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Reference Physiological Parameters in Pharmacokinetic Modeling

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ABSTRACT

This document presents a compilation of measured values for physiological parameters used in pharmacokinetic modeling. The physiological parameters include body weight, tissue volumes, cardiac output, cardiac output distribution, and the respiration parameters. Reference values for use in risk assessment are given for each of the physiological parameters based on analyses of valid measurements obtained from the literature and other reliable sources. The proposed reference values are for generic mice and rats without regard to sex or strain. Reference values for humans are without regard to age or sex. Differences between the sexes in mice, rats, and humans are accounted for by scaling the reference parameters within species on the basis of body weight. Reference physiological parameters are for a 0.025 kg mouse, 0.25 kg rat, and a 70 kg man.

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1. SUMMARY

Table 1-1 summarizes the recommended reference physiological parameters for use in pharmacokinetic modeling.

TABLE 1-1. REFERENCE PHYSIOLOGICAL PARAMETERS

	Mouse	Rat	Human
Body weights (kg)	0.025	0.25	70.0
Tissue volumes (fractions)			
Liver	0.055	0.04	0.026
Fat	0.10	0.07	0.19
VRG	0.05	0.05	0.05
MG	0.70	0.75	0.62
Cardiac output (l/min)	0.017	0.083	6.2
Tissue perfusion (fractions)			
Liver	0.25	0.25	0.26
Fat	0.09	0.09	0.05
VRG	0.51	0.51	0.44
MG	0.15	0.15	0.25
Minute volume (l/min)	0.037	0.174	7.5
Alveolar ventilation (l/min)	0.025	0.117	5.0

2. INTRODUCTION

Pharmacokinetics is the science of quantitatively predicting the fate of an exogenous substance in an organism. Utilizing computational techniques, pharmacokinetics provides the means of studying the uptake, distribution, metabolism, and excretion of chemicals by the body. This is accomplished by dividing the body into various anatomical compartments. The mathematical representation of these compartments provides a description of the time course of drug disposition throughout the body. Pharmacokinetics eliminates some of the ambiguities in determining the risk of human exposure to environmental chemicals and provides a basis for evaluating the scientific assumptions upon which the risk assessment process is based.

A recent development in the area of pharmacokinetics is the advent of physiologically-based pharmacokinetic (PBPK) models. Relying on actual physiological parameters such as body weight, breathing rates, cardiac output, blood flow rates, tissue volumes, etc., to describe the metabolic process, the PBPK models can relate exposure concentrations to organ concentrations over a range of exposure conditions. This report provides a literature review of the physiological parameters used in PBPK models, and recommends reference physiological parameters for use in risk assessment.

3. PHARMACOKINETIC MODELING

3.1. DESCRIPTION

A pharmacokinetic model is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based (NRC, 1986). A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body. In applying these models, time-course concentration curves are first determined from in vivo animal experiments. Then, model compartment volumes and rate constants are determined by trial and error so that the model predictions fit the empirical data. These models are useful for interpolation and limited extrapolation within the <u>same</u> species. However, since the parameters in these data-based models generally do not correspond to physiologically-identifiable entities, they do not allow for extrapolation <u>across</u> animal species.

A physiologically-based pharmacokinetic model is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates (for volatile compounds) and, possibly, membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. The uniqueness of the physiologically-based approach is this reliance on measured physiological and biochemical parameters. An appealing aspect of these physiological models is that they allow ready extrapolation of observed

experimental results from a test species to an untested species simply by placing the appropriate physiological and biochemical parameters in the model. Similarly, the effect of route of administration can be investigated by allowing for different administration pathways.

It should be pointed out that no one pharmacokinetic model can be used to determine the distribution of all chemicals. The number of compartments and the way they are connected will vary from chemical to chemical depending upon the chemical's metabolic behavior and the nature of the questions being asked concerning dose to target tissues.

Despite this fact, most physiologically-based pharmacokinetic models in current use divide the body into four physiological groups, all connected by the arterial and venous blood flow pathways (see Figure 3-1 and Table 3-1). The first group is the vessel-rich group (VRG) and is made up of those tissues most profusely supplied with blood vessels. These include the brain, heart, kidney, and viscera. The second group is composed of muscle and skin and is called the muscle group, (MG). The third group is composed of adipose (fat) tissue. The fourth group contains organs with a high capacity to metabolize (principally liver). Each tissue group is described mathematically by a set of differential equations which calculate the rate of change of the amount of chemical in each compartment. Metabolism, occurring chiefly in the liver, is described by a combination of a linear metabolic component and a Michaelis-Menten component accounting for saturable metabolism. Again, we stress that other model descriptions are possible, but they will, in general, have the same physiological parameters.

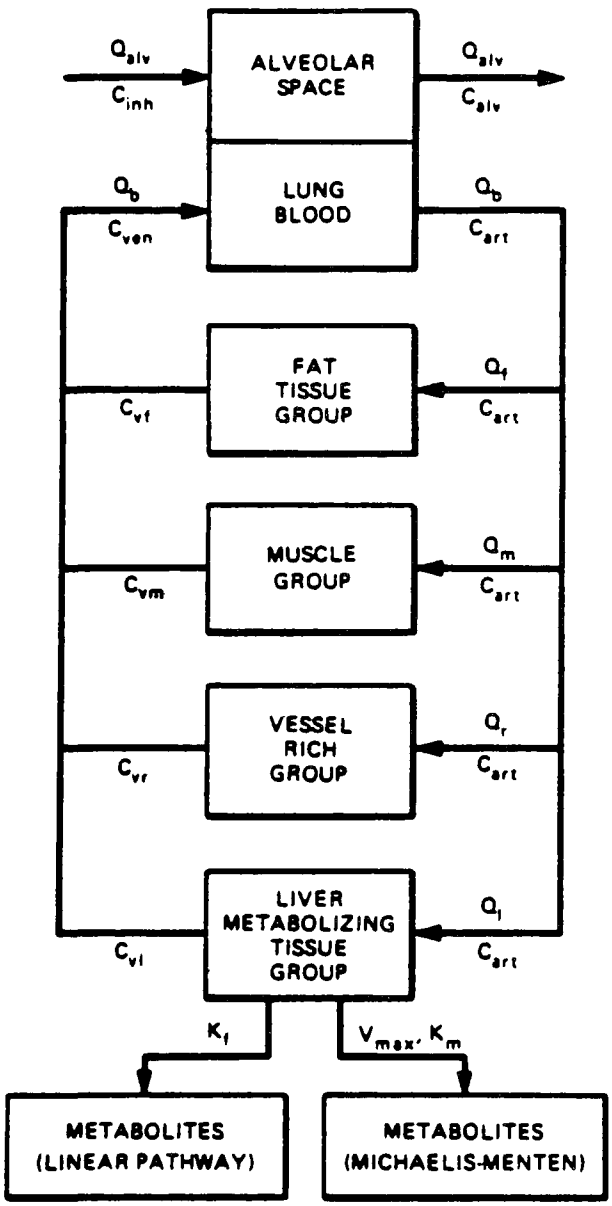

FIGURE 3-1. Diagram of a typical pharmacokinetic model used to simulate the behavior of inhaled volatile organics. The model divides the body into four physiological groups, all connected by blood flow pathways. The symbols are defined in Table 3-1.

TABLE 3-1. NOMENCLATURE USED IN DESCRIBING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL

Q_{alv}	Alveolar ventilation rate (liters air/hr)
C_{inh}	Concentration in inhaled air (mg/liter air)
C_{alv}	Concentration in alveolar air (mg/liter air)
λ_b	Blood/air partition coefficient (liters air/liters blood)
Q_b	Cardiac output (liters blood/hr)
C_{art}	Concentration in arterial blood (mg/liter blood)
C_{ven}	Concentration in mixed venous blood (mg/liter blood)
V_{max}	Michaelis-Menten metabolism rate (mg/hr)
K_m	Michaelis constant (mg/liter blood)
K_f	Linear metabolism rate (hr^{-1})
A_m	Amount metabolized in the liver (mg)
Q_i	Blood flow rate to tissue group i (liters blood/hr)*
V_i	Volume of tissue group i (liters)
C_i	Concentration in tissue group i (mg/liter)
A_i	Amount in tissue group i (mg)
C_{vi}	Concentration in venous blood leaving tissue group i (mg/liter blood)
λ_i	Tissue/blood partition coefficient for tissue i (liters blood/liter i)
$\lambda_{i/a}$	Tissue/air partition coefficient for tissue i (liters air/liter i)
k	Gavage or oral rate constant (hr^{-1})
D_o	Total quantity of PCE absorbed via gavage route (mg)

*Subscripts (i) for tissue groups or compartments:

l	Liver (metabolizing tissue group)
f	Fat tissue group
r	Vessel-rich tissue group
m	Muscle tissue group

4. PHYSIOLOGICAL PARAMETERS

The physiological parameters typically used in pharmacokinetic modeling are listed below.

TABLE 4-1. PHYSIOLOGICAL PARAMETERS USED FOR MODELING.

PARAMETERS
Body weight (kg)
Cardiac output (l/min)
Minute volume (l/min)
Alveolar ventilation (l/min)
Physiological dead space (%)
Frequency (breaths/min)
ORGANS
(Volumes and Blood Flows)
Liver
Fat
Vessel-Rich Group
Muscle Group

Measured values of these parameters in mice and rats are age, sex, and strain-dependent. For example, female rats tend to have higher mass-specific ventilation rates than males, and young rats have values higher than mature rats. In addition, the status of the animals during measurement (body position, conditioning, etc.,) and the measurement technique can have substantial influences. Lack of data for many physiological parameters, however, limits attempts to account for these factors. Our reference parameters are for a generic mouse or rat, without regard to sex or strain. Differences between sexes are accounted for by

scaling the reference parameters within species on the basis of body weight. Reference physiological values for humans are for a resting 70 kg man. For rodents, the reference physiological parameters are for a 0.025 kg mouse and a 0.25 kg rat at rest.

We will now review the measured values of these parameters found in the literature. Each section is organized as follows: first, a summary table of the recommended reference values is presented; then a literature review is undertaken to support the recommended reference values; and finally, a summary of the actual values of parameters used in various pharmacokinetic models is presented.

4.1. BODY WEIGHTS

4.1.1. Reference Values

TABLE 4-2. REFERENCE BODY WEIGHTS

Mice	Rats	Humans
0.025 kg	0.25 kg	70.0 kg

4.1.2. Documentation of Reference Values

Mice

The U.S. Environmental Protection Agency (1980) recommends a standard body weight of 0.03 kg for an adult mouse. Other reported standards in the literature include 0.035 kg (ARS/Sprague-Dawley, 1974), 0.023 kg (Boxenbaum, 1982) and 0.02 kg (Lehman, 1959). Altman and Dittmer (1972)

provided growth data on seven strains of mice from birth to about six months of age, by which time their body weights were considered stable. The mean terminal body weight for both sexes of all strains combined was 0.032 kg (Durkin, 1985). Therefore, the reference value of 0.03 kg recommended by the EPA seems reasonable. However, most pharmacokinetic studies are performed on mice before they reach terminal body weight. For the purposes of pharmacokinetic modeling, we are recommending a reference body weight of 0.025 kg.

Rats

The U.S. EPA (1980) recommends a standard body weight of 0.35 kg for an adult rat. Other reported standards in the literature were 0.45 kg (ARS/Sprague-Dawley, 1974), 0.25 kg (Boxenbaum, 1982) and 0.40 kg (Lehman, 1959). Growth data for two strains of rats were provided by Altman and Dittmer (1972), in which the mean terminal body weight for both sexes and strains combined was 0.334 kg (Durkin, 1985). Thus, the reference value of 0.35 kg for rats proposed by the EPA seems justifiable; however, most pharmacokinetic studies are performed on rats before they reach terminal body weight. For the purposes of pharmacokinetic modeling, we are recommending a reference body weight of 0.25 kg.

Humans

The International Commission on Radiological Protection (ICRP) recommends a body weight of 70 kg for an adult reference man (Snyder et al., 1975). This value is derived from the total body weight of organs, tissues, and components assumed to include blood vessels and other body fluids. The U.S. EPA (1980) concurs with the ICRP (1975) in recommending

70 kg as the acceptable reference value for an adult man.

4.2. TISSUE VOLUMES

Tissue volumes cited in pharmacokinetic models generally reference the power functions reported by Adolph (1949). When these functions are applied to mice and rats, they are only approximately correct. It seems prudent to base tissue volumes on direct measurements when possible; however, they can be determined indirectly through optimization of the appropriate parameters in a pharmacokinetic model.

4.2.1. Reference Values

Reference tissue volumes are presented in Table 4-3 as a percentage of total body weight. Tissue volumes in liters may be obtained by multiplying total body weight (section 4.1.) by the tissue volume fraction and assuming that one kilogram of tissue has a volume of one liter.

TABLE 4-3. REFERENCE TISSUE VOLUME FRACTIONS

	Mouse	Rat	Human
Liver	0.055	0.04	0.026
Fat	0.10	0.07	0.19
VRG	0.05	0.05	0.05
MG	0.70	0.75	0.62

4.2.2. Documentation of Reference Values

Data indicate that the liver grows steadily throughout life and remains in a fairly constant relationship to body weight. Liver weight/body weight ratios appear to be highly strain-dependent.

Liver Volume

Liver weight/body weight ratios in mice are more variable than in rats, ranging from 3.5 to 8.0%, depending on strain. Spector (1956) recorded liver volume measurements of 5.63% of body weight for the jumping mouse and 4.56% of body weight for the meadow mouse. Kurnick and Kernen (1962) reported that after weaning (10 weeks), liver weight maintained a uniform relationship to body weight (4.5 to 5.8%) in mice. Bischoff et al. (1971) reported a value of 6.0%, while Tuey and Matthews (1980) found a value of 5.8%. On the basis of limited data, Crispens (1975) reported values of about 3.5%. Gellatly (1975) reported the liver weight of mice on a stock pelleted diet (standard diet) as 5.64% of body weight for males and 5.44% for females.

Pieri et al. (1980) found male Balb/c mice at 2 months of age had a liver weight/body weight ratio of 4.8%, compared to a 4.4 to 4.5% range at 12 to 24 months. Kjellstrand et al. (1981) reported a liver weight/body weight range of 3.6 to 5.2% in control NMRI mice weighing 0.027 to 0.036 kg. Ruebner et al. (1984) reported liver weight/body weight ratios in three strains of control mice. In male C57Bl/6 mice, 43 to 132-weeks old, the liver weight/body weight range was 4.7 to 7.7%. The geometric mean of the values was 5.68%. In male C3H/He mice, 41 to 111-weeks old, the liver

weight/body weight range was 4.3 to 8.0%. The geometric mean of the values was 5.48%. In male $B6C3F_1$ mice, 21 to 119-weeks old, the liver weight/body weight range was 4.0 to 7.3%. The geometric mean of the values was 5.6%. De Marte and Enesco (1986) reported a liver weight/body weight ratio of 5.7% for eight-week old male Swiss Albino mice weighing 0.034 kg. For mice 24 to 78-weeks old, the percentage remained fairly constant from 4.2 to 4.7%.

The above data generally indicate that young mice have liver weight/body weight ratios higher than older mice. Based on body weight, our reference mouse of 0.025 kg would qualify as a young mouse. Therefore, the reference liver volume of 5.5% of total body weight is a reasonable one.

Jackson (1913) found that in the albino rat the liver was on the average 4.42% of total body weight at one year of age. Webster et al. (1947) determined liver weight/body weight ratios in 500 Albino rats with no consideration given to age. Rats weighing 0.250 kg gave a liver weight/body weight ratio of 4.09% and 0.300 kg rats, 4.0%. Addis and Gray (1950) found a range of 3.0 to 6.0% in Albino rats; the 6.0% value was for young rats. No values higher than 3.8% were found for rats weighing more than 0.200 kg. De Leeuw-Israel (1971) cited a liver weight/body weight ratio of 3.2% for control rats 18 to 24-months old and 3.1% for control rats 24 to 27-months old. Coniglio et al. (1979) studied the liver weight/body weight ratio as a function of age in male Fischer rats. They found body weight reached its peak at 12 months, then declined steadily from 12 to 30 months. From six to 20 months, the liver weight/body weight ratio remained fairly constant at 3.1 to 3.5%. For a young rat 2 to 4-months old, the liver weight/body weight ratio was 3.8%. Kjellstrand et

al. (1981) reported a liver weight/body weight ratio of 3.89 to 4.29% in control Sprague-Dawley rats weighing 0.200 to 0.394 kg. Van Bezooijen (1984) reported liver weight/body weight ratio as a function of age in six different strains of rats. From one to 27 months, the male Fischer 344 rat gave a liver weight/body weight ratio of 2.9 to 2.7%, declining with age. Similar findings were reported for both the male and female Wistar rat and the male and female WAG/Rij rats. Male Sprague-Dawley rats also showed a decline in the liver weight/body weight ratio with a range of 4.5 to 3.4% from three to 16 months of age. A measured liver volume percentage of 4.0% of body weight was reported by Lutz et al. (1977) and a range of 4.2 to 6.3% by Jansky and Hart (1968).

The above data indicate that liver weight/body weight ratios in rats decline with age. Based on body weight, our reference rat of 0.250 kg would qualify as a young rat. Therefore, the reference liver volume of 4.0% of total body weight is a reasonable one.

A liver volume fraction of 2.6% in the adult reference man is recorded in ICRP (1975; Boyd, 1941). Sherlock (1968) reported the liver comprised 2.0% of the adult body weight. DeLand and North (1968) found a linear relationship exists between liver weight and body weight. They reported a liver weight volume of 2.2% in a 70 kg man. We are recommending a reference human liver volume of 2.6%.

Fat Volume

The recommended fat volume fraction for mice is supported by measured values of 9.8% (Tuey and Matthews, 1980), and an average of 10.7% (range of 8.3 to 15.5%) for four different strains of mice (Dawson, 1970). Dawson (1970) found that body weight was not a good predictor of fat content in

the four strains of mice. We recommend a reference fat volume percentage for mice of 10%.

An empirical determination of 7.0% of the body fat fraction of rats was reported by Caster et al. (1956)and Lutz et al. (1977). Reed et al. (1930), feeding rats special diets rich in fats and carbohydrates, reported an average value of 8.8%. The fat volume percentage in humans varies from 11.5 to 36% in males and 15 to 38% in females. We follow Reference Man and recommend a fat volume percentage of 19.0%.

VRG and MG Volumes

The VRG and muscle volumes are not necessarily supported by empirical measurements since these compartments are difficult to identify. The VRG as defined by one investigator may include or delete organs considered in another's definition of VRG. In order to be exact, it becomes necessary to summate measured values from the individual organs which comprise the VRG. For example, Ramsey and Andersen (1984) include the brain, heart, kidney, and viscera in their definition of VRG. To obtain an accurate measured value for the VRG, one would have to summate the individual measurements of the four organs to recommend a total value for the VRG.

Our definition of MG includes the muscle and skin. Skeletal muscle represents 40% of total body weight. The weight of this tissue includes the connective tissue, blood vessels, blood, lymph, etc., which is normally associated with skeletal muscle (ICRP, 1975). Our reference muscle volume value of 62% also includes smooth muscle. Skin accounts for 3.7% of total body weight in a 70 kg man.

4.2.3. Values Used in Pharmacokinetic Models

Since direct measurement of many of the physiological parameters used in pharmacokinetic models is difficult, many investigators believe that the best determination of the parameters results from optimization. It is important to clarify that the physiological parameters used in these model simulations produce the best fit to experimental data and may not represent physiological values for a reference man. We now review the combination of empirically-determined and optimized parameters for tissue volumes which have appeared in the literature. The values are given as a percentage of total body weight for each species.

Mice

Bischoff et al. (1971) used tissue volumes verified from laboratory measurements. The tissue volumes for a 0.022 kg mouse were obtained for six compartments:

Tissue	Percent
Blood	7.6
Muscle	45.0
Liver	5.9
Kidney	1.5
GI tract	6.8
Gut lumen	6.8

The gastrointestinal tract and the gut-lumen were the two tissue groups not independently measured. Total tissue volume accounted for approximately 74% of body weight.

Dedrick et al. (1973) based most of his tissue volumes for a 0.022 kg mouse on the values reported by Bischoff et al. (1971).

Tissue	Percent
Blood	7.6
Lean	45.0
Liver	5.9
Kidney	1.5
Heart	0.43
Gut lumen	6.8
Marrow	2.7

Unlike Bischoff (1971), Dedrick did not include a separate compartment for the gastrointestinal tract. Marrow tissue represented approximately 3.0% of body weight and heart tissue 0.43%. Total tissue volume accounted for 70% of total body weight. Neither Bischoff (1971) or Dedrick et al. (1973) recognized fat as a tissue compartment.

Tuey and Matthews (1980) provided physiological values for a 0.038 kg mouse, using the same tissue volumes for the blood, muscle, and gut lumen compartments as Dedrick et al. (1973). The average values for the skin and fat compartments were 14.5 and 9.8% of body weight, respectively, based on measurements obtained from complete dissection of mice in their laboratory. Total tissue volume accounted for 89% of the total body weight of the mouse.

Ramsey and Andersen (1984) used the physiological values for a 0.022 kg mouse suggested by previous investigators with one important exception. They included fat as a tissue with a volume representing 9.0% of body weight.

Tissue	Percent
Liver	4.0
Fat	9.0
Richly perfused	5.0
Muscle	73.0

The sum of the tissue volumes accounted for 91% of total body weight of the mouse, with the remaining 9.0% designated as skeletal tissue. Unlike previous investigators, Ramsey and Andersen (1984) did not specify a blood volume, since the blood did not act as a significant repository for the chemical under investigation.

Andersen et al. (1987) reported the following physiological values for a 0.0345 kg mouse:

Tissue	Percent
Liver	4.0
Fat	4.0
Rapidly perfused	5.0
Slowly perfused	78.0

In summary, values used in pharmacokinetic modeling for mice tissue volumes varied from 4.0 to 6.0% for the liver, 4.0 to 9.0% for fat, 50% for VRG and 73 to 78% for the muscle group.

Rats

Bischoff et al. (1971) provided tissue volumes for a 0.200 kg rat based on his previous work and the correlations of Adolph (1949):

Tissue	Percent
Blood	7.5
Muscle	50.0
Kidney	0.95
Liver	4.15
GI tract	5.5
Gut lumen	5.5

Tissue volumes accounted for approximately 74% of total body weight.

Bischoff's model neglects the fat compartment.

Harrison and Gibaldi (1977) gave tissue volumes for a 0.360 kg rat based on measurements by Thompson and Hollis (1958), Jansky and Hart (1968) and the correlations of Adolph (1949):

Tissue	Percent
Blood	4.92
Skeletal muscle	50.0
Kidneys	0.94
Liver	3.72
Heart	0.50
GI tissues	3.0
GI contents	4.8
Skin, fat, etc[a]	25.0

[a] Miscellaneous compartment for all other body regions

Harrison and Gibaldi (1977) included the heart as a separate compartment, in addition to recognizing fat as a miscellaneous compartment for all other body regions (skin, etc). The sum of tissue volumes accounted for approximately 93% of total body weight.

Lutz et al. (1977) gave the following tissue volumes for a 0.250 kg rat:

Tissue	Percent
Blood	9.0
Muscle	50.0
Liver	4.0
Skin	16.0
Fat	7.0
Gut lumen	5.6

Lutz et al. (1977) based their muscle volume of 50% of total body weight on the data of Bischoff et al. (1971). Liver volume was measured; skin and adipose (fat) tissues represented average values obtained by laboratory dissection of the rats. These values are also consistent with the

previously published data of Freudenberger (1933) and Reed et al. (1930). Tissue volumes accounted for approximately 92% of total body weight.

Ramsey and Andersen (1984) reported tissue volumes for a 0.30 kg rat as:

Tissue	Percent
Liver	4.0
Fat	9.0
Richly perfused	5.0
Muscle	73.0

Total tissue volume accounted for 91% of total body weight.

Fiserova-Bergerova and Hughes (1983) estimated the following tissue volumes (liver designated as a separate compartment) for a 0.250 kg rat:

Tissue	Percent
Liver	4.0
Fat	0.40
VRG	5.6
Muscle	72.0

Another compartment accounting for 15.4% of the total tissue volume represented the skeleton, blood, and lungs. The parameters for the rat were tested in a model simulation of halothane in a 0.200 kg rat (Fiserova-Bergerova and Kawiecki, 1984). The fat parameter is quite low in comparison with other model simulations. This can be attributed to the young age of the rat under study and the desire to obtain the best fit to experimental data (Fiserova-Bergerova, 1987).

Andersen et al. (1987) reported tissue volumes for a 0.233 kg rat:

Tissue	Percent
Liver	4.0
Fat	7.0
Rapidly perfused	5.0
Slowly perfused	75.0

Humans

Mapleson (1963) used the following tissue percentages in his model simulation:

Tissue	Percent
Adrenals	0.11
Kidneys	1.52
Thyroid	0.09
Gray matter	1.60
Heart	0.64
Other small organs and glands	0.30
Liver plus portal system	6.97
White matter	1.21
Red marrow	2.10
Muscle	43.38
Skin plus nutritive shunt	4.33
Non-fat subcutaneous	6.91
Fat	14.46

Each value listed includes the volume of blood in equilibrium with the tissue. Bone cortex, fatty marrow tissue, and arterial and venous blood accounted for approximately 21% of total tissue volume.

Eger (1963) recommended the following tissue volume percentages for a 70 kg man:

Tissue	Percent
VRG	8.6
Fat	21.0
Muscle	47.0
VPG	18.0

Eger's VRG included the brain, heart, kidneys, hepatoportal system (liver) and the endocrine glands. The VPG included bone and cartilage.

Bischoff et al. (1971) provided the following tissue volumes for a 70 kg man:

Tissue	Percent
Blood	7.15
Muscle	50.0
Kidney	0.40
Liver	2.0
GI tract	3.0
Gut lumen	3.0

The gut and gut-lumen volumes were not independently measured, but are actually effective values. Total percentage of tissue volumes represented 66% of body weight for a 70 kg man. Bischoff neglects the fat compartment for man.

The tissue volumes cited by Dedrick et al. (1972) were essentially taken from the data of Mapleson (1963):

Tissue	Percent
Blood	3.8
Liver	2.4
Gut	4.5
Heart	0.64
Kidney	1.5
Lean	38.6
Marrow	2.8

Each values listed includes the volume of blood in equilibrium with the tissue. Calculation of the liver, and gut values were derived from Mapleson (1963) as well as other sources. The muscle value was lowered to 38.6% from the original value of 58.7% to achieve an adequate simulation of the data (Dedrick et al., 1972).

Fiserova-Bergerova et al. (1984) estimated the following tissue volumes for a 70 kg man at rest:

Tissue	Percent
Liver	4.0
Fat	15.0
VRG	5.0
Muscle	49.0

The VRG included brain, gastrointestinal tract, glands, heart, kidneys, and spleen. The muscle group included muscles and skin, and the fat compartment included adipose tissue and white marrow.

Ramsey and Andersen (1984) provided the following tissue volumes for an 83 kg man:

Tissue	Percent
Liver	4.0
Fat	9.0
Richly perfused	5.0
Muscle	73.0

These tissue volumes were assumed to be proportional to body weight, and were scaled up in direct proportion to the ratio of body weights of a man to that of the rat (i.e., 83 kg/0.30 kg = 277, Ramsey and Andersen, 1984). The 9% fat value for a 70 kg man is an unrealistic reference physiological value, but represents a good fit to the experimental data. The sum of the

tissue volumes represented 91% of the total body weight for an 83 kg man.

Droz (1985) used the following tissue volumes for his model simulation:

Tissue	Percent
Liver	2.4
Fat	16.0
VRG	10.0
Muscle group	52.0

These values are for a 70 kg man at rest.

Andersen et al. (1987) reported the tissue volumes for a 70 kg man. The volume percentages are:

Tissue	Percent
Liver	3.14
Fat	23.1
Rapidly perfused	3.71
Slowly perfused	62.1

These percentages are in close accord with data from the medical literature (ICRP, 1975; Davis and Mapleson, 1981). The 23.1% tissue fraction for fat in humans is much closer to the ICRP recommendation of 19% than the 9% used by Ramsey and Andersen (1984).

4.3. CARDIAC OUTPUT

Cardiac output is defined as the volume of blood pumped by <u>each</u> ventricle of the heart per minute. Cardiac output can be determined by multiplying the heart rate and the volume of blood ejected by each ventricle during each beat (Vander et al., 1975):

Cardiac output = heart rate x stroke volume

The major determinant of cardiac output in all species is the oxygen demand of the tissues. During physical activity, cardiac output increases, but to a smaller extent than alveolar ventilation (Astrand, 1983). As a result, the perfusion-ventilation ratio is decreased by exercise. Thus, the ratio of cardiac output to alveolar ventilation decreases from a value of 1.3 at rest to a value of 0.4 to 0.5 with mild activity and a value of 0.4 with strenuous activity (Astrand, 1983).

4.3.1. Reference Values

Several direct laboratory measurements of cardiac output in rats and humans are available in the literature. However, we were only able to locate two direct measurements of cardiac output in the mouse. Based on data available to us we are recommending the following reference values for cardiac output (l/min):

TABLE 4-4. REFERENCE CARDIAC OUTPUT VALUES

Mouse (0.025 kg)	Rat (0.25 kg)	Human (70.0 kg)
0.017 l/min	0.083 l/min	6.2 l/min

4.3.2. Documentation of Reference Values

The reference cardiac output of 0.017 l/min for mice was calculated using the power function suggested in section 5.1, using the reference mouse body weight of 0.025 kg. The reference cardiac output of 0.083 l/min

for the rat was also calculated using the power function suggested in section 5.1, using the reference rat body weight of 0.25 kg.

Mice

TABLE 4-5. ABSOLUTE CARDIAC OUTPUT OF MICE

CO (l/min)	Method	Ref.
0.0110	1	Gjedde and Gjedde (1980)
0.0118	2	Wetterlin and Pettersson (1979)
0.0160	-	Blizard and Welty (1971)

1. Indicator fractionation
2. Soluble indicator

Gjedde and Gjedde (1980) measured cardiac output in anesthetized, female BALB/c mice weighing 0.025 kg. Using the indicator fractionation technique developed by Sapirstein (1958), cardiac output was determined to be 0.011 l/min. Relative cardiac output was 0.440 l/min·kg.

Wetterlin and Pettersson (1979) determined cardiac output in 35 male and female NMRI, anesthetized mice. The mice weighed between 0.025 to 0.030 kg. Cardiac output measured 0.0118 to 0.0028 l/min. Relative cardiac output determined from this study was 0.435 l/min·kg.

Blizard and Welty (1971) measured heart rates in 70 unanesthetized, unrestrained mice with an average body weight of 0.0225 kg. Mean heart rate 60 minutes after handling was 537.4 min^{-1}. Using an average stroke volume of 0.03 ml (Wetterlin and Pettersson, 1979) for anesthetized mice, we obtain an estimate of cardiac output in mice of 0.016 l/min, with a

relative cardiac output of 0.711 l/min·kg.

Table 4-6 summarizes data available on the relative cardiac output of mice.

TABLE 4-6. RELATIVE CARDIAC OUTPUT OF MICE
(l/min·kg)

CO	Range	Ref.
0.440	-	Gjedde and Gjedde (1980)
0.435	0.333 - 0.537	Wetterlin and Pettersson (1979)
0.711	-	Blizard and Welty (1971)

Rats

Measurements of absolute cardiac output of unanesthetized rats are listed in Table 4-7:

TABLE 4-7. ABSOLUTE CARDIAC OUTPUT OF UNANESTHETIZED RATS

CO (l/min)	Method	Ref.
0.0730	1	Guyton (1947)
0.0918	2	Popovic and Kent (1964)
0.1010	2	Jansky and Hart (1968)
0.1107	2	Tsuchiya et al. (1978)
0.1167	2	Tsuchiya et al. (1978)
0.1193	2	Tsuchiya et al. (1978)
0.1340	3	Coleman (1974)

1. Respirograph
2. Fick
3. Dye-dilution

Guyton (1947) used the oscilloscopic respirograph to determine cardiac output in 35 white rats with an average weight of 0.113 kg. Cardiac output was 0.0730 l/min.

Popovic and Kent (1964) conducted an extensive, 120-day study of cardiac output in unanesthetized rats. Using the Fick method, they determined a cardiac output of 0.0918 l/min in rats weighing 0.319 kg. Jansky and Hart (1968) measured cardiac output in warm- and cold-acclimated rats and reported a cardiac output of 0.1010 l/min. Average weight of the rats was 0.355 kg. Tsuchiya et al. (1978) measured cardiac output in three strains of conscious rats. Six male Wistar-Kyoto rats, weighing 0.447 ± 0.020 kg, gave an average cardiac output of 0.1107 l/min. Eight male hypertensive rats of the Akamoto-Aoki strain, weighing 0.390 ± 0.012 kg, provided an average cardiac output of 0.1167 l/min. Five male American Wistar rats, weighing 0.473 ± 0.010 kg, recorded a mean cardiac output of

0.1193 l/min. All experiments were done using the direct Fick principle. Coleman (1974) measured cardiac output in conscious Wistar rats weighing 0.512 ± 0.016 kg using a modified dye-dilution technique. Cardiac output was 0.134 l/min.

Measurements of absolute cardiac output of anesthetized rats are listed in Table 4-8.

TABLE 4-8. ABSOLUTE CARDIAC OUTPUT OF ANESTHETIZED RATS

CO (l/min)	Method	Ref.
0.027	4	Walsh et al. (1976)
0.040	1	Walsh et al. (1976)
0.047	1 (a)	Blood et al. (1950)
0.047	-	Clarkson (1956)
0.063	1, 6	Chiu (1974)
0.070	5	Ackermann and Veress (1980)
0.079	3	Dyundikova et al. (1981)
0.093	3	Dyundikova et al. (1981)
0.095	3	Lin et al. (1970)
0.097	3	Dyundikova et al. (1981)
0.100	3	Dyundikova et al. (1981)
0.120	2	Holt et al. (1968)

1. Fick (a) atrial cannula
2. Indicator-dilution
3. Thermodilution
4. Probe method
5. Microsphere
6. Catheterization

Walsh et al. (1976) reported the cardiac output for 15 Sprague-Dawley and 12 Wistar rats under basal resting conditions. Using the direct Fick procedure for determination of cardiac output, Walsh et al. (1976) compared the results with simultaneous electromagnetic flowmeter techniques (Probe method). Body weight ranged from 0.175 to 0.250 kg for both the Sprague-Dawley and Wistar rats. Fick cardiac output measurements in Sprague-Dawley and Wistar rats under basal resting conditions were 0.041 l/min and 0.040 l/min, respectively. Using the Probe method, Sprague-Dawley rats had a 0.029 l/min reading for cardiac output, while the Wistar rats measured 0.027 l/min. Thus, cardiac output using the Fick procedure was between 40 and 50% greater than with the Probe method.

Blood et al. (1950) determined cardiac output in young adult, anesthetized rats at normal and high altitudes. The University of Denver strain mice weighed between 0.180 to 0.200 kg. The mean cardiac output for 52 rats at normal altitude was found to be 0.0465 ± 0.0156 l/min. Clarkson (1956) reported cardiac output in an anesthetized, 0.18 kg rat as 0.047 l/min, with a range of 0.015 to 0.079 l/min.

Chiu (1974) used a modified version of the catheterization technique popularized by Popovic and Kent (1964) and used again by Jansky and Hart (1968). Chiu measured cardiac output in 25 male adult albino Wistar rats, weighing 0.304 ± 0.005 kg, under "conscious" conditions. Cardiac output was 0.0625 ± 0.0028 l/min. This measurement was obtained when the rats regained consciousness following administration of 40 mg/kg i.p. of sodium pentobarbital. In comparison with other measurements for unanesthetized rats, it is clear the value reported by Chiu (1974) is more in line with those of anesthetized rats. Chiu (1974) suggested cardiac output should not be affected by the residual effects of light anesthesia. However, the

amount of sodium pentobarbital used for the rats is equal to the amount reported for anesthetized rats in the study by Popovic and Kent (1964). Chiu (1974) did not specify the time lapse between the administration of the anesthetic and the regaining of consciousness.

Lin et al. (1970) measured cardiac output in anesthetized, Sprague-Dawley rats in an attempt to prove the reliability of the thermodilution method for measuring cardiac output. Cardiac output ranged from 0.066 to 0.124 l/min for rats that ranged in weight from 0.330 to 0.494 kg. The author notes that the thermodilution method results in higher cardiac output values than those obtained by other methods.

Ackermann and Veress (1980) measured cardiac output in 24 male Sprague-Dawley rats. Body weight was 0.394 ± 0.008 kg. Cardiac output was measured as 0.0701 l/min. Dyundikova et al. (1981) measured cardiac output in male rats as a function of age. Rats weighing 0.345 kg (ages 5 to 9 months) gave a cardiac output reading of 0.100 l/min. Ten to 16-month old rats, weighing 0.383 kg, gave a cardiac output reading of 0.097 l/min. Seventeen to 23-month old rats, weighing 0.420 kg, gave a cardiac output reading of 0.078 l/min. Twenty-four to 29 month old rats, weighing 0.411 kg, gave a cardiac output reading of 0.093 l/min. Thus, cardiac output decreases with age, reaching a minimum at 17 to 23 months. However, rats older than 24 months approached the values found for rats between 17 to 23 months (Dyundikova et al., 1981). Holt et al. (1968) reported a cardiac output measurement of 0.12 l/min in a controlled experiment using three anesthetized rats weighing 0.49 kg.

Relative cardiac output measurements of unanesthetized and anesthetized rats are summarized in Table 4-9 and Table 4-10.

TABLE 4-9. RELATIVE CARDIAC OUTPUT OF UNANESTHETIZED RATS (l/min·kg)

CO	Range	Ref.
0.248	-	Tsuchiya et al. (1978)
0.252	-	Tsuchiya et al. (1978)
0.265	0.252 - 0.278	Coleman (1974)
0.278	0.255 - 0.301	Malik et al. (1976)
0.285	-	Jansky and Hart (1968)
0.286	0.261 - 0.311	Popovic and Kent (1964)
0.299	-	Tsuchiya et al. (1978)
0.305	0.264 - 0.346	Malik et al. (1976)
0.402	0.383 - 0.421	Muller and Mannesmann (1981)
0.646	-	Guyton (1947)

TABLE 4-10. RELATIVE CARDIAC OUTPUT OF ANESTHETIZED RATS
(l/min·kg)

CO	Range	Ref.
0.204	0.186 - 0.222	Popovic and Kent (1964)
0.205	-	Sapirstein (1958)
0.207	0.203 - 0.210	Chiu (1974)
0.210	0.176 - 0.242	Bullard (1959)
0.228	0.213 - 0.243	Coleman (1974)
0.238	0.196 - 0.299	Richardson et al. (1962)
0.245	-	Holt et al. (1968)
0.245	0.163 - 0.327	Blood et al. (1950)
0.249	0.240 - 0.258	Richardson et al. (1962)
0.261	-	Clarkson (1956)

Humans

Measurements of absolute cardiac output of humans are summarized in Table 4-11.

TABLE 4-11. ABSOLUTE CARDIAC OUTPUT OF HUMANS

CO (l/min)	Method	Ref.
4.60	1	Shaw et al. (1985)
4.88	6	Starr and Shroeder (1940)
5.20	4	Frostell et al. (1983)
5.21	2	Astrand et al. (1964)
5.30	4	Reeves et al. (1961)
5.51	5	Cournand et al. (1945)
5.60	-	Guyton (1971)
5.73	6	Starr and Shroeder (1940)
6.00	3	Johnson and Miller (1968)
6.00	5	Stead et al. (1945)
6.21	6	Tanner (1949)
6.30	-	Cowles et al. (1971)
6.49	2	Brandfonbrener et al. (1955)

1. Doppler
2. Dye-dilution
3. Breath-holding
4. Direct Fick
5. Catheterization
6. Ballistocardiograph

Tanner (1949) reported cardiac output data for 50 healthy men measured by the ballistocardiograph. Mean cardiac output was 6.21 ± 0.79 l/min.

Tanner also reported cardiac output measurements by other investigators for both males and females. Ballistocardiograph measurements ranged from 4.88 to 6.21 l/min (Starr and Shroeder, 1940; Tanner, 1949). Catheterization resulted in cardiac output measurements of 5.51 l/min and 6.00 l/min (Stead et al., 1945; Cournand et al., 1945).

Guyton (1971) recommends a cardiac output of 5.6 liters per minute for a normal, resting adult man.

Astrand et al. (1964) measured cardiac output in 23 healthy men and women using the dye-dilution technique. Cardiac output at rest ranged from 3.8 to 6.7 l/min. Average cardiac output was 5.21 l/min.

Reeves et al. (1961) reported a measured value of 5.3 l/min for a resting 72 kg man.

Johnson and Miller (1968) reported a resting cardiac output of 6.0 l/min. Shaw et al. (1985) measured cardiac output in 10 subjects using the pulsed Doppler technique. Resting cardiac output was 4.6 $\pm$ 1.0 l/min (range of 3.2 to 6.2 l/min). These measurements are in agreement with those of Astrand et al. (1964).

Cowles et al. (1971) reported a cardiac output of 6.3 l/min based on a statistical analysis of 510 measurements by 45 investigators.

Brandfonbrener et al. (1955) measured cardiac output in 67 healthy males, 19 to 86 years of age. The mean cardiac output for a 23.6 year old man was 6.49 l/min.

The best summaries of data for cardiac output in humans appear to be Tanner (1949), Brandfonbrener et al. (1955), and Cowles et al. (1971). These studies indicate that cardiac output decreases with age but is about 6.2 to 6.5 l/min for men between the ages of 20 to 30 years old. Thus, we are recommending a reference cardiac output of 6.2 l/min.

4.3.3. Values Used in Pharmacokinetic Models

Table 4-12 summarizes cardiac output values that have been used in pharmacokinetic models.

TABLE 4-12. CARDIAC OUTPUT
(l/min)

Source	Mouse	Rat	Human
Mapleson (1963)	-	-	6.48
Munson and Bowers (1967)	-	-	5.00
Dedrick and Bischoff (1968)	-	-	6.48
Bischoff et al. (1971)	0.0044	0.03	4.04
Dedrick et al. (1972)	-	-	4.04
Dedrick et al. (1973)	0.0044	-	4.04
Harrison and Gibaldi (1977)	-	0.0673	-
Lutz et al. (1977)	-	0.0244	-
Fernandez et al. (1977)	-	-	6.5
Tuey and Matthews (1980)	0.0047	-	-
Ramsey and Andersen (1984)	0.015	0.0940	4.83
Fiserova-Bergerova (1985)	-	-	6.54
Andersen et al. (1987)	0.039	0.0850	5.80

4.4. CARDIAC OUTPUT DISTRIBUTION

4.4.1. Reference Values

Cardiac output distribution depends on the oxygen demand of the tissues which increases with physical exercise and decreases with anesthesia (Astrand, 1983). Blood flow rates, like tissue volumes, can be independently measured in the laboratory. All blood flow measurements listed in this section are calculated in liters of blood per hour and presented as a percentage of total blood flow (cardiac output).

TABLE 4-13. REFERENCE TISSUE PERFUSION RATES
(fraction of cardiac output)

	Mouse	Rat	Human
Liver	0.25	0.25	0.26
Fat	0.09	0.09	0.05
VRG	0.51	0.51	0.44
MG	0.15	0.15	0.25

4.4.2. Documentation of Reference Values

Mice

Wetterlin et al. (1977) reported measurements of blood flow distribution in anesthetized NMRI mice of both sexes. Blood flow to the VRG (brain, heart, kidney, and viscera) accounted for 47.8% of total cardiac output (brain, 2%; heart, 2.8%; kidneys, 14.6%; and the viscera, 30.2%). Blood flow to the liver measured 8.4 ± 0.8% (arterial blood flow

only).

Quintana et al. (1979) measured the distribution of cardiac output in BALB/c mice using the radioactive microsphere method. The cardiac output distribution (%) was expressed in per gram of tissue. We used the organ weights reported by Crispens (1975) for this particular strain of mice. When the organ weights were not available for the BALB/c strain, an average of the reported values was used. Blood flow to the liver was 21%. The total percentage of blood flow to the VRG was 54% (Brain, 13%; Heart, 6%; and kidneys, 35%). No values were given for fat or the MG.

Rats

Sasaki and Wagner (1971) reported measurements of blood flow distribution in unanesthetized rats. Blood flow to the VRG (brain, heart, kidney, and viscera) accounted for 48.2% of the total cardiac output (brain, 1.2 ± 0.31%; heart, 2.9 ± 0.43%; kidneys, 17.8 ± 2.2%; and the viscera, 26.3%). Blood flow to the liver measured 6.7 ± 1.5% (arterial blood flow only). Malik et al. (1976) measured the fraction of blood flow to the liver in 15 conscious Sprague-Dawley rats using the reference sample method. Blood flow was 20.26 ± 1.9%. Herd et al. (1968) reported an approximate blood flow rate of 4 to 5% to adipose tissue in white, male Holtzman rats.

Tsuchiya et al. (1978) determined regional cardiac output distribution in three strains of unanesthetized rats. Rats included in this study were five male American Wistar rats (0.473 ± 0.010 kg); six male Wistar-Kyoto rats (0.447 ± 0.020 kg); and eight male hypertensive, Okamoto-Aoki rats (0.390 ± 0.012 kg). For the three strains of rats, blood flow to the VRG accounted for 43.5% of total cardiac output. The mean cardiac output

distributing into the liver (includes portal) was 17% for the three strains of rats.

Humans

Bradley et al. (1945) reported a human liver blood flow value of 26%. Jones (1950) reported the same value for liver as unpublished observations. Leggett and Williams (1985) designated 27% for liver blood flow. Venous blood accounted for 20% and arterial blood flow, 7.0%.

Our fat blood flow distribution in humans was assigned a value of 5% in accordance with the recommendation of ICRP (1975). Price et al. (1960) reported a body fat blood flow fraction of 4.6%. Cowles et al. (1971) reported a body fat blood flow fraction of 4.5%.

The values for the vessel-rich group are a compilation of measured values suggested for the particular tissues which make up the group. The tissues include the brain, heart, kidney, and viscera. The blood flow distribution of 13% in the brain was supported by measured values reported by Kety and Schmidt (1945). Jones (1950), and Chapman and Mitchell (1965). Brobeck (1979) recommended a slightly higher value of 15%. Blood flow distribution to the heart in humans was measured at 4.0% by Chapman and Mitchell (1965) and Brobeck (1979). Jones (1950) suggested a lower value of 2.6%. For the kidney, a blood flow value of 23% was reported by Smith (1943) and Jones (1950). Brobeck (1979) recommended a lower value of 20% and Chapman and Mitchell (1965) suggested 19%. Edwards (1975) suggested an interspecies blood flow of 26% of cardiac output to the kidney. Brobeck (1979) reported a measured value of 30% for the viscera (includes liver). Subtracting 26% of blood flow distribution for the liver results in a blood flow value of 4.0% for the viscera.

Assuming a blood flow distribution of 13% to the brain, 4.0% to the heart, 23% to the kidney and 4.0% to viscera, results in a reference value of 44% for the VRG. The range in this estimate is 39 to 48%.

Our definition of the muscle group includes the muscle and skin. Brobeck (1979) reported two values of 15 and 17% for the muscle. Chapman and Mitchell (1965) reported a higher value of 21%. Blood flow to the skin was measured at 9.0% (Chapman and Mitchell, 1965) and 10.0% (Brobeck, 1979). Cowles et al. (1971) reported 15.6% blood flow to the muscle and skin of a 70 kg man.

4.4.3. Values Used in Pharmacokinetic Models

Mice

Bischoff et al. (1971) reported blood flow rates for a 0.022 kg mouse as follows:

Tissue	Fraction
Liver	0.25
Kidney	0.18
Muscle	0.11

A total blood flow value of 0.0044 l/min was used to calculate the blood flow percentages to the different compartments. Blood flow to the gut (21%) was assumed to redistribute through the liver.

Dedrick et al. (1973) provided the following blood flow rates for a 0.022 kg mouse:

Tissue	Fraction
Liver	0.41
Heart	0.06
Kidney	0.30
Lean	0.19
Marrow	0.04

Plasma values were converted to blood values based on a hematocrit of 0.40, and the blood flow rates for the liver, kidney, and gut were scaled in proportion to the data of Bischoff et al. (1971). They also used a total blood flow value of 0.0044 l/min and assumed the perfusion of blood in the marrow tissue of mice was equal to that in the rat.

Tuey and Matthews (1980) reported the following blood flow rates for a 0.038 kg mouse:

Tissue	Fraction
Liver	0.41
Fat	0.01
Muscle	0.19
Skin	0.02

Blood flow to the muscle and liver were taken from the data of Dedrick et al. (1973) and scaled per ml of tissue. Blood flow values for the skin and adipose tissue compartments were values scaled from a 0.250 kg rat (Lutz et al., 1977) in proportion to the three-fourths power of the body weight (Adolph, 1949).

Ramsey and Andersen (1984) reported blood flow distribution in a 0.022 kg mouse to the following tissue compartments:

Tissue	Fraction
Liver	0.37
Fat	0.09
Richly perfused	0.42
Muscle	0.12

Andersen et al. (1987) reported the following blood flow fractions in a 0.038 kg mouse:

Tissue	Fraction
Liver	0.24
Fat	0.05
Rapidly perfused	0.52
Slowly perfused	0.19

Rats

Bischoff et al. (1971) reported blood flow measurements in a 0.200 kg rat as:

Tissue	Fraction
Liver	0.31
Kidney	0.24
Muscle	0.14

As with the mice, the measurements were based on a 0.40 hematocrit and organ weight-to-body weight relationships formulated by Adolph (1949).

Harrison and Gibaldi (1977) provided blood flow fractions for a 0.360 kg rat as the following:

Tissue	Fraction
Liver	0.33
Kidney	0.27
Skeletal muscle	0.16
Skin, fat, etc.	0.16
Heart	0.08

Total blood flow was 0.0534 l/min. Blood flows for the rat were not scaled in this study due to differences in the partition coefficients of the chemical between rats and humans.

Lutz et al. (1977) reported blood flow distribution in a 0.250 kg rat to the following compartments:

Tissue	Fraction
Liver	0.19
Fat	0.05
Muscle	0.09
Skin	0.006

The fraction of blood distributing into the skin is a measurement of effective blood flow. The actual skin flow rate used in the model was reduced by 10-fold in order to simulate the behavior of the chemical under investigation in the skin (Lutz et al., 1977). The blood values were in close agreement with previously published data.

Fiserova-Bergerova and Hughes (1983) estimated the following blood flow rates for a 0.250 kg rat:

Tissue	Fraction
Liver	0.29
Fat	0.006
VRG	0.57
Muscle	0.07

Again, as with the fat volume of this model, the blood flow to the fat appears to be underestimated.

Ramsey and Andersen (1984) reported blood flow distribution in a 0.30 kg rat to the following tissue compartments:

Tissue	Fraction
Liver	0.37
Fat	0.09
Richly perfused	0.42
Muscle	0.12

The blood flow to the liver, which represented 37% of cardiac output, exceeded the more realistic value of 25%. Ramsey and Andersen (1984) surmised the need to increase the cardiac output was related to the extrahepatic metabolism of the chemical under investigation.

Andersen et al. (1987) reported blood flow rates in a 0.233 kg rat for four tissue compartments:

Tissue	Fraction
Liver	0.24
Fat	0.05
Rapidly perfused	0.52
Slowly perfused	0.19

These blood flow fractions were used for the mouse, rat, and human species.

Humans

Mapleson (1963) reported the blood flow distribution in a multi-compartmental model for a 70 kg man that included the following fractions:

Tissue	Fraction
Adrenals	0.02
Kidneys	0.19
Thyroid	0.01
Gray matter	0.09
Heart	0.04
Other small glands and organs	0.01
Liver plus portal system	0.25
White matter	0.03
Red marrow	0.02
Muscle	0.09
Skin a) nutritive	0.01
b) shunt	0.20
Non-fat subcutaneous	0.01
Fat	0.03

Total blood flow was 6.48 l/min. Mapleson assumed that the blood flow to any tissue compartment is a fixed fraction of total cardiac output.

Eger (1963) listed the following perfusion rates for a 70 kg man:

Tissue	Fraction
Liver	0.26
Fat	0.05
VRG	0.49
Muscle	0.18
VPG	0.02

Eger included liver in his vessel-rich compartment, and the vessel-poor compartment included bone and cartilage.

Munson and Bowers (1967) reported the distribution of blood flow in humans as 75% to the VRG (included liver and brain), 19.6% for the muscle

group (includes bone), and 5.4% to fat. These values are used for simulation of uptake during clinical anesthesia. If liver is designated as a separate compartment, these values become:

Tissue	Fraction
Liver	0.26
Fat	0.05
VRG	0.49
MG	0.20

Bischoff et al. (1971) reported the fraction of blood flow in a 70 kg man as:

Tissue	Fraction
Liver	0.22
Kidney	0.19
Muscle	0.11

Total blood flow was 3.67 l/min. Blood flow to the gut (19%) was assumed to redistribute through the liver. As with the rodent data, the blood values are based on a hematocrit of 0.40 and organ weight-to-body weight relationships.

Dedrick et al. (1972) reported blood flow rates for a 70 kg man essentially derived from the work of Mapleson (1963). The blood flow fraction for each compartment was:

Tissue	Fraction
Liver	0.36
Kidney	0.31
Lean	0.23
Heart	0.06
Marrow	0.04

Dedrick et al. (1973) reported the following blood flow rates for a 70 kg man:

Tissue	Fraction
Liver	0.36
Heart	0.06
Kidney	0.31
Lean	0.23
Marrow	0.04

Fiserova-Bergerova et al. (1984) used the following blood distribution fractions in her model simulation of a 70 kg resting man:

Tissue	Fraction
Liver	0.23
Fat	0.05
VRG	0.45
Muscle	0.27

A separate compartment for the lung was also included in their model simulation.

Ramsey and Andersen (1984) reported the distribution of blood flow in humans as equal to those values given for the mouse and rat:

Tissue	Fraction
Liver	0.37
Fat	0.09
Richly perfused	0.42
Muscle	0.12

Andersen et al. (1987) reported the same blood flow fractions for a 70 kg man as that of their 0.038 kg mouse and 0.233 kg rat:

Tissue	Fraction
Liver	0.24
Fat	0.05
Richly perfused	0.52
Muscle	0.19

4.5. VENTILATION

Ventilation is a cyclic, dynamic process of circulation and exchange of gases in the lungs that is basic to respiration. Three primary concepts used to quantify the ventilation process are: minute volume, dead space, and alveolar ventilation.

Minute Volume

The total volume of air exhaled per minute is known as the minute volume or total ventilation rate.

Dead Space

Not all inhaled air is available for gas exchange in the alveolar compartments. The volume of the respiratory tract where no gas exchange

occurs is termed the dead space. Anatomical dead space is the internal volume of the conducting airway from the nose and mouth down to the alveoli. The physiological dead space includes the anatomical dead space and, in addition, the conducting airways of the lower respiratory tract where no significant exchange of oxygen and carbon dioxide between gas and blood occurs.

Alveolar Ventilation

The traditional definition of alveolar ventilation is the amount of inspired gas which enters the alveoli per minute. Thus, alveolar ventilation is defined as:

Alveolar ventilation = minute ventilation - frequency x dead space

$$\dot{V}_{alv} = \dot{V}E - f \times V_D,$$

where V_D is equal to anatomical dead space.

For the purposes of pharmacokinetic modeling, alveolar ventilation should be defined as:

$$\dot{V}_{alv} = \dot{V}E - f \times V_D,$$

where V_D is equal to physiological dead space.

4.5.1. Reference Values

Recommendations for reference respiration parameters are given in Table 4-14. The recommended minute volumes are calculated from power

functions suggested in Section 5.1. The alveolar ventilation rates are calculated assuming alveolar ventilation is 67% of minute volumes for mice, rats, and humans. Physiological dead space is assumed to be 33% in mice, rats, and humans.

TABLE 4-14. REFERENCE RESPIRATION PARAMETERS

	Species		
Parameter	Mouse	Rat	Human
Body weight (kg)	0.025	0.25	70.0
Minute volume (l/min)	0.037	0.174	7.5
Alveolar ventilation (l/min)	0.025	0.117	5.0
Physiological dead space (%)	33.0	33.0	33.0
Frequency (breaths/min)	163.0	85.0	15.0

4.5.2. Documentation of Reference Values

The reference minute volume of 0.037 l/min for mice was calculated using the power function suggested in section 5.1., using a reference mouse body weight of 0.025 kg. The reference minute volume of 0.174 l/min for the rat was calculated using the power function suggested for rats in section 5.1., using a reference rat body weight of 0.25 kg. Alveolar ventilation reference values for the mouse and the rat were obtained by taking 67% of the minute volumes for each species. Physiological dead space was calculated by taking the remaining 33% of minute volume for each species. The reference minute volume of 7.5 l/min for humans was taken from ICRP (1975).

Minute Volumes

Absolute minute volumes of unanesthetized mice are summarized in Table 4-15.

TABLE 4-15. ABSOLUTE MINUTE VOLUMES OF UNANESTHETIZED MICE

$\dot{V}_E$ (l/min)	Range	Method	Ref.
0.024	0.011 - 0.036	1	Guyton (1947)
0.028	0.021 - 0.036	2	Guyton (1947)
0.049	0.035 - 0.063	3	Schlenker (1985)
0.052	0.046 - 0.058	3	Vinegar et al. (1979)

1. Respirograph
2. Head valve
3. Plethysmograph

Guyton (1947) measured minute volume in 56 unanesthetized mice with an average body weight of 0.02 kg. Minute volume was 0.024 l/min with a range of 0.011 to 0.036 l/min. Schlenker (1985) measured minute volume in unanesthetized Swiss Webster mice with a mean body weight of 0.0304 ± 0.0026 kg. Minute volume was 0.0488 ± 0.014 l/min.

Vinegar et al. (1979) measured minute volume in male CD-1 mice weighing 0.027 ± 0.002 kg. Using the body plethysmograph, minute volume was measured at 0.052 l/min (range of 0.046 to 0.058 l/min).

Absolute minute volumes of anesthetized mice are summarized in Table 4-16.

TABLE 4-16. ABSOLUTE MINUTE VOLUMES OF ANESTHETIZED MICE

$\dot{V}_E$ (l/min)	Range	Method	Ref.
0.021	0.009 - 0.046	2	Crosfill and Widdicombe (1961)
0.021	0.019 - 0.022	1	Vinegar et al. (1979)
0.052	0.038 - 0.066	1	VonBucher (1949)

1. Plethysmograph
2. Tracheal cannula

A minute volume of 0.021 l/min (range of 0.009 to 0.046 l/min) for a 0.032 kg, anesthetized mouse was reported by Crosfill and Widdicombe (1961).

Vinegar et al. (1979) measured minute volume in anesthetized CD-1 mice and recorded a minute volume of 0.021 l/min (range of 0.019 to 0.022 l/min). The minute volume measurement for the anesthetized mice represented a 40% drop in minute volume from the preanesthetic level.

VonBucher (1949) measured minute volume in 14 anesthetized mice. Minute volume measured 0.052 l/min (range of 0.038 to 0.066 l/min).

A summary of relative minute volumes of unanesthetized and anesthetized mice is presented in Table 4-17 and Table 4-18.

TABLE 4-17. RELATIVE MINUTE VOLUMES OF UNANESTHETIZED MICE
(l/min·kg)

$\dot{V}_E$	Range	Method	Ref.
1.239	0.925 - 1.377	1	Guyton (1947)
1.357	1.420 - 1.708	2	Guyton (1947)
1.612	1.151 - 2.072	3	Schlenker (1985)
1.925	1.701 - 2.148	3	Vinegar et al. (1979)

1. Respirograph
2. Head valve
3. Plethysmograph

TABLE 4-18. RELATIVE MINUTE VOLUMES OF ANESTHETIZED MICE
(l/min·kg)

$\dot{V}_E$	Range	Method	Ref.
0.720	0.240 - 1.720	1	Crosfill and Widdicombe (1961)
0.777	0.704 - 0.815	2	Vinegar et al. (1979)
0.941	0.712 - 1.143	3	Guyton (1947)
2.26	1.652 - 2.869	2	VonBucher (1949)

1. Tracheal cannula
2. Plethysmograph
3. Tracheal valve

Dead Space

The difficulty in obtaining accurate respiratory measurements in animals smaller than rats precluded our obtaining sufficient data for mice. Based on the interspecific consistency in anatomical dead space values, we can conjecture physiological dead space values are also consistent between species. Therefore, we are recommending a physiological dead space

reference value of 33% for mice.

Alveolar Ventilation

We are recommending an alveolar ventilation reference value of 67% of minute volume in mice based on corresponding data in rats and humans.

Frequency

Measured respiratory frequencies of unanesthetized mice are summarized in Table 4-19.

TABLE 4-19. RESPIRATORY FREQUENCIES OF UNANESTHETIZED MICE

f (br/min)	Range	Ref.
100	-	Loosli et al. (1943)
163	85 - 230	Guyton (1947)
176	157 - 195	Jaeger and Gearhart (1982)
186	143 - 226	Jaeger and Gearhart (1982)
193	176 - 210	Jaeger and Gearhart (1982)
213	-	Crossland et al. (1977)
294*	250 - 338	Jaeger and Gearhart (1982)
316*	275 - 357	Jaeger and Gearhart (1982)
346*	314 - 378	Jaeger and Gearhart (1982)

* Unrestrained animals

Measured frequencies of anesthetized mice are summarized in Table 4-20.

TABLE 4-20. RESPIRATORY FREQUENCIES OF ANESTHETIZED MICE

f (br/min)	Range	Ref.
109	97 - 123	Crosfill and Widdicombe (1961)
154	-	Drorbaugh (1960)
168	133 - 203	Morrison and Elsner (1962)
198	-	Morrison and Elsner (1962)
210	174 - 246	Morrison and Elsner (1962)
-	80 - 200	Kleinman and Radford (1964)

Rats

Minute Volume

Tables 4-21 through 4-24 summarize the absolute and relative minute volumes of unanesthetized and anesthetized rats.

Blume (1936) measured minute volume in 23 unanesthetized rats weighing 0.111 kg. Minute volume was 0.228 l/min. In 1943, Blume and Zollner used the head mask to determine minute volume in 14 unanesthetized rats. Minute volume measured 0.336 l/min for the 0.229 kg rats.

Guyton (1947) determined the minute volume in 35 white, unanesthetized rats (average body weight of 0.113 kg). Minute volume was 0.073 l/min with a range of 0.050 to 0.101 l/min. Clarkson (1956) reported a minute volume of 0.100 l/min (range of 0.075 to 0.130 l/min) for a rat (body weight unavailable). Leong et al. (1964) determined the minute volume for four groups of male, unanesthetized Wistar rats. Minute volume rose accordingly with the increase in body weight. For 10 rats weighing 0.211 $\pm$ 0.007 kg,

TABLE 4-21. ABSOLUTE MINUTE VOLUMES OF UNANESTHETIZED RATS

$\dot{V}_E$ (l/min)	Method	Ref.
0.057	4 (a)	Bartlett and Tenney (1970)
0.073	1	Guyton (1947)
0.087	1	Leong et al. (1964)
0.089	4 (a)	Olson and Dempsey (1978)
0.096	1	Davis and Morris (1953)
0.100	-	Clarkson (1956)
0.113	1	Leong et al. (1964)
0.115	3	Palecek (1969)
0.147	4 (a)	Polianski et al. (1984)
0.150	4	Thomas and Morgan (1969)
0.153	7	Nattie (1977)
0.154	4	Mauderly (1986)
0.161	4	Dorato et al. (1983)
0.162	1	Leong et al. (1964)
0.169	4	Lamm et al. (1982)
0.174	4	Landry et al. (1983)
0.186	4	Dorato et al. (1983)
0.189	3	Palecek (1969)
0.189	4 (a)	Polianski et al. (1984)
0.194	4 (a)	Pappenheimer (1976)
0.215	2, 4	Ito et al. (1976)
0.215	6	Mauderly et al. (1979)
0.223	4	Holloway and Heath (1984)
0.225	1	Leong et al. (1964)
0.228	1	Blume (1936)
0.247	4	Thomas and Morgan (1969)
0.254	4	Mauderly (1986)
0.264	4	Mauderly (1986)
0.336	5	Blume and Zollner (1943)

1. Respirograph
2. Gas dilution, FRC
3. Boyle's Law, FRC
4. Plethysmograph, (a) barometric
5. Head mask
6. Nonrebreathing valves
7. Bellows pneumogram

TABLE 4-22. ABSOLUTE MINUTE VOLUMES OF ANESTHETIZED RATS

$\dot{V}_E$ (l/min)	Method	Ref.
0.046	3	Mauderly and Sifford (1978)
0.050	3	Mauderly and Sifford (1978)
0.064	3	Robertson and Farhi (1965)
0.064	3	Thomas and Morgan (1969)
0.076	6	Guyton (1947)
0.085	3	Palecek and Rochova (1968)
0.092	3	Palecek et al. (1967)
0.092	3	Thomas and Morgan (1969)
0.112	3	Palecek et al. (1967)
0.118	3	Palecek and Chvalova (1976)
0.119	1	Schutz (1960)
0.127	3, 5	Chvalova et al. (1974)
0.131	3	Palecek (1969)
0.146	1	Schutz (1960)
0.149	3, 5	Palecek (1969)
0.150	3	Thomas and Morgan (1969)
0.160	2	Crosfill and Widdicombe (1961)
0.161	3	Diamond and O'Donnell (1977)
0.171	1	Schutz (1960)
0.175	3	Johanson and Pierce (1971)
0.203	3	Palecek (1969)
0.237	3, 4	Ito et al. (1976)
0.388	3	VonBucher (1949)

1. Gas meter
2. Passive inflation
3. Plethysmograph
4. Gas dilution, FRC
5. Boyle's Law, FRC
6. Tracheal valve

TABLE 4-23. RELATIVE MINUTE VOLUMES OF UNANESTHETIZED RATS

Relative $\dot{V}_E$ (l/min·kg)	Method	Ref.
0.001	6	Blume and Zollner (1943)
0.142	3 (a)	Bartlett and Tenney (1970)
0.326	3 (a)	Olson and Dempsey (1978)
0.411	5	Palecek (1969)
0.540	3	Lamm et al. (1982)
0.561	7	Manderly et al. (1979)
0.614	8	Nattie (1977)
0.646	1	Guyton (1947)
0.711	5	Palecek (1969)
0.733	2	Davis and Morris (1953)
0.755	1	Leong et al. (1964)
0.752	4	Ito et al. (1976)
0.768	1	Leong et al. (1964)
0.773	3	Landry et al. (1983)
1.027	1	Leong et al. (1964)
1.673	1	Leong et al. (1964)
2.054	1	Blume (1936)

1. Respirograph
2. Respirometer
3. Plethysmograph (a) barometric
4. Gas dilution, FRC
5. Boyle's Law, FRC
6. Head mask
7. Nonrebreathing valves
8. Bellows pneumogram

TABLE 4-24. RELATIVE MINUTE VOLUMES OF ANESTHETIZED RATS

Relative VE (l/min·kg)	Method	Ref.
0.170	3	Mauderly and Sifford (1978)
0.201	3	Robertson and Farhi (1965)
0.239	3	Mauderly and Sifford (1978)
0.393	3	Chvalova et al. (1974)
0.415	3	Palecek and Rochova (1968)
0.434	3	Palecek et al. (1967)
0.435	3	Johanson and Pierce (1971)
0.457	3	Palecek and Chvalova (1976)
0.472	3	Palecek et al. (1967)
0.595	3	Palecek (1969)
0.600	1	Schutz (1960)
0.627	2	Crosfill and Widdicombe (1961)
0.635	1	Schutz (1960)
0.637	3, 5	Palecek (1969)
0.691	6	Guyton (1947)
0.691	3	Diamond and O'Donnell (1977)
0.707	3, 4	Ito et al. (1976)
0.730	1	Schutz (1960)
0.886	3	Palecek (1969)
1.630	3	VonBucher (1949)

1. Gas meter
2. Passive inflation
3. Plethysmograph
4. Gas dilution, FRC
5. Boyle's Law, FRC
6. Tracheal valve

minute volume was measured at 0.162 ± 0.042 l/min. The rats weighing 0.298 ± 0.008 kg measured a minute volume of 0.225 ± 0.028 l/min.

Landry et al. (1983) measured minute volume in male Fischer 344 rats with an average body weight of 0.225 kg. At the optimal breathing capacity for the rats, minute volume was measured at 0.174 ± 0.039 l/min.

Dead Space

Stahl (1967) predicted a dead space value of 0.0004 liters for a 0.250 kg rat. Chvalova and Palecek (1977) measured respiratory dead space in male Wistar rats as 0.00035 liters. Ward et al. (1983) estimated dead space in Porton rats as 0.00034 liters. A representative tidal volume for a 0.250 kg rat is about 0.0015 liters (Crosfill and Widdicombe, 1961; Leong et al., 1964; Dorato et al., 1983). Based on these data, anatomical dead space in rats is 23% of tidal volume. This number is corroborated by Lai et al. (1981) who estimated anatomical dead space in male Sprague-Dawley rats to be 22% of tidal volume.

The only study found estimating physiological dead space in rats was Olson et al. (1978), who estimated dead space in male Sprague-Dawley rats to be 37% of tidal volume. However, our analysis shows that anatomical dead space values are consistent between species. We conjecture that physiological dead space should also be consistent between species. Therefore, we are recommending a physiological dead space reference value of 33% of tidal volume for rats.

Alveolar Ventilation

We are recommending an alveolar ventilation reference value of 67% of minute volume for rats.

Frequency

Respiratory frequencies of unanesthetized and anesthetized rats are listed in Tables 4-25 and 4-26:

TABLE 4-25. RESPIRATORY FREQUENCIES OF UNANESTHETIZED RATS

f (br/min)	Range	Ref.
60	-	McCutcheon (1951)
82	72 - 92	Aggarwal et al. (1976)
84.9	68.3 - 101.5	Bartlett and Tenney (1970)
85	66 - 114	Guyton (1947)
86	-	Pappenheimer (1976)
91	80 - 102	Palecek (1969)
94.5	90.8 - 98.2	Ito et al. (1976)
102	80 - 124	Mauderly et al. (1979)
109	103 - 115	Olson and Dempsey (1978)
110.2	87.7 - 132.7	Leong et al. (1964)
116.1	103.5 - 128.7	Leong et al. (1964)
119	109 - 129	Palecek (1969)
119	113 - 125	Nattie (1977)
121.4	113.7 - 129.1	Leong et al. (1964)
130	-	Thomas and Morgan (1969)
131	-	Mauderly (1986)
134	-	Blume and Zollner (1943)
136	-	Mauderly (1986)
139.3	123.5 - 155.1	Leong et al. (1964)
139	-	Thomas and Morgan (1969)
142	120 - 164	Lamm et al. (1982)
142	-	Mauderly (1986)
152	-	Blume (1936)
152.5	-	Davis and Morris (1953)

TABLE 4-26. RESPIRATORY FREQUENCIES OF ANESTHETIZED RATS

f (br/min)	Range	Ref.
47	-	Mauderly and Sifford (1978)
48	-	Mauderly and Sifford (1978)
68	-	Thomas and Morgan (1969)
69	64.3 - 73.7	Robertson and Farhi (1965)
79	-	Thomas and Morgan (1969)
80	-	Drorbaugh (1960)
90	81 - 99	Vizek et al. (1975)
92.8	87.1 - 98.5	Chvalova et al. (1974)
96	88.3 - 103.7	Palecek (1969)
97	84 - 126	Crosfill and Widdicombe (1961)
102	98.9 - 105.1	Ito et al. (1976)
104	93 - 115	Palecek (1969)
108	79 - 137	Johanson and Pierce (1971)
108	98.7 - 117.3	Palecek and Chvalova (1976)
110	-	Agostoni et al. (1959)
112	103.3 - 120.7	Palecek (1969)
115	96 - 134	VonBucher (1949)
115	94 - 136	Diamond and O'Donnell (1977)

Minute volume

Absolute minute volumes of humans are reported in Table 4-27.

TABLE 4-27. ABSOLUTE MINUTE VOLUMES OF HUMANS

$\dot{V}_E$ (l/min)	Range	Ref.
6.02	-	Tobin et al. (1983)
6.1	-	Frostell et al. (1983)
6.4	-	Crosfill and Widdicombe (1961)
6.5	6.0 - 7.0	Stahl (1967)
7.43	5.8 - 10.3	Taylor (1941)
7.5	-	ICRP (1975)
7.5	-	Brobeck (1979)
7.7	-	Frostell et al. (1983)
8.20*	5.38 - 9.14	Bergman (1967)
8.73	4.9 - 12.2	Guyton (1947)
9.0	-	Mead (1960)

* Anesthetized

Brobeck (1979) reported a minute volume of 7.5 l/min for a 70.0 kg man. ICRP (1975) also recommended a 7.5 l/min minute volume for Reference Man. Taylor (1941) measured minute volume in three male subjects and reported a minute volume of 7.43 l/min (range of 5.8 to 10.3) in a resting state. Guyton (1947) measured minute volume in a 68.5 kg man using the

oscilloscopic respirograph. Minute volume was 8.73 l/min (range of 4.9 to 12.2). Crosfill and Widdicombe (1961) reported a minute volume of 6.4 for a 70 kg man. Bergman (1967) measured a minute volume range of 5.38 to 9.14 l/min in anesthetized subjects breathing 23 to 30% oxygen. Mead (1960) reported an average minute volume measurement of 9.0 l/min for 27 subjects at rest. Stahl (1967) reported a minute volume range of 6.0 to 7.0 l/min for a 70 kg man.

Relative minute volumes of humans are summarized in Table 4-28.

TABLE 4-28. RELATIVE MINUTE VOLUMES OF HUMANS

Relative $\dot{V}E$ (l/min·kg)	Range	Ref.
0.0142	0.0768 - 0.1306	Bergman (1967)
-	0.0857 - 0.1000	Stahl (1967)
0.091	-	Crosfill and Widdicombe (1961)
0.1071	-	Brobeck (1979)
0.1071	-	ICRP (1975)
0.1265	0.0710 - 0.1768	Guyton (1947)

Dead Space

There are more extensive measurements of both anatomical and physiological dead space in humans. It is generally accepted that anatomical dead space as measured by the Bohr equation at normal ventilation is subject to over-estimation (Chakrabarti et al., 1986). ICRP (1975) recommended an anatomical dead space value of 0.160 liters and a tidal volume of 0.75 liters for humans. Based on these data, anatomical

dead space in humans is 21% of tidal volume.

Nunn and Hill (1960) measured the ratio of physiological dead space to tidal volume in 12 normal subjects and found the ratio to average 0.32. Wasserman et al. (1967) found the ratio of physiological dead space to tidal volume in 10 healthy males to average 0.33 under normal resting conditions and 0.17 during exercise. Mohsenifar et al. (1985) state that normal values for the physiological dead space to tidal volume ratio are 0.33 at rest and 0.25 during mild exercise. Based on these data, we are recommending a physiological dead space reference value for humans of 33% of tidal volume.

Table 4-29 lists anatomical dead space measurements for humans.

TABLE 4-29. ANATOMICAL DEAD SPACE OF HUMANS

V_D (liters)	Ref.
0.130 ± 16 (< 40 Yr)	Tsunoda et al. (1972)
0.136 ± 19 (< 40 Yr)	Fowler (1949)
0.147	Tatsis et al. (1984)
0.155 ± 24 (> 40 Yr)	Fowler (1949)
0.156 ± 16 (> 40 Yr)	Tsunoda et al. (1972)
0.160	Svanberg (1957)
0.160	ICRP (1975)

Alveolar Ventilation

Comroe et al. (1955) recommended an alveolar ventilation rate of 4.2 l/min in a normal, adult male. Mead (1960) reported an average alveolar ventilation rate of 5.2 l/min for 27 subjects at rest. Fenn and Rahn (1965) list an alveolar ventilation rate of 5.3 l/min. Rackow et al. (1965) recommended an alveolar ventilation of 5.6 l/min based on two-thirds of the expiratory minute volume of an anesthetized subject during the first five minutes of uptake. Salzano et al. (1984) reported alveolar ventilation rates for divers at rest and during exercise. The resting values were taken while the divers inspired air containing 50% oxygen. For subject 1, resting alveolar ventilation was 7.0 $\pm$ 0.9 l/min; subject 2, 6.8 $\pm$ 0.9 l/min; subject 3, 5.6 $\pm$ 1.1 l/min; subject 4, 5.4 l/min; and subject 5, 6.6 $\pm$ 0.8 l/min.

We are recommending an alveolar ventilation reference value in humans of 5.0 l/min, which is 67% of our reference minute volume.

Frequency

Respiratory frequencies of humans are summarized in Table 4-30.

TABLE 4-30. RESPIRATORY FREQUENCIES OF HUMANS

f (br/min)	Range	Ref.
10.3	8.1 - 12.7	Bergman (1967)
11.7	10.1 - 13.1	Taylor (1941)
14.2	10.5 - 19.3	Guyton (1947)
14.8	-	Svanberg (1957)
15	-	ICRP (1975)
15.6	-	Fowler (1948)
16	-	Crosfill and Widdicombe (1961)
-	11 - 22	Stahl (1967)

4.5.3. Values Used in Pharmacokinetic Models

Pharmacokinetic models use alveolar ventilation, rather than minute volume, as an input parameter. Table 4-31 summarizes alveolar ventilation values that have been used in pharmacokinetic models.

TABLE 4-31. ALVEOLAR VENTILATION
(l/min)

Source	Mouse	Rat	Human
Mapleson (1963)	-	-	4.0
Munson and Bowers (1967)	-	-	4.0
Ramsey and Andersen (1984)	0.0121	0.075	3.83
Fiserova-B. et al. (1984)	-	-	5.80
Fiserova-Bergerova (1985)	-	-	5.3
Andersen et al. (1987)	0.039	0.085	5.80

5. SCALING

Many of the physiological parameters used in pharmacokinetic modeling are directly correlated to the body weight of the particular organism. These physiological parameters generally vary with the body weight according to a power function expressed as:

$$y = a\ BW^{b}$$

where y is a physiological parameter of interest, and a and b are constants (Fiserova-Bergerova and Hughes, 1983). If the constant b equals one, the physiological parameter y correlates directly with body weight. If the constant b equals two-thirds, the parameter y correlates with surface area. This formula was taken from the classical paper of Adolph (1949), which is generally recognized as the definitive source on the quantitative relationship between body weight and the physiological parameters.

The most desirable method of obtaining the physiological parameters used in a pharmacokinetic model is direct measurement. When such values are not available, necessary biological parameters for an untested species can be obtained through scaling. Scaling is defined as the orderly variation of anatomic and physiologic properties with body weights (Adolph, 1949). Animal scale-up is possible because both large and small animals are physiologically similar. With only minor exceptions, the mechanisms of absorption, renal excretion, distribution, and storage are relatively similar in all species of animals, including humans (Fiserova-Bergerova and Hughes, 1983). The concept of using body weight scaling in pharmacokinetic modeling was introduced by Dedrick (Dedrick, 1973; Dedrick and Bischoff, 1980). Many of the anatomical and physiological parameters can be

correlated among species as exponential functions of body weight:

Property	Constant (a)	Exponent (b)
Kidney weight	.0212	0.85
Brain weight	.081	0.70
Heart weight	.0066	0.98
Lungs weight	.0124	0.99
Liver weight	.082	0.87
Stomach and intestines weight	.112	0.94
Blood weight	.055	0.99

Adapted from Adolph (1949).

5.1. CARDIAC OUTPUT

Cardiac output is defined as the volume of blood pumped by <u>each</u> ventricle of the heart per minute. Interspecies scaling of cardiac output is known to depend on the 0.75 power of body weight (Stahl, 1967; White et al., 1968; Holt et al., 1968; Takezawa et al., 1980). In fact, there is considerable evidence that both cardiac output and minute volume scale across species with the three-fourths power of body weight (Kleiber, 1961; Holt et al., 1968; Schmidt-Nielsen, 1970). It can therefore be assumed that intraspecies extrapolations of cardiac output and minute volume should also scale with the three-fourths power of body weight (Andersen et al., 1987).

Correlations based on empirical observations of interspecies scaling of cardiac output have found the following power functions:

TABLE 5-1. CARDIAC OUTPUT
(l/min)

Constant (a)	Exponent (b)	Ref.
0.102	0.9988	Patterson et al. (1965)
0.162	0.76	White et al. (1968)
0.166	0.78	Holt et al. (1968)
0.187	0.81	Stahl (1967)

It is known that these power functions slightly underpredict cardiac output in small mammals (Guyton, 1947).

Empirical measurements of cardiac output in mice, rats, and humans follow.

5.1.1. Mice

Empirical measurements of cardiac output of mice are shown in Table 5-2.

TABLE 5-2. SCALING CARDIAC OUTPUT OF MICE

CO (l/min)	BW (kg)	$CO/BW^{0.75}$	Ref.
0.0110*	0.025	0.175	Gjedde et al. (1980)
0.0118*	0.0272	0.176	Wetterlin et al. (1979)
0.0160	0.0225	0.275	Blizard et al. (1971)

* Anesthetized

Using the estimate of cardiac output in unanesthetized mice (Blizard and Welty, 1971) and assuming cardiac output is related to the 0.75 power of body weight results in the following power function, where cardiac output is expressed in liters per minute (l/min) and body weight in kilograms (kg):

$$CO = 0.275\ (BW)^{0.75}$$

5.1.2. Rats

Empirical measurements of cardiac output of unanesthetized rats are shown in Table 5-3.

TABLE 5-3. SCALING CARDIAC OUTPUT OF UNANESTHETIZED RATS

CO (l/min)	BW (kg)	$CO/BW^{0.75}$	Ref.
0.0730	0.113	0.375	Guyton (1947)
0.0918	0.319	0.216	Popovic and Kent (1964)
0.1010	0.355	0.220	Jansky and Hart (1968)
0.1107	0.447	0.203	Tsuchiya et al. (1978)
0.1167	0.390	0.237	Tsuchiya et al. (1978)
0.1193	0.473	0.209	Tsuchiya et al. (1978)
0.1340	0.512	0.221	Coleman (1974)

Assuming that cardiac output is related to the 0.75 power of body weight and taking the geometric mean of the ratios of $CO/BW^{0.75}$ from Table 5-3, results in the following power function for cardiac output in

unanesthetized rats, where cardiac output is expressed in l/min and body weight in kg:

$$CO = 0.235\ (BW)^{0.75}$$

Measurements of absolute cardiac output of anesthetized rats are listed in Table 5-4.

TABLE 5-4. SCALING CARDIAC OUTPUT OF ANESTHETIZED RATS

CO (l/min)	BW (kg)	$CO/BW^{0.75}$	Ref.
0.027	0.213	0.086	Walsh et al. (1976)
0.040	0.213	0.128	Walsh et al. (1976)
0.047	0.190	0.163	Blood et al. (1950)
0.047	0.180	0.170	Clarkson (1956)
0.063	0.304	0.154	Chiu (1974)
0.070	0.394	0.141	Ackermann et al. (1980)
0.095	0.412	0.185	Lin et al. (1970)
0.120	0.490	0.205	Holt et al. (1968)

Assuming that cardiac output is related to the 0.75 power of body weight and taking the geometric mean of the ratios of $CO/BW^{0.75}$ from Table 5-4, results in the following power function for cardiac output in anesthetized rats, where cardiac output is expressed in l/min and body weight in kg:

$$CO = 0.150\ (BW)^{0.75}$$

5.1.3. Humans

Measurements of absolute cardiac output of humans are summarized in Table 5-5.

TABLE 5-5. SCALING ABSOLUTE CARDIAC OUTPUT OF HUMANS

CO (l/min)	BW (kg)	$CO/BW^{0.75}$	Ref.
4.60	73	0.184	Shaw et al. (1985)
4.88	63	0.218	Starr et al. (1940)
5.20	-	-	Frostell et al. (1983)
5.21	69	0.218	Astrand et al. (1964)
5.30	72	0.214	Reeves et al. (1961)
5.51	68	0.233	Cournand et al. (1945)
5.60	70	0.231	Guyton (1971)
5.73	73	0.229	Starr et al. (1940)
6.00	75	0.235	Johnson et al. (1968)
6.00	75	0.235	Stead et al. (1945)
6.21	72	0.251	Tanner (1949)
6.30	70	0.260	Cowles et al. (1971)
6.49	68	0.274	Brandfonbrener et al. (1955)

The best summaries of data for cardiac output in humans appear to be Tanner (1949), Brandfonbrener et al. (1955), and Cowles et al. (1971). These studies indicate that cardiac output decreases with age but is about

6.2 to 6.5 l/min for men between the ages of 20 to 30 years old. Thus, we are recommending a reference cardiac output of 6.2 l/min.

5.2. MINUTE VENTILATION

Ventilation is a cyclic process of circulation and exchange of gases in the lungs that is basic to respiration. Total ventilation or minute volume is defined as the volume of air exhaled per minute. Minute volume has been correlated with the three-fourths power of body weight:

TABLE 5-6. MINUTE VOLUME
(l/min)

Constant (a)	Exponent (b)	Ref
0.332	0.74	Adolph (1949)
0.373	0.75	Guyton (1947)
0.379	0.80	Stahl (1967)

For mice, minute volume was shown to scale, as was cardiac output, with a mass exponent of 0.75.

Empirical measurements of minute volume in mice, rats, and humans follow.

5.2.1. Mice

A summary of empirical studies of unanesthetized mice for which both minute volume and body weight were available is provided in Table 5-7.

TABLE 5-7. SCALING MINUTE VOLUMES OF UNANESTHETIZED MICE

$\dot{V}_E$ (l/min)	BW (kg)	$VE/BW^{0.75}$	Ref.
0.0245	0.0198	0.464	Guyton (1947)
0.0281	0.0207	0.515	Guyton (1947)
0.0489	0.0304	0.672	Schlenker (1985)
0.0521	0.0270	0.782	Vinegar et al. (1979)

Assuming minute volume is related to the 0.75 power of body weight and taking the geometric mean of the ratios of $\dot{V}_E/BW^{0.75}$ from Table 5-7 results in the following power function of minute volume in unanesthetized mice, where minute volume is expressed in l/min and body weight in kg:

$$V_E = 0.595\ (BW)^{0.75}$$

Measurements of minute volumes of anesthetized mice are listed in Table 5-8.

TABLE 5-8. SCALING MINUTE VOLUMES OF ANESTHETIZED MICE

$\dot{V}_E$ (l/min)	BW (kg)	$\dot{V}_E/BW^{0.75}$	Ref.
0.021	0.032	0.278	Crosfill and Widdicombe (1961)
0.021	0.027	0.315	Vinegar et al. (1979)
0.052	0.023	0.881	VonBucher (1949)

Assuming minute volume is related to the 0.75 power of body weight and taking the geometric mean of the ratios of $\dot{V}E/BW^{0.75}$ from Table 5-8, results in the following power function of minute volume in anesthetized mice, where minute volume is expressed in l/min and body weight in kg:

$$\dot{V}E = 0.426\ (BW)^{0.75}$$

5.2.2. <u>Rats</u>

Table 5-9 presents data on minute volumes of unanesthetized rats.

TABLE 5-9. SCALING MINUTE VOLUMES OF UNANESTHETIZED RATS

$\dot{V}_E$ (l/min)	BW (kg)	$\dot{V}_E/BW^{0.75}$	Ref.
0.037	0.400	0.113	Bartlett and Tenney (1970)
0.073	0.113	0.375	Guyton (1947)
0.087	0.052	0.799	Leong et al. (1964)
0.089	0.273	0.236	Olson and Dempsey (1978)
0.096	0.131	0.441	Davis and Morris (1953)
0.113	0.110	0.592	Leong et al. (1964)
0.115	0.280	0.299	Palecek (1969)
0.147	0.294	0.368	Polianski et al. (1984)
0.153	0.249	0.434	Nattie (1977)
0.154	0.219	0.481	Mauderly (1986)
0.161	0.218	0.505	Dorato et al. (1983)
0.162	0.211	0.520	Leong et al. (1964)
0.169	0.313	0.404	Lamm et al. (1982)
0.174	0.225	0.533	Landry et al. (1983)
0.186	0.248	0.529	Dorato et al. (1983)
0.189	0.266	0.510	Palecek (1969)
0.189	0.296	0.471	Polianski et al. (1984)
0.215	0.222	0.665	Ito et al. (1976)
0.215	0.383	0.442	Mauderly et al. (1979)
0.225	0.298	0.558	Leong et al. (1964)
0.228	0.111	1.186	Blume (1936)
0.254	0.255	0.708	Mauderly (1986)
0.264	0.219	0.825	Mauderly (1986)
0.336	0.229	1.015	Blume and Zollner (1943)

Assuming that minute volume is related to the 0.75 power of body weight and taking the geometric mean of the ratios of $\dot{V}_E/BW^{0.75}$ from Table 5-9, results in the following power function for minute volume in unanesthetized rats, where minute volume is expressed in l/min and body weight in kg:

$$\dot{V}_E = 0.492\ (BW)^{0.75}$$

Table 5-10 lists minute volumes of anesthetized rats.

TABLE 5-10. SCALING MINUTE VOLUMES OF ANESTHETIZED RATS

V_E (l/min)	BW (kg)	$VE/BW^{0.75}$	Ref.
0.046	0.271	0.123	Mauderly et al. (1978)
0.050	0.209	0.162	Mauderly et al. (1978)
0.064	0.318	0.151	Robertson and Farhi (1965)
0.076	0.110	0.398	Guyton (1947)
0.085	0.205	0.279	Palecek and Rochova (1968)
0.092	0.195	0.314	Palecek et al. (1967)
0.112	0.258	0.309	Palecek et al. (1967)
0.118	0.258	0.326	Palecek et al. (1976)
0.119	0.160	0.470	Schutz (1960)
0.127	0.323	0.296	Chvalova et al. (1974)
0.131	0.220	0.408	Palecek (1969)
0.146	0.240	0.426	Schutz (1960)
0.149	0.234	0.443	Palecek (1969)
0.160	0.280	0.416	Crosfill and Widdicombe (1961)
0.161	0.233	0.480	Diamond et al. (1977)
0.171	0.285	0.438	Schutz (1960)
0.175	0.402	0.347	Johanson et al. (1971)
0.203	0.229	0.613	Palecek (1969)
0.237	0.335	0.538	Ito et al. (1976)
0.388	0.238	1.139	VonBucher (1949)

Assuming that minute volume is related to the 0.75 power of body weight and taking the geometric mean of the ratios of $\dot{V}E/BW^{0.75}$ from Table

5-10, results in the following power function for minute volume in anesthetized rats, where minute volume is expressed in l/min and body weight in kg:

$$V_E = 0.359\ (BW)^{0.75}$$

5.2.3. Humans

Minute volumes of humans are reported in Table 5-11.

TABLE 5-11. SCALING MINUTE VOLUMES OF HUMANS

V_E (l/min)	BW (kg)	$V_E/BW^{0.75}$	
6.02	-	-	Tobin et al. (1983)
6.4	70	0.265	Crosfill and Widdicombe (1961)
7.43	-	-	Taylor (1941)
7.5	70	0.310	ICRP (1975)
7.5	70	0.310	Brobeck (1979)
8.73	68.5	0.367	Guyton (1947)
6.5	70	0.269	Stahl (1967)

APPENDIX A

This appendix provides a limited review of the literature on partition coefficients for use in pharmacokinetic modeling. A partition coefficient is an expression of the solubility of a chemical. It is used to describe the partitioning of a given chemical between air and blood, and blood and tissues. Partition coefficients can be determined in the laboratory using a vial equilibration technique (Sato and Nakajima, 1979).

PARTITION COEFFICIENTS FOR MICE, RATS, AND HUMANS AS REPORTED IN THE LITERATURE.

CHEMICAL	SPECIES	OIL/BLOOD	OIL	BLOOD	LIVER	FAT	MUSCLE	KIDNEY	PLASMA	LUNG	VESSEL RICH	VESSEL POOR	SERUM	REF
Acetone	human	---	---	313	---	---	---	---	---	---	---	---	---	2
Acetone	human	0.4	---	245+/-32	---	---	---	---	---	---	---	---	---	11
Acetone	human	---	---	341	---	---	---	---	---	---	---	---	---	2
Acetone	human	---	86	245	---	---	---	---	---	---	---	---	---	2
Acetone	human	---	---	302	---	---	---	---	---	---	---	---	---	2
Acetylene	human	---	---	0.87	---	---	---	---	---	---	---	---	---	2
Acetylene	human	---	---	0.89	---	---	---	---	---	---	---	---	---	2
Acrylonitrile	human	---	---	118	---	---	---	---	---	---	---	---	---	2
Allylbenzene	human	158	---	50.9+/-3.1	---	---	---	---	---	---	---	---	---	11
Allylbenzene	human	---	8049	51	---	---	---	---	---	---	---	---	---	2
Argon	mouse	---	0.15	---	---	---	---	---	---	---	---	---	---	3
Benzene	human	---	---	7.7	---	---	---	---	---	---	---	---	---	2
Benzene	human	---	492	7.8	---	---	---	---	---	---	---	---	---	2
Benzene	human	63	---	7.8+/-1.1	---	---	---	---	---	---	---	---	---	11
Benzene	human	---	---	5.1-7.8	---	---	---	---	---	---	---	---	---	2
Benzene	human	---	---	7.50-7.80	---	---	---	---	---	---	---	---	---	13
Benzene	human	---	---	7.8	---	---	---	---	---	---	---	---	---	2
Benzene	human	---	461	6.5	---	---	---	---	---	---	---	---	---	2
Benzene	human	---	---	---	---	406.22+/-10.10	---	---	---	---	---	---	---	9
Benzene	human	---	---	9.0	---	---	---	---	---	---	---	---	---	2
Benzene	human	---	---	7.43-8.10	---	---	---	---	---	---	---	---	---	13
Benzene	rat	---	---	7.5	---	---	---	---	---	---	---	---	---	2
Benzene	rat	---	---	7.1	---	---	---	---	---	---	---	---	---	2
Bromobenzene	human	---	---	106	---	---	---	---	---	---	---	---	---	2
Carbon disulfide	human	---	---	2.4	---	---	---	---	---	---	---	---	---	2
Carbon tetrachloride	human	---	---	0.6	---	---	---	---	---	---	---	---	---	2
Carbon tetrachloride	human	---	361	2.4	---	---	---	---	---	---	---	---	---	2
Carbon tetrachloride	human	---	---	5.8	---	---	---	---	---	---	---	---	---	2
Carbon tetrachloride	human	---	142	---	---	---	---	---	6	---	---	---	---	5
Carbon tetrachloride	human	---	---	0.6	---	---	---	---	---	---	---	---	0.3	4
Carbon tetrachloride	human	---	361+/-10	2.4+/-0.3	---	---	---	---	---	---	---	---	---	10
Carbon tetrafluoride	mouse	---	0.072	---	---	---	---	---	---	---	---	---	---	3
Chlorobenzene	human	---	---	37	---	---	---	---	---	---	---	---	---	2
Chlorobenzene	human	---	3763	30.8	---	---	---	---	---	---	---	---	---	2
Chlorobutane, 1-	human	---	350+/-8	4.3+/-0.4	---	---	---	---	---	---	---	---	---	10
Chlorobutane, 1-	human	---	350	4.3	---	---	---	---	---	---	---	---	---	2
Chloroform	human	---	130	---	---	---	---	---	15	---	---	---	---	5
Chloroform	human	---	---	11.0	---	---	---	---	---	---	---	---	---	2
Chloroform	human	---	---	10.3	---	---	---	---	---	---	---	---	---	6
Chloroform	human	---	---	8.2	---	---	---	---	---	---	---	---	---	2
Chloroform	human	---	---	8.0	---	280	---	---	---	---	---	---	---	1
Chloroform	human	---	---	9.0	---	---	---	---	---	---	---	---	---	2
Chloroform	human	---	401+/-28	10.3+/-1.0	---	---	---	---	---	---	---	---	---	10
Chloroform	human	---	401	10.3	---	---	---	---	---	---	---	---	---	2
Chloroform	human	---	---	9.0	---	---	---	---	---	---	---	---	7.6	4
Chloropentane, 1-	human	---	977+/-38	7.4+/-0.4	---	---	---	---	---	---	---	---	---	10
Chloropentane, 1-	human	---	977	7.4	---	---	---	---	---	---	---	---	---	2
Chloropropane, 1-	human	---	119	2.9	---	---	---	---	---	---	---	---	---	2
Chloropropane, 1-	human	---	119+/-5	2.9+/-0.4	---	---	---	---	---	---	---	---	---	10

CONTINUED.

CHEMICAL	SPECIES	OIL/BLOOD	OIL	BLOOD	LIVER	FAT	MUSCLE	KIDNEY	PLASMA	LUNG	VESSEL RICH	VESSEL POOR	SERUM	REF
Cryofluorane	human	---	---	0.15	---	---	---	---	---	---	---	---	---	2
Cumene	human	168	---	37.0+/-1.3	---	---	---	---	---	---	---	---	---	11
Cumene	human	---	6215	37	---	---	---	---	---	---	---	---	---	2
Cyclohexane	human	---	---	4.3	---	---	---	---	---	---	---	---	---	2
Cyclohexane	human	---	293+/-11.0	1.3+/-0.1	10.8+/-0.9	260+/-11.0	10.5+/-0.7	7.2+/-1.0	---	2.7+/-0.1	---	---	---	7
Cyclopropane	human	---	---	0.35	---	---	---	---	---	---	---	---	---	2
Cyclopropane	human	---	---	0.43	---	---	---	---	---	---	---	---	---	2
Cyclopropane	human	---	---	0.58	---	---	---	---	---	---	---	---	---	2
Cyclopropane	human	---	---	0.55	---	8	---	---	---	---	---	---	---	1
Cyclopropane	human	---	---	0.41	---	14.7	0.92	---	---	---	1.34	1.0	---	6
Cyclopropane	human	---	---	0.51	---	---	---	---	---	---	---	---	---	2
Cyclopropane	human	---	---	0.52	---	---	---	---	---	---	---	---	---	2
Dichlorobenzene, o-	human	---	27080+/-967	201.4+/-10.5	---	---	---	---	---	---	---	---	---	10
Dichlorobenzene, o-	human	---	27080	201	---	---	---	---	---	---	---	---	---	2
Dichlorobenzene, o-	human	---	39920+/-1042	423.0+/-13.6	---	---	---	---	---	---	---	---	---	10
Dichlorobenzene, o-	human	---	39920	423	---	---	---	---	---	---	---	---	---	2
Dichloroethane 1,2-	human	---	164	---	---	---	---	---	30	---	---	---	---	5
Dichloroethane, 1,1-	human	---	---	4.5	---	---	---	---	---	---	---	---	---	2
Dichloroethane, 1,1-	human	---	187	4.7	---	---	---	---	---	---	---	---	---	2
Dichloroethane, 1,1-	human	---	113	---	---	---	---	---	8	---	---	---	---	5
Dichloroethane, 1,1-	human	---	---	6.0	---	---	---	---	---	---	---	---	---	2
Dichloroethane, 1,1-	human	---	---	4.5	---	---	---	---	---	---	---	---	4.8	4
Dichloroethane, 1,1-	human	---	187+/-31	4.7+/-0.5	---	---	---	---	---	---	---	---	---	10
Dichloroethane, 1,2-	human	---	447	19.5	---	---	---	---	---	---	---	---	---	2
Dichloroethane, 1,2-	human	---	447+/-28	19.5+/-0.5	---	---	---	---	---	---	---	---	---	10
Dichloroethane, 1,2-	human	---	---	19.7	---	---	---	---	---	---	---	---	---	2
Dichloroethane, 1,2-	human	---	---	20	---	---	---	---	---	---	---	---	---	2
Dichloroethane, 1,2-	human	---	---	20.0	---	---	---	---	---	---	---	---	18.2	4
Dichloroethylene, cis-1,2-	human	---	270	9.2	---	---	---	---	---	---	---	---	---	2
Dichloroethylene, cis-1,2-	human	---	270+/-14	9.2+/-0.2	---	---	---	---	---	---	---	---	---	10
Dichloroethylene, trans-1,2-	human	---	189	5.8	---	---	---	---	---	---	---	---	---	2
Dichloroethylene, trans-1,2-	human	---	---	5.6	---	---	---	---	---	---	---	---	---	2
Dichloroethylene, trans-1,2-	human	---	189+/-4	5.8+/-0.5	---	---	---	---	---	---	---	---	---	10
Dichloropropane, 1,2-	human	---	747	10.7	---	---	---	---	---	---	---	---	---	2
Dichloropropane, 1,2-	human	---	747+/-36	10.7+/-0.5	---	---	---	---	---	---	---	---	---	10
Diethyl ether	human	---	---	11.9	---	---	---	---	---	---	---	---	---	2
Diethyl ether	human	---	---	11.6	---	---	---	---	---	---	---	---	---	2
Diethyl ether	human	---	---	12.3	---	---	---	---	---	---	---	---	---	2
Diethyl ether	human	---	---	12.0	---	50	---	---	---	---	---	---	---	1
Diethyl ether	human	---	---	11.2	---	---	---	---	---	---	---	---	---	2
Diethyl ether	human	---	---	15.2	---	2.0	1.0	---	---	---	1.14	1.0	---	6
Diethyl ether	human	---	---	12.8	---	---	---	---	---	---	---	---	---	2
Diethyl ether	human	---	---	12.5	---	---	---	---	---	---	---	---	---	2
Diethyl ketone	human	4.8	---	168+/-6	---	---	---	---	---	---	---	---	---	11
Diethyl ketone	human	---	808	168	---	---	---	---	---	---	---	---	---	2
Difluoro-2-chloroethylene, 1,1-	human	---	14	0.83	---	---	---	---	---	---	---	---	---	2
Dimethylbutane, 2,2-	human	---	71+/-5.5	0.26+/-0.08	3.5+/-1.1	66+/-4.0	1.0+/-0.8	1.4+/-1.1	---	0.6+/-0.06	---	---	---	7
Divinyl ether	human	---	---	2.6	---	40	---	---	---	---	---	---	---	1

CONTINUED.

CHEMICAL	SPECIES	OIL/BLOOD	OIL	BLOOD	LIVER	FAT	MUSCLE	KIDNEY	PLASMA	LUNG	VESSEL RICH	VESSEL POOR	SERUM	REF
Enflurane	human	---	---	2.0-2.3	---	---	---	---	---	---	---	---	---	2
Enflurane	human	---	---	1.7	---	---	---	---	---	---	---	---	---	2
Enflurane	human	---	---	1.9	--	70	---	---	---	---	---	---	---	1
Enflurane	human	---	---	1.3-2.2	---	---	---	---	---	---	---	---	---	2
Enflurane	human	---	---	1.9	---	---	---	---	---	---	---	---	---	2
Enflurane	rat	---	---	2.0	---	---	---	---	---	---	---	---	---	2
Ethane	human	---	---	0.10	---	---	---	---	---	---	---	---	---	2
Ethane	human	---	---	0.08	---	---	---	---	---	---	---	---	---	2
Ethane	human	---	---	0.05	---	---	---	---	---	---	---	---	---	2
Ethane	mouse	---	11	---	---	---	---	---	---	---	---	---	---	3
Ethyl chloride	human	---	---	1.9	---	---	---	---	---	---	---	---	1.2	4
Ethyl chloride	human	---	---	1.9	---	---	---	---	---	---	---	---	---	2
Ethyl chloride	human	---	26	---	---	---	---	---	2.3	---	---	---	---	5
Ethyl formate	human	---	---	44.6	---	---	---	---	---	---	---	---	---	2
Ethyl octane	human	---	---	74.6	---	---	---	---	---	---	---	---	---	2
Ethylbenzene	human	---	3791	28.4	---	---	---	---	---	---	---	---	---	2
Ethylbenzene	human			32.1	---	---	---	---	---	---	---	---	---	2
Ethylbenzene	human	133	---	28.4+/-1.7	---	---	---	---	---	---	---	---	---	11
Ethylene	human	---	---	0.15	---	0.95	---	---	---	---	---	---	---	1
Ethylene	human	---	---	0.14	---	5.9	1.0	---	---	---	1.0	1.0	---	6
Fluorocarbon 11	human	---	27	---	---	---	---	---	0.9	---	---	---	---	5
Fluorocarbon 11	human	---	---	0.87	---	---	---	---	---	---	---	---	---	2
Fluorocarbon 113	human	---	32	---	---	---	---	---	0.8	---	---	---	---	5
Fluorocarbon 114	human	---	5	---	---	---	---	---	0.2	---	---	---	---	5
Fluorocarbon 12	human	---	3	---	---	---	---	---	0.2	---	---	---	---	5
Fluorocarbon 12	human	---	---	0.15	---	---	---	---	---	---	---	---	---	2
Fluroxene	human	---	---	1.4	---	34	---	---	---	---	---	---	---	1
Fluroxene	human	---	---	1.6	---	---	---	---	---	---	---	---	---	2
Fluroxene	human	---	---	1.5	---	---	---	---	---	---	---	---	---	2
Fluroxene	human	---	---	1.3	---	---	---	---	---	---	---	---	---	2
Fluroxene	human	---	---	1.4	---	---	---	---	---	---	---	---	---	2
Halothane	human	---	---	2.4	---	155	---	---	---	---	---	---	---	1
Halothane	human	---	---	1.9	---	---	---	---	---	---	---	---	---	2
Halothane	human	---	---	2.6	---	---	---	---	---	---	---	---	---	2
Halothane	human	---	---	2.5	---	---	---	---	---	---	---	---	---	2
Halothane	human	---	---	2.3	---	60.0	3.5	---	---	---	2.5	1.0	---	6
Halothane	human	---	---	1.9-2.8	---	---	---	---	---	---	---	---	---	2
Halothane	human	---	---	2.8	---	---	---	---	---	---	---	---	---	2
Halothane	human	---	---	2.3-2.7	---	---	---	---	---	---	---	---	---	2
Halothane	rat	---	---	3.6	---	---	---	---	---	---	---	---	---	2
Heptane, n-	human	---	452+/-20.0	1.9+/-0.1	10.8+/-1.0	385+/-13.0	12.5+/-0.6	8.9+/-1.2	---	2.5+/-0.2	---	---	---	7
Heptanone, 2-	human	---	6791	199	---	---	---	---	---	---	---	---	---	2
Hexafluoroethane	mouse	---	0.13	---	---	---	---	---	---	---	---	---	---	3
Hexane, n-	human	---	146+/-6.9	0.80+/-0.08	5.2+/-0.7	104+/-10.0	5.0+/-0.9	3.0+/-1.1	---	1.0+/-0.07	---	---	---	7
Isoflurane	human	---	---	1.3	---	---	---	---	---	---	---	---	---	2
Isoflurane	human	---	---	1.4	---	68	---	---	---	---	---	---	---	1
Isoflurane	human	---	---	1.5	---	---	---	---	---	---	---	---	---	2
Isoflurane	human	---	---	1.4-1.6	---	---	---	---	---	---	---	---	---	2
Isoflurane	rat	---	---	1.6	---	---	---	---	---	---	---	---	---	2
Krypton	mouse	---	0.50	---	---	---	---	---	---	---	---	---	---	3

CONTINUED.

CHEMICAL	SPECIES	OIL/BLOOD	OIL	BLOOD	LIVER	FAT	MUSCLE	KIDNEY	PLASMA	LUNG	VESSEL RICH	VESSEL POOR	SERUM	REF
Methane	human	---	---	0.041	---	---	---	---	---	---	---	---	---	2
Methoxyflurane	human	---	---	12.9	---	---	---	---	---	---	---	---	---	2
Methoxyflurane	human	---	---	11-17	---	---	---	---	---	---	---	---	---	2
Methoxyflurane	human	---	---	12.3	---	---	---	---	---	---	---	---	---	2
Methoxyflurane	human	---	---	11	---	670	---	---	---	---	---	---	---	1
Methoxyflurane	human	---	---	13.2	---	---	---	---	---	---	---	---	---	2
Methoxyflurane	human	---	---	14-17	---	---	---	---	---	---	---	---	---	2
Methoxyflurane	rat	---	---	9	---	---	---	---	---	---	---	---	---	2
Methyl chloride	human	---	---	0.8	---	---	---	---	---	---	---	---	0.8	4
Methyl chloride	human	---	8	---	---	---	---	---	1.7	---	---	---	---	5
Methyl chloride	human	---	---	0.8	---	---	---	---	---	---	---	---	---	2
Methyl ethyl ketone	human	---	263	202	---	---	---	---	---	---	---	---	---	2
Methyl ethyl ketone	human	1.3	---	202+/-10	---	---	---	---	---	---	---	---	---	11
Methyl isobutyl ketone	human	10	---	90+/-11	---	---	---	---	---	---	---	---	---	11
Methyl isobutyl ketone	human	---	926	90	---	---	---	---	---	---	---	---	---	2
Methyl n-butyl ketone	human	---	---	---	---	---	---	---	---	---	---	---	---	2
Methyl n-butyl ketone	human	13	---	127+/-7	---	---	---	---	---	---	---	---	---	11
Methyl pentyl ketone	human	34	---	199+/-24	---	---	---	---	---	---	---	---	---	11
Methyl propyl ketone	human	4.2	---	150+/-12	---	---	---	---	---	---	---	---	---	11
Methyl propyl ketone	human	---	626	150	---	---	---	---	---	---	---	---	---	2
Methylcyclopentane	human	---	202+/-11.0	0.86+/-0.08	7.8+/-1.0	176+/-10.0	5.0+/-0.8	4.7+/-1.1		1.7+/-0.04	---	---	---	7
Methylene chloride	human	---	---	7.0	---	---	---	---	---	---	---	---	---	2
Methylene chloride	human	---	152+/-5	9,7+/-0.4	---	---	---	---	---	---	---	---	---	10
Methylene chloride	human	---	---	7.0	---	---	---	---	---	---	---	---	9.5	4
Methylene chloride	human	---	75	---	---	---	---	---	11	---	---	---	---	5
Methylene chloride	human	---	---	5.3-6.6	---	---	---	---	---	---	---	---	---	2
Methylene chloride	human	---	152	9.7	---	---	---	---	---	---	---	---	---	2
Methylene chloride	human	---	---	9.4	---	---	---	---	---	---	---	---	---	2
Methylene chloride	rat	---	---	12.8	---	---	---	---	---	---	---	---	---	2
Methylhexane, 3-	human	---	311+/-24.0	1.3+/-0.1	10.6+/-1.1	277+/-24.0	10.8+/-0.7	7.3+/-2.1	---	---	---	---	---	7
Methylpentane, 2-	human	---	103+/-7.3	0.41+/-0.07	4.5+/-1.1	87+/-7.0	2.9+/-0.9	2.0+/-1.1	---	0.8+/-0.06	---	---	---	7
Methylpentane, 3-	human	---	118+/-8.0	0.43+/-0.07	4.9+/-1.0	102+/-8.0	3.8+/-0.8	2.5+/-1.0	---	0.9+/-0.06	---	---	---	7
Monochlorobenzene	human	---	3763+/-97	30.8+/-1.9	---	---	---	---	---	---	---	---	---	10
Nitrogen	mouse	---	0.072	---	---	---	---	---	---	---	---	---	---	3
Nitromethane	human	---	---	425	---	---	---	---	---	---	---	---	---	2
Nitrous oxide	human	---	---	0.44	---	---	---	---	---	---	---	---	---	2
Nitrous oxide	human	---	---	0.47	---	2.3	1.13	---	---	---	1.06	1,0	---	6
Nitrous oxide	human	---	---	0.42	---	---	---	---	---	---	---	---	---	2
Nitrous oxide	human	---	---	0.47	---	1.4	---	---	---	---	---	---	---	1
Nitrous oxide	mouse	---	1.4	---	---	---	---	---	---	---	---	---	---	3
Pentane, n-	human	---	47+/-2.3	0.38+/-0.08	2.1+/-0.9	39.6+/-2.6	0.7+/-0.4	0.6+/-0.3	---	0.5+/-0.03	---	---	---	7
Propyl ether	human	---	---	8.8	---	---	---	---	---	---	---	---	---	2
Propylbenzene	human	208	---	47.0+/-2.4	---	---	---	---	---	---	---	---	---	11
Propylbenzene	human	---	9775	47	---	---	---	---	---	---	---	---	---	2
Sevoflurane	human	---	53	0.6	---	---	---	---	---	---	---	---	---	2
Styrene	human	---	---	64	---	---	---	---	---	---	---	---	---	2
Styrene	human	105	---	51.9+/-2.0	---	---	---	---	---	---	---	---	---	11
Styrene	human	---	4100	32	---	---	---	---	---	---	---	---	---	2
Styrene	human	---	5465	32	---	---	---	---	---	---	---	---	---	2
Styrene	rat	---	---	40	2.7	50	1.0	---	---	---	5.7	---	---	8

CONTINUED.

CHEMICAL	SPECIES	OIL/BLOOD	OIL	BLOOD	LIVER	FAT	MUSCLE	KIDNEY	PLASMA	LUNG	VESSEL RICH	VESSEL POOR	SERUM	REF
Sulfur hexafluoride	human	---	---	0.0049	---	---	---	---	---	---	---	---	---	2
Sulfur hexafluoride	human	---	---	0.0064	---	---	---	---	---	---	---	---	---	2
Sulfur hexafluoride	human	---	---	0.0053	---	---	---	---	---	---	---	---	---	2
Sulfur hexafluoride	mouse	---	0.30	---	---	---	---	---	---	---	---	---	---	3
Tetrachloroethane, 1,1,1,2-	human	---	4306	30	---	---	---	---	---	---	---	---	---	2
Tetrachloroethane, 1,1,1,2-	human	---	---	72.6	---	---	---	---	---	---	---	---	78.2	4
Tetrachloroethane, 1,1,1,2-	human	---	4306+/-175	30.4+/-2.1	---	---	---	---	---	---	---	---	---	10
Tetrachloroethane, 1,1,1,2-	human	---	13211+/-303	121.4+/-5.1	---	---	---	---	---	---	---	---	---	10
Tetrachloroethane, 1,1,2,2-	human	---	---	73	---	---	---	---	---	---	---	---	---	2
Tetrachloroethane, 1,1,2,2-	human	---	---	141	---	---	---	---	---	---	---	---	---	2
Tetrachloroethane, 1,1,2,2-	human	---	1110	---	---	---	---	---	220	---	---	---	---	5
Tetrachloroethane, 1,1,2,2-	human	---	13211	121	---	---	---	---	---	---	---	---	---	2
Tetrachloroethylene	human	---	1917	13.1	---	---	---	---	---	---	---	---	---	2
Tetrachloroethylene	human	---	---	9.1	---	---	---	---	---	---	---	---	---	2
Tetrachloroethylene	human	---	---	18.9	---	---	---	---	---	---	---	---	---	2
Tetrachloroethylene	human	---	490	---	---	---	---	---	32	---	---	---	---	5
Tetrachloroethylene	human	---	1917+/-129	13.1+/-1.1	---	---	---	---	---	---	---	---	---	10
Tetrachloroethylene	human	---	---	9.1	---	---	---	---	---	---	---	---	---	4
Thioethoxyflurane	human	---	7320	68	---	---	---	---	---	---	---	---	---	2
Toluene	human	94	---	15.6+/-1.7	---	---	---	---	---	---	---	---	---	11
Toluene	human	---	1380	15.6	---	---	---	---	---	---	---	---	---	2
Toluene	human	---	---	7.5-13.1	---	---	---	---	---	---	---	---	---	2
Toluene	human	---	---	16.3	---	---	---	---	---	---	---	---	---	2
Toluene	human	---	---	---	---	1296.06+/-91.52	---	---	---	---	---	---	---	9
Toluene	human	---	---	14.7	---	---	---	---	---	---	---	---	---	2
Toluene	human	---	1471	15.6	---	---	---	---	---	---	---	---	---	2
Toluene	human	---	---	14.24-14.56	---	---	---	---	---	---	---	---	---	13
Toluene	human	---	---	14.34-15.53	---	---	---	---	---	---	---	---	---	13
Toluene	rat	---	---	15.2	---	---	---	---	---	---	---	---	---	2
Toluene	rat	---	---	6.4	---	---	---	---	---	---	---	---	---	2
Trichloroethane, 1,1,1-	human	---	---	1.4	---	---	---	---	---	---	---	---	3.4	4
Trichloroethane, 1,1,1-	human	---	356+/-20	3.3+/-0.6	---	---	---	---	---	---	---	---	---	10
Trichloroethane, 1,1,1-	human	---	---	1.4	---	---	---	---	---	---	---	---	---	2
Trichloroethane, 1,1,1-	human	---	139	---	---	---	---	---	7	---	---	---	---	5
Trichloroethane, 1,1,1-	human	---	356	3.3	---	---	---	---	---	---	---	---	---	2
Trichloroethane, 1,1,2-	human	---	380	---	---	---	---	---	56	---	---	---	---	5
Trichloroethane, 1,1,2-	human	---	---	44.2	---	---	---	---	---	---	---	---	37.1	4
Trichloroethane, 1,1,2-	human	---	2273+/-237	38.6+/-4.6	---	---	---	---	---	---	---	---	---	10
Trichloroethane, 1,1,2-	human	---	---	44.2	---	---	---	---	---	---	---	---	---	2
Trichloroethane, 1,1,2-	human	---	2273	38.6	---	---	---	---	---	---	---	---	---	2
Trichloroethylene	human	---	---	9.92+/-0.63	---	674.40+/-34.08	---	---	---	---	---	---	---	12
Trichloroethylene	human	---	714	9.0	---	---	---	---	---	---	---	---	---	2
Trichloroethylene	human	---	---	9.0	---	600	---	---	---	---	---	---	---	1
Trichloroethylene	human	---	---	9.5	---	---	---	---	---	---	---	---	---	2
Trichloroethylene	human	---	---	9.9	---	---	---	---	---	---	---	---	---	2
Trichloroethylene	human	---	718	9.5	---	---	---	---	---	---	---	---	---	2
Trichloroethylene	human	---	718+/-8	9.5+/-0.6	---	---	---	---	---	---	---	---	---	10
Trichloroethylene	human	---	---	9.1	---	---	---	---	---	---	---	---	---	6
Trichloroethylene	human	---	---	5.9-10.2	---	---	---	---	---	---	---	---	---	2

CONTINUED.

CHEMICAL	SPECIES	OIL/BLOOD	OIL	BLOOD	LIVER	FAT	MUSCLE	KIDNEY	PLASMA	LUNG	VESSEL RICH	VESSEL POOR	SERUM	REF
Trichloroethylene	rat	---	---	26	---	---	---	---	---	---	---	---	---	2
Trichloroethylene	rat	---	---	25.82+/-1.70	1.69+/-0.37	25.59+/-1.08	0.63+/-0.09	1.55+/-0.48	---	1.03+/-0.17	---	---	---	12
Trichloroethylene	rat	---	---	7.4	---	---	---	---	---	---	---	---	---	2
Trichloroethylene, 1,1,2-	human	---	220	---	---	---	---	---	15	---	---	---	---	5
Trichloroethylene, 1,1,2-	human	---	---	9.5	---	---	---	---	---	---	---	---	5.9	4
Trifluoro-2-chloroethane, 1,1,1-	human	---	24	1.4	---	---	---	---	---	---	---	---	---	2
Xenon	human	---	---	0.14	---	1.3	---	---	---	---	---	---	---	1
Xenon	human	---	1.9	0.14	---	---	---	---	---	---	---	---	---	2
Xenon	mouse	---	2.0	---	---	---	---	---	---	---	---	---	---	3
Xylene (mixture)	human	---	4050	42.1	---	---	---	---	---	---	---	---	---	2
Xylene, m-	human	146	---	26.4+/-0.9	---	---	---	---	---	---	---	---	---	11
Xylene, m-	human	---	3842	26.4	---	---	---	---	---	---	---	---	---	2
Xylene, m-	human	---	---	26.50-30.98	---	---	---	---	---	---	---	---	---	13
Xylene, m-	human	---	---	---	---	3604.67+/-198.7	---	---	---	---	---	---	---	9
Xylene, m-	human	---	---	29.0	---	---	---	---	---	---	---	---	---	2
Xylene, m-	human	---	---	27.92-30.67	---	---	---	---	---	---	---	---	---	13
Xylene, o-	human	---	4360	31.1	---	---	---	---	---	---	---	---	---	2
Xylene, o-	human	140	---	31.1+/-2.3	---	---	---	---	---	---	---	---	---	11
Xylene, p-	human	---	3694	37.6	---	---	---	---	---	---	---	---	---	2
Xylene, p-	human	---	---	36.2	---	---	---	---	---	---	---	---	---	2
Xylene, p-	human	98	---	37.6+/-3.5	---	---	---	---	---	---	---	---	---	11

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