercising humans, the expected values for QA in humans doing light to moderate work would be on the order of 18–24 L/min; strenuous work, 28–52 L/min; and maximal work, 40–80 L/min. The values for light to moderate work are consistent with those used by Dankovic and Bailer (1994) in their recent reevaluation of the Andersen et al. (1987) methylene chloride PBPK model under light work conditions.

DISCUSSION

Sensitivity analyses of a number of PBPK models have been conducted to identify the parameters that have the greatest effect on model output (Bois et al., 1990, 1991; Hetrick et al., 1991; Woodruff et al., 1992; Gearhart et al., 1993; Hattis et al., 1993; Clewell et al., 1994; Evans et al., 1994). Although PBPK model simulations of the pharmacokinetic behavior of volatile organic compounds tend to be most sensitive to the values selected for metabolic parameters, they also can be influenced markedly by the values selected for physiological parameters, such as the volume of and blood flow to the fat compartment, alveolar ventilation rate, and blood flow to the liver. For example, Evans et al. (1994) demonstrated that PBPK model-derived estimates of metabolic rate constant values for carbon tetrachloride in rats were most sensitive to values selected for blood:air partition coefficient, followed by fat partition and fat volume; then slowly perfused partition, ventilation rate, cardiac output, and fat blood flow percentage; and, finally liver blood flow percentage and slowly perfused blood flow percentage. Therefore, accurate characterization of values for physiological parameters such as fat volume and ventilation rate is important for the accurate determination of metabolic rate constants with the model. Accurate characterization of the physiological parameter values in such a model is especially important when the model is used to derive metabolic rate constants for compounds for which the production of active metabolites "drives" the risk assessment.

The most accurate means of identifying physiological parameter values used in PBPK models is direct measurement of the values in animals of the same age, strain, and species as the animals in which the pharmacokinetic behavior of the compound is being studied. Ideally, these values also should be obtained under the same conditions as those used in the pharmacokinetic study. However, not all modelers have access to experimental facilities, nor is it necessary to determine experimentally the physiological parameter values for each new model when the parameters are unaffected by the compound being modeled. It is important, however, for modelers to have access to data from which valid and representative default values can be derived for the physiological parameters used in PBPK models and to have an understanding of the conditions under which it is appropriate to use default values for the parameters.

The goals of this document have been to provide modelers with representative values for physiological parameters, to provide an indication of the experimental variability associated with determining the parameter values, and to discuss the factors that have the greatest impact on individual variability of the physiological parameters. Unlike previous compilations, this document does not suggest a single set of "standard" reference values for these parameters. Rather, a range of values (each usually a mean over a sample of animals) is identified from what were thought to be valid studies. For each such array of determinations, mean parameter values are provided along with the standard deviation of the mean. Such an approach is intended to provide modelers with sufficient data to make decisions about what constitutes reasonable and representative parameter values for their model. The representation of the variability associated with the values should be useful when the need exists to adjust parameter values to obtain a better fit of model-derived simulations to experimental data. Also, explicit representation of biologically plausible ranges for the parameter values may be useful for modelers who employ the Monte Carlo approach.

In some cases, reference physiological parameter values proposed in other documents have been derived from the results of relatively few studies. The approach taken in this document has been to conduct an extensive search of the literature and, whenever possible, to derive the mean value for the parameter from as many valid studies as possible. The criteria used to identify what constitutes a "valid" study are discussed in each section. Briefly, values were selected only from studies in which healthy, resting, unanesthetized, young adult animals were used. Care also was taken to avoid the use of values from studies in which intervention by the researchers (e.g., placement of a tracheostomy) could have an effect on the measurement of the parameter value.

Representative values for some of the physiological parameters used in PBPK models have been difficult to obtain from the existing compilations of such data. For example, a reference value for the volume of fat in the mouse does not appear in the compilation developed by Davies and Morris (1993), despite the importance of this species in pharmacokinetic modeling. Modelers also have had difficulty accessing physiological parameter values for individual organs in some species and in determining parameter values for anatomically or physiologically heterogenous tissues when the tissue is represented in different compartments in the model (e.g., subcutaneous and internal fat). Hopefully, modelers with a need for such data will find this document useful. Although an attempt was made to provide data for the organs and tissues of interest to most modelers, an exhaustive compilation of the volume of and blood flow to all organs and tissues is beyond the scope of this document. Furthermore, no attempt was made to include values for all of the organs or tissues that may be necessary for models developed to describe the pharmacokinetic behavior of compounds under special circumstances, such as pregnancy. Those interested in developing PBPK models that include a fetal compartment are encouraged to refer to the papers by Fisher et al. (1989, 1990), Luecke et al. (1994), and O'Flaherty et al. (1992) for the necessary parameter values.

A number of long-standing assumptions regarding default values for physiological parameters are explored in this paper. Specifically, we have examined the validity of the following five assumptions: (1) that an appropriate reference body weight for mice and rats is 25 and 250 g, respectively; (2) that values for the volume of the fat compartment of a PBPK model can be

derived from the weight of dissectible fat; (3) that it is appropriate to derive values for blood flow parameters from studies in which anesthetized animals were used; (4) that the relative blood flow to the liver is constant across species; and (5) that the compound being modeled has no effect on physiological processes that are represented in the model.

Regarding the selection of values for body weight in a reference mouse or rat, the values proposed by Arms and Travis (1988) are representative of relatively young animals (9–10 weeks old) that are in a rapid phase of growth. In contrast, the value selected for the weight of a reference human is representative of adult weight. Use of these reference body weights in a PBPK model to scale animal data to humans may introduce error because the species are in different stages of development. In addition, use of the reference body weight for mice and rats proposed by Arms and Travis (1988) may introduce error into estimates of the volume of the fat compartment in mice and rats of "nonstandard" weight. Therefore, consideration should be given to values for this parameter that are either more representative of the body weight of the animal over the majority of its lifespan or that occur during a period of less rapid growth.

Values selected for the volume of the fat compartment are among the most important in PBPK models of lipophilic compounds. Because most PBPK model simulations are carried out for a relatively short time, it is not necessary to account for age-related changes in the volume of the fat compartment. However, when the pharmacokinetic behavior of the compound is simulated over an extended time course, as is required for compounds with a long residence half-life, then it may be important to account for age-related changes in body composition.

When model simulations are carried out for extended time periods, it also may be necessary to account for compound-induced changes in compartment volume. For example, exposure to some compounds can increase or decrease liver volume over time. However, changes in liver volume do not necessarily result in a change in hepatic clearance. Compound-induced changes in intrinsic metabolic capacity should be accounted for as well before incorporating changes in liver volume into the model.

Anesthesia has the potential to markedly affect regional hemodynamics. As a result, the blood flow values presented in Table 23 were derived only from studies that used unanesthetized animals. The mean values derived for blood flow to the liver of mice and rats are somewhat lower than the reference values selected by Arms and Travis (1988) for this parameter. This difference is perhaps due to the reliance by Arms and Travis (1988) on data from anesthetized animals or to imprecision in selecting a reference value from the available data. The default value selected by Arms and Travis (1988) for this parameter (25% of the cardiac output) has been used widely in PBPK models and may have resulted in an overestimate of metabolic clearance of highly cleared compounds in the liver.

Data on blood volume of specific organs and pharmacokinetic compartments is important when diffusion-limited uptake is assumed, when it is necessary to correct tissue:blood partition coefficients for residual blood volume, or when it is necessary to represent explicitly the arterial and venous blood compartments. However, these values are not provided in the Arms and Travis

(1988) or Davies and Morris (1993) documents. The mean values and ranges provided in Table 30 are probably most useful when correcting tissue:blood partition coefficients for residual blood. However, these values represent the blood present in both large and small vessels in the organs. Because the blood in equilibrium with the tissue in an organ is capillary blood, direct use of the values in Table 30 in a PBPK model will result in an overestimate of the volume of capillary blood in the tissue.

A large variability is evident in the values for some blood volume parameters. It is not clear whether the wide range of values represents biological variability or differences in experimental technique. Modelers should keep this variability in mind when selecting values for these parameters.

Organ blood volume can change as a result of changes in posture and physical activity. Perhaps the most important effect to note from a modeling perspective is the shift of blood from the lower body and liver to the lungs following an increase in physical activity.

Representation of diffusion-limited uptake in a PBPK model requires not only data on residual blood volume but values for a diffusion parameter as well. The diffusion parameter might be described as a quasi-physiological parameter, equivalent to the product of the cell area/volume ratio, an anatomical term, and capillary permeability, a parameter with compound-specific values. Because it is not strictly a physiological or anatomical parameter, and because values for this parameter often are obtained by fitting the model to a certain data set, this term is not addressed in any detail in this document. However, investigators with a need to represent membrane-limited diffusion in their models may find it useful to refer to the discussions offered by Dedrick and Bischoff (1968) and Dedrick et al. (1982) on the derivation of this term. Also, use of a diffusion term to account for membrane-limited uptake is demonstrated in the PBPK models developed by Lutz et al. (1977) and Baxter et al. (1994). Use of this approach may be necessary to represent the uptake of hydrophilic compounds in some organs (e.g., brain, testes) with fairly effective capillary barriers to many substances and the uptake of large molecules such as antibodies.

Use of default values for alveolar ventilation is based on the assumption that the compound being modeled has no effect on respiratory dynamics. However, Johanson and Filser (1992) have shown that the clearance uptake of compounds in a closed chamber may be overpredicted when the reference value for alveolar ventilation proposed by Arms and Travis (1988) is used to derive the clearance values. Based on empirical observations, Johanson and Filser have used an alveolar clearance value that is 60% of the default value proposed by Arms and Travis (1988) for mice and rats in their subsequent PBPK models. Although alveolar ventilation may not actually be reduced by 60% in animals exposed to volatile compounds in a closed chamber, use of this reduced value is required to accurately predict the disappearance of some compound from the headspace. The mean value for alveolar ventilation provided in Table 31 for rats is even higher than the Arms and Travis (1988) reference value for this parameter. Therefore, although the mean value provided in Table 31 may be representative of the alveolar ventilation rate in unanesthetized rats breathing uncontaminated air, it may not be appropriate for direct incorporation into a PBPK model of a volatile compound.

In summary, this document provides modelers with mean values for the physiological parameters that are used most often in PBPK models, with an indication of the variability among studies associated with these parameter values, and with a discussion of the factors that have the greatest impact on the values. Rather than providing "reference" values, sufficient information is provided to allow modelers to select representative values for these parameters. In addition, the validity of a number of long-standing assumptions regarding physiological parameter values has been explored, and a discussion is provided on when caution should be exercised in using default values for these parameters in a PBPK model.

The data used to prepare the summary tables on organ weight and blood flow data are available from the corresponding author. Data are also available on the some organs not discussed in the text such as the ovaries, testes, and thymus. However, these organs do not expand at the same rate as the body weight; their growth is highly age dependent.

Although the intent of this document is to provide investigators with physiological parameter values for the species that are used most commonly in pharmacokinetic studies (mouse, rat, dog, and human); physiological parameter values may be required for other species as well. Physiological parameter values for gerbils, goats, guinea pigs, hamsters, horses, oxen, rabbits, and non-human primates are provided in Tables 33–35. Additionally, interspecies allometric equations also are provided in Table 36 to estimate physiological parameter values for various species.

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TABLE 33. Relative Organ Weight (% Body Weight) Values for Other Species

	Gerbil		Guinea Pig			Goat	Hamster			
	Zeeman (1967)		Breazile and Brown (1976)	Altman and Katz (1977)		Neff-Davis et al. (1975)	Altman and Katz (1977)		Kowaleski (1969)	
	Male	Female		Male	Female		Male	Female	Male	Female
Adrenal glands	0.05 ± 0.01	0.05 ± 0.01	0.08	0.05	0.10					
Bone	1.24 ± 0.16	1.58 ± 0.07	7.11			6.30			0.02	0.01
Brain			0.48	0.42	0.41	0.29				
GI tract				1.46	1.87	6.40				
Stomach			3.16	0.32	0.43					
Small intestine			0.05	0.63	0.75					
Large intestine			3.11	0.51	0.69					
Heart	0.37 ± 0.04	0.35 ± 0.04		0.21	0.25	0.48	0.38		0.34	0.28
Kidney	0.77 ± 0.06	0.74 ± 0.08	0.68	0.55	0.56	0.35	0.45	0.47	0.71	0.64
Liver	3.22 ± 0.24	2.87 ± 0.08	4.72	2.95	3.40	1.95	3.76	3.76	4.48	3.67
Lung			0.56	0.47	0.52	0.88	0.48	0.48		
Muscle			35.56			45.50				
Pancreas			0.28	0.05						
Reproductive organs										
Ovaries					**0.02**			**0.02**		
Testes	1.37 ± 0.15			0.30			1.81			
Skin						9.20				
Spleen	0.13 ± 0.40	**0.13 ± 0.02**		0.05	0.07	0.25	0.08	**0.11**		
Thymus				0.06	0.07					
Thyroid			0.01							
Body weight (g) (kg)	77	66	900	1054	1027	39	94.7	109.5	135	153
Age (weeks)	NS	NS	NS	62	77	NS	14	14	17	17
Strain			NS	B/Lac	B/Lac	NS	ALAC/Lac	ALAC/Lac	M. quratas	M. quratas

TABLE 34. Relative Organ Weight (% Body Weight) Values for Other Species

	Horse	Rabbit		Ox
	Webb and Weaver (1979)	Kozma et al. (1974)		Matthews et al. (1975)
		Male	Female	
Adrenals				
Bone	14.60	0.36	0.37	12.70
Brain	0.21			0.06
GI tract	5.80			3.80
Stomach				
Small intestine				
Large intestine				
Heart	0.66	0.20	0.20	0.37
Kidneys	0.36	0.52	0.51	0.24
Liver	1.30	2.87	3.28	1.22
Lung	0.89			0.71
Muscle	40.10			38.50
Pancreas				
Reproductive organs				
Ovaries			0.01	
Testes		0.109		
Skin	7.40			8.30
Spleen	1.11	0.04	0.04	0.16
Thymus		0.15	0.16	
Thyroid		0.01	0.01	
Body weight (kg)	308	2.78	2.54	620
Age (weeks)	NS	NS	NS	
Strain	NS	NZW	NZW	
Sex	NS	M	F	
n	NS	23	21	

TABLE 35. Relative Organ Weight (% Body Weight) Values for Nonhuman Primates

	Baboon				Rhesus monkey			Squirrel monkey			
	Mahaney et al. (1993[a,b])		Frank (1976)		Fremming et al. (1955)	Kerr et al. (1969)		Beischer and Furry (1964)		Middleton and Rosal (1972)	
	Male	Female	Male	Female	Male	Male	Female	Male	Female	Male	Female
Adrenal glands	0.03 ± 0.01	0.03 ± 0.01	0.02	0.02	0.03	0.03 ± 0.01	0.04 ± 0.02	0.05	0.03	0.03	0.03
Bone											
Brain	1.67 ± 0.12	1.50 ± 0.13	2.50	2.40	1.69	1.38 ± 0.43	1.61 ± 0.59	3.50	3.48	3.08	3.47
GI tract					3.34						
Stomach											
Small intestine											
Large intestine											
Heart	1.20 ± 0.02	0.69 ± 0.14	0.42	0.42	0.38	0.45 ± 0.12	0.39 ± 0.09	0.54	0.47	0.43	0.42
Kidney	0.75 ± 0.24	0.57 ± 0.15	0.42	0.46	0.38	0.40 ± 0.13	0.48 ± 0.25	0.59	0.53	0.39	0.46
Liver	3.95 ± 1.10	2.99 ± 0.78	2.35	2.44	2.56	2.39 ± 0.56	2.56 ± 0.93	3.12	2.64	2.44	3.02
Lung	1.91 ± 0.42	1.20 ± 0.40	0.54	0.58	0.88	0.92 ± 0.37	1.00 ± 0.41	0.84	0.72	0.69	0.71
Muscle											
Pancreas	0.25 ± 0.05	0.18 ± 0.03									
Reproductive organs											
Ovaries				**0.01**					**0.04**		**0.14**
Testes	0.58 ± 0.12		0.07		0.21			0.43		0.41	
Skin											
Spleen		0.21 ± 0.09	0.09	**0.10**	0.07	0.08 ± 0.04	0.08 ± 0.05	0.26	**0.24**	0.13	**0.14**
Thymus						0.02 ± 0.01	0.02 ± 0.02				
Thyroid		0.02 ± 0.01			0.01						
Body weight (g) (kg)	25	15	3.5	3.25	5.72	6.19	5.59	0.61	0.62	0.78	0.66
Age (weeks)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Strain											
Sex	M	F	M	F	M	M	F	M	F	M	F
n			25	29	66	27	15	7	3	40	40

TABLE 36. Interspecies Allometric Equations for Organ Weight

Adipose tissue	$67.10\ BW^{1.140}$	Pitts and Bullard (1968)
Adrenals	$0.63\ BW^{0.920}$	Adolph (1949)
	$0.27\ BW^{0.800}$	Stahl (1965)
Bone (skeleton)	$61.00\ BW^{1.090}$	Prange et al. (1979)
Brain	$15.40\ BW^{0.760}$	Adolph (1949)
	$10.90\ BW^{0.755}$	Martin (1981)
	$9.30\ BW^{0.730}$	Stahl (1965)
GI tract	$74.00\ BW^{0.940}$	Adolph (1949)
Heart	$5.75\ BW^{0.980}$	Adolph (1949)
	$4.34\ BW^{1.000}$	Holt et al. (1968)
	$5.80\ BW^{0.980}$	Stahl (1967)
Kidneys	$7.52\ BW^{0.850}$	Adolph (1949)
	$7.32\ BW^{1.000}$	Brody (1945)
	$7.10\ BW^{0.850}$	Prothero (1984)
	$7.30\ BW^{0.850}$	Stahl (1965)
Liver	$33.40\ BW^{0.870}$	Adolph (1949)
	$37.00\ BW^{0.849}$	Boxenbaum (1980)
	$35.44\ BW^{0.870}$	Prothero (1982)
Lung	$11.57\ BW^{0.990}$	Adolph (1949)
	$7.72\ BW^{1.030}$	Bennett and Tenney (1982)
	$11.30\ BW^{0.990}$	Stahl (1967)
Skin	$139.00\ BW^{0.942}$	Pace et al. (1979)
Spleen	$2.50\ BW^{1.02}$	Stahl (1965)
Thyroid	$0.13\ BW^{0.92}$	Stahl (1965)

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