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# Extrapolation of physiological parameters for physiologically based simulation models

Vera Fiserova-Bergerova

*Department of Anesthesiology, University of Miami School of Medicine, PO Box 016370, Miami, FL 33101, USA*

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Abstract

Masses of organs and fluids, pulmonary ventilation and cardiac output and its distribution are the basic input data used in physiologically based pharmacokinetic models. Since these parameters are rarely measured in pharmacokinetic studies, the values found in reference books or extrapolated to meet the specific exposure conditions are used in the models. In this review of the extrapolation of pertinent physiological parameters, power equations **for** scaling across mammals, adjustments to body build (lean body mass) and physical activity of humans and their significance **for** risk assessment of human exposure to solvents using animal data are assessed.

*Keywords:* Inhaled dose; Pharmacokinetic compartments; Physiologically based pharmacokinetic models; Risk assessment

## 1. Introduction

Physiological parameters, such as mass of organs and fluids, pulmonary ventilation and cardiac output and its distribution (perfusion rates of organs), are the basic input data for physiologically based pharmacokinetic models (PBPK) [1–5]. These parameters are rarely measured in experimental pharmacokinetic studies and the choice of their values relies either on the values suggested for a reference man [6] and animals [7,8], or on extrapolation across species based on body weight [9–15]. In this review of extrapolation schemes, the adjustments to body build and physical activity are stressed.

## 2. Tissue **mass**

### *2.1. Scaling across young adult mammals*

Weights of organs were measured in adult humans [6], experimental animals [14], domestic animals (cattle) [10] and African ungulates [9]. It was found that, across the species, the weights of vital organs (such as liver, kidney, heart, glands and brain) correlate with **body** weight. The data were analyzed by numerous investigators and power equations were derived for extrapolations of weights of organs of young adult mammals.

* **Corresponding author, Vera Thomas, Ph.D., Department of Anesthesiology, University of Miami School of Medicine, PO Box 016370, Miami, FL 33101, USA.**


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**Table 1**
**Constants for extrapolation of organ weights across adult species (using Eq. (1))**

| Organ BW (kg) | *a* | *b* | Mouse | Rat | Man |
|---|---|---|---|---|---|
| | | | 0.022 | 0.20 | 70 |
| Adrenals [11] | 0.0011 | 0.92 | 0.019 | 0.14 | 31.5 (14) |
| Brain [11] | 0.081 | 0.70 | 0.70 (0.60) | 3.3 (2.0) | 200 (1400) |
| Heart [13] | 0.002 | 1.043 | 0.050 | 0.50 | 226 (330) |
| Kidneys [13] | 0.0218 | 0.843 | 0.30 (0.34) | 1.9 (1.9) | 265 (310) |
| Liver [13] | 0.0859 | 0.885 | 1.32 (1.3) | 9.3 (8.3) | 1667 (1800) |
| Lungs [13] | 0.00316 | 1.104 | 0.096 | 1.1 | 706 (440) |
| Spleen [13] | 0.00452 | 0.901 | 0.073 | 0.54 | 105 (180) |
| Muscle [13] | 0.463 | 1.009 | 10.5 (10) | 97.1 (100) | 35 833 (28 000) |

**Constants *a* and *b* are taken from Mordenti [13] or Adolph [11] . Body weights of species shown in kg have to be converted to grams before substitution in Eq. (1). The calculated weights of organs are given in grams. The experimentally determined values for the reference man [6] and rodents [14,16] are shown in parentheses.**

Table 1 shows constants ***a*** and ***b*** which should be substituted in Eq. (1) in order to calculate weights of vital organs (***X*** in **g**) from body weight (BW in g) [11,13].

$$X = a \times BW^b \quad (1)$$

To exemplify the accuracy of the prediction, values measured for a 22 **g** mouse [14,16] a 200 g rat [14,16] and a **70** kg man [6] are shown in Table 1 in parentheses. There **is** a striking difference between the predicted and measured mass of the human brain. The difference is in agreement with the observation that the mass of human brain per kilo of body weight is about ten times larger than that of non-primate mammals [16]. Two different equations were designed for calculation of the brain mass **of** young adult mammals [16]:
For non-human primates:

$$\text{Brain mass (g)} = 26.9 \times BW^{0.68} \quad (2)$$

For mammals other than primate:

$$\text{Brain mass (g)} = 6.72 \times BW^{0.72} \quad (3)$$

where **BW** is given in kg. Thus the brain masses of a 70 kg human, a non-human primate and a non-primate mammal are 1.4 **kg,** 0.48 kg and 0.14 kg, respectively.

Scaling of skin based on body **surface and skin** thickness **is** biased by regional and interspecies differences of skin thickness [6,17]. Body build should be considered in the scaling of mass of muscles and fat.

### *2.2. Scaling for body build in humans*

The variation in the amount of body fat (adipose tissues) [18] is the main source of inaccuracy in the estimation of the weights of organs and compartments. Therefore, relating masses **of** organs and compartments to lean body mass (LBM) seems to be appropriate [5,19]. Estimates of **LBM** and fat can be based on girth measurement [20], skinfold thickness measurement [21], total body water [6,19,22,23], specific gravity [5,24], or creatinine excretion [24]. No girth or skinfold measurements (which provide the most accurate information) were found in pharmacokinetic studies.

The LBM of hurnans can be estimated from total body water (T]3W in kg), the calculation of which takes **into account** the body build, defined by body **weight (BW in kg), body height (BH in cm) and sex [6,19,22,23].**
For a man [22]:

$$TBW = -12.86 + 0.1757 \times BH + 0.3331 \times BW \quad (4)$$

and for a woman [22]:

$$TBW = -2.097 + 0.1069 \times BH + 0.2466 \times BW \quad (5)$$

Assuming that T
[6]
LBM (kg) = TB
The LBM cal
kg, 170 cm) is
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cm tall) 70 kg m
62.1 kg (89%
women account
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BMI = BW/(0.0

Table 2
Comparison of calc
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| | R | N |
|---|---|---|
| BW/BH (kg/cm) | 7 | |
| TBW (kg) | 4 | |
| LBM (kg) | 5 | |
| Adipose tissues (kg) | 1 | |
| Muscles (kg) | 2 | |
| Skin (kg) | 2 | |
| Major organs (kg) | | |
| Brain | 1 | |
| Bone marrow | 3 | |
| Heart | ( | |
| Intestine | | |
| Kidneys | ( | |
| Liver | | |
| Lungs | ( | |
| Spleen | ( | |
| Stomach | | |
| Total | | |
| Small organs (kg) | | |
| Total[c] | | |

[a]ICRP [6].
[b]Since adipose t
LBM was calcula
and adipose tissue
[c]The difference
result of differenc

Assuming that TBW accounts for 73.2% of LBM [6]

$$LBM\ (kg) = TBW/0.732 \quad (6)$$

The LBM calculated for a reference man (70 kg, 170 cm) is 54.9 kg (78% of BW). The LBM calculated for obese (150 cm tall) and slim (200 cm tall) 70 kg men are 50.1 kg (72% of BW) and 62.1 kg (89% of BW), respectively. LBMs of women account for a smaller fraction of BW than for men (see Table 2). Similar equations for LBM calculation were tested by Hume [23].

The body mass index [25] is suggested for identifying the extremes in body build for which the calculation may be invalid.

$$BMI = BW/(0.01 \times BH)^2 \quad (7)$$

**Table 2**
**Comparison of calculated weights of organs with values recommended for a reference man and woman**

| | Reference[a] | | Calculated | | Fraction |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | |
| BW/BH (kg/cm) | 70/170 | 58/160 | 70/170 | 58/160 | |
| TBW (kg) | 42 | 30 | 40.2 | 29.3 | |
| LBM (kg) | 57.5[b] | 41[b] | 54.9 | 40.0 | |
| Adipose tissues (kg) | 12.5 | 17 | 15.1 | 18.0 | |
| Muscles (kg) | 28 | 17 | 24.7 | 18.0 | 0.4508 |
| Skin (kg) | 2.6 | 1.8 | 2.4 | 1.8 | 0.0446 |
| Major organs (kg) | | | | | |
| Brain | 1.4 | 1.2 | 1.5 | 1.07 | 0.0268 |
| Bone marrow | 3.0 | 2.6 | 3.2 | 2.31 | 0.0578 |
| Heart | 0.33 | 0.24 | 0.32 | 0.23 | 0.0058 |
| Intestine | 1.0 | 0.95 | 1.1 | 0.81 | 0.0203 |
| Kidneys | 0.31 | 0.27 | 0.33 | 0.24 | 0.0060 |
| Liver | 1.8 | 1.4 | 1.80 | 1.31 | 0.0327 |
| Lungs | 0.44 | 0.36 | 0.45 | 0.33 | 0.0082 |
| Spleen | 0.18 | 0.15 | 0.19 | 0.14 | 0.0034 |
| Stomach | 1.5 | 1.4 | 1.65 | 1.20 | 00301 |
| Total | 9.96 | 8.57 | 10.54 | 7.54 | 0.1910 |
| Small organs (kg) | | | | | |
| Total[c] | 0.415 | 0.704 | 0.67 | 0.49 | 0.0122 |

[a] ICRP [6].
[b] Since adipose tissues in ICRP are better defined than LBM, LBM was calculated as the difference between body weight and adipose tissues weight.
[c] The difference in weights of small organs is mainly the result of differences in reproductive organs.

Normal values of BMI are between 17 and 30 (mean 24)

The mass of organs can be calculated as a fraction of the LBM by using the fractional coefficients shown in Table 2. The weight of adipose tissues, BF, is calculated as the difference between body weight and lean body mass:

$$BF = BW - LBM \quad (8)$$

Body height cannot be used for evaluation of body build of animals. It remains to be seen whether specific gravity or creatinine excretion, both easily measurable in animals, can be used for adjustments to body build. The LBMs of humans extrapolated from these parameters are not always in agreement with values based on TBW.

### 2.3. Scaling of mass of compartments

The mass of the vessel rich compartment, VRG, was calculated as a sum of the weights of the major and small organs listed in Table 2 (the liver and lungs are excluded). Weights of the muscles, skin and connective tissues (which account for 7.3% of body weight [6]) are included in the muscle compartment, MG. The masses of the compartments represent the following fractions of LBM: liver, 0.0327; VRG, 0.126; MG, 0.52. The fat compartment, FG, equals the difference between BW and LBM. Sizes of compartments calculated for a reference man are compared in Table 3 with the default values recommended by the EPA [26] and with the values used by some investigators who pioneered the PBPK models.

### 2.4. Scaling for growth

It has been shown by Brody [10] that there is a correlation between organ and body weights of young growing animals. Special power equations were derived to describe the growth of organs of some mammals at various stages of development. These equations may differ considerably from equations used for extrapolation for young adults. For example, Eq. (9), suggested for the calculation of TBW for children in the prepubertal age [6], differs notably from Eqs. (4) and (5):

$$TBW = 0.135 \times BW^{0.666} \times BH^{0.535} \quad (9)$$

Table 3
Weights or volumes of compartments used for a reference man

| | Calculated (kg) | EPA [26] (kg) | Eger [1] (kg) | Mapleson [2] (l) | Lowe [3][a] (l) |
|---|---|---|---|---|---|
| Liver | 1.8 | 1.8 | —[c] | 3.9[b] | 4.0[b] |
| VRG | 6.9 | 3.5 | 6.0' | 2.32 | 2.2[d] |
| MG | 28.6 | 43.4 | 33.0 | 37.4 | 29.8 |
| FG | 15.1 | 13.3 | 14.5 | 12.8 | 10.5 |

'Lowe gives the volumes for a 100 kg man. The volumes for a 70 kg man were extrapolated using a multiplying factor of 0.7
[b]All splanchnic tissues.
[c]Liver is a part of the VRG compartment.
[d]Include only heart, brain and kidney.

## 3. Pulmonary ventilation

Minute ventilation and alveolar ventilation depend on the size and physical activity of the subject. Both ventilations correlate with oxygen consumption, which, at rest, is mainly related to heat dissipation (i.e. to the body surface) [10] and is increased by physical activity of the subject [27].

### 3.1. Scaling across young adult mammals

Minute ventilation and alveolar ventilation are determined by three parameters: tidal volume (Tv), anatomic dead space (Ds), and respiratory rate (Rr).

Minute ventilation: $V = \mathrm{Tv} \times \mathrm{Rr}$ (10)

Alveolar ventilation: $V_{alv} = (\mathrm{Tv} - \mathrm{Ds}) \times \mathrm{Rr}$ (11)

Stahl [12] measured pulmonary parameters in resting adults (unanesthetized humans and experimental animals) and described the scaling across the species by the following equations:

Tidal volume: $\mathrm{Tv\ (ml)} = 7.69 \times \mathrm{BW}^{1.04}$ (12)

Dead space: $\mathrm{Ds\ (ml)} = 2.76 \times \mathrm{BW}^{0.96}$ (13)

Respiratory rate: $\mathrm{Rr\ (per\ min)} = 53.5 \times \mathrm{BW}^{-0.26}$ (14)

where BW is body weight in kg. After substituting in Eqs. (10) and (11), minute and alveolar ventilations (in l/min) of resting subjects can be calculated as follows:

$V\ (\mathrm{l/min}) = 0.4114 \times \mathrm{BW}^{0.78}$ (15)

$V_{alv}\ (\mathrm{l/min}) = 0.4114 \times \mathrm{BW}^{0.78} - 0.1477 \times \mathrm{BW}^{0.70}$ (16)

Eq. (15) is similar to Eqs. (17) and (18), which were obtained in two studies by optimum fit of the direct measurements of minute ventilation [12,28].

$V\ (\mathrm{l/min}) = 0.379 \times \mathrm{BW}^{0.80}$ (17)

$V\ (\mathrm{l/min}) = 0.3735 \times \mathrm{BW}^{0.75}$ (18)

Table 4 compares the values of minute ventilation and alveolar ventilation, predicted by Eqs. (15) through (18) for adult humans and some

Table 4
Minute ventilation and alveolar ventilation for resting adults

| | Mouse | Kat | Monkey | Dog | Human |
|---|---|---|---|---|---|
| | BW in kg | | | | |
| | 0.025 | 0.25 | 5.0 | 10 | 70 |
| Minute ventilation (l/min) | | | | | |
| EPA [26] | 0.037 | 0.174 | | | 7.5 |
| Eq. (15) | 0.023 | 0.140 | 1.44 | 2.48 | 11.3 |
| Eq. (17) | 0.02 | 0.125 | 1.37 | 2.39 | 11.3 |
| Eq. (18) | 0.023' | 0.132 | 1.25 | 2.10 | 9.0 |
| Alveolar ventilation (l/min) | | | | | |
| EPA [26] | 0.025 | 0.117 | | | 5.0 |
| Eq. (16) | 0.012 | 0.084 | 0.99 | 1.74 | 8.42 |
| | (52) | (60) | (69) | (70) | (75) |

Values in parentheses indicate fractions of minute ventilation calculated by using Eq. (15). The EPA document [26] assumes that the alveolar ventilation of all animal species accounts for 67% of the minute ventilation.

experimental animals with the default values recommended by the EPA [26] based on review of experimental data. The values taken from the EPA document [26] are lower for humans and higher for laboratory animals' than the values derived by using the equations based on Stahl's [12] and Guyton's, [28] data. The different values are the result of the unconformity of the EPA database which includes data for an anesthetized man and non-anesthetized animals. This in turn affects the slope of the regression.

### 3.2. Scaling for humans

***Basal conditions.*** The data for basal conditions were obtained in anesthetized humans. Basal alveolar ventilation ($V^*_{alv}$) can be calculated using the perfusion ventilation ratio (which at basal conditions equals 1.25) and cardiac output ($Q^*$) [1]:

$$V^*_{alv} = Q^*/1.25 \quad (19)$$

Cardiac output of a resting human ($Q^*$ in l/min) is related to body surface (SA in $m^2$) [24] and can be estimated as follows:

$$Q^*(\text{l/min}) = 3.3 \times SA \quad (20)$$

$$SA\ (m^2) = 0.0072 \times (BW^{0.425}) \times (BH^{0.725}) \quad (21)$$

where BW is body weight in kg and BH is body height in cm. Basal alveolar ventilation can be calculated after substituting in Eq. (19):

$$V^*_{alv}\ (\text{l/min}) = 0.019 \times (BW^{0.425}) \times (BH^{0.725}) \quad (22)$$

Basal cardiac output and alveolar ventilation calculated for a reference man using Eqs. (20) and (22) are 5.95 l/min and 4.78 l/min, respectively. These values are smaller than values obtained by using Eq. (16) which is based on measurements in non-anesthetized mammals.

***Working conditions.*** It can be estimated from studies by Astrand [27] that physical activity increases alveolar ventilation of an adult by about 0.28 l/min per watt of energy expenditure. Thus alveolar ventilations for an active man ($V_{alv}$) can be scaled by using Eq. (23):

$$V_{alv}\ (\text{l/min}) = V^*_{alv} + 0.28 \times W \quad (23)$$

where $W$ denotes energy expenditure in watts. According to Eq. (23), a reference man performing moderate work (50 watts) has an alveolar ventilation of 18.8 l/min, which is the value measured in laboratory exercise studies [27]. Dejours [19] estimated a somewhat smaller increment in alveolar ventilation (0.22 l/min per watt) which corresponds, at moderate activity, to an alveolar ventilation of 15.8 l/min.

## 4. Tissue perfusion

Cardiac output, like pulmonary ventilation, depends on the size and physical activity of the subject. Measurements and extrapolations of distribution of cardiac output are confounded by the dependence of cardiac output on the activity and posture of the subject [27], the environmental temperature [29], the altitude [30] and the measuring technique. In a resting man, the perfusion rates of organs included in the VRG compartment are closely related to oxygen consumption by basal metabolism [10]. Therefore, their perfusion rates are closely related to basal cardiac output and are affected very little by physical activity. On the other hand, the oxygen consumption and perfusion rates of muscles, skin and adipose tissues are profoundly affected by physical activity and are therefore closely related to the increase of cardiac output during the activity.

### 4.1. Scaling perfusion of organs across young adult mammals

Since oxygen consumption is related to heat dissipation, it is expected that, at rest, cardiac output and perfusion rates are related to the body surface. The following power equations were derived for scaling of cardiac output [12,15]:

$$\text{Cardiac output (l/min)}: = 0.187 \times BW^{0.81} \quad (24)$$

$$\text{(l/min)}: = 0.211 \times BW^{0.75} \quad (25)$$

Plasma perfusion rates were measured in livers, kidneys, spleens and muscles of five experimental animal species [13,14]. Below are power equations derived from these data by Mordenti [13] and re-calculated for blood flow using a hematocrit of 0.45 and BW in kg:

$$\text{Hepatic flow (l/min)}: = 0.0408 \times BW^{0.792} \quad (26)$$

Table 5
Distribution of cardiac output among the compartments (physical activity is not included)

| Species | Reference | Cardiac output (l/min) | Fraction of cardiac output | | | |
|---|---|---|---|---|---|---|
| | | | Liver | VRG | MG | FG |
| Anesthetized reference man | Eger [1] | 6.0 | 0.75[a] | | 0.18 | 0.054 |
| | Mapleson [2] | 6.48 | 0.24 | 0.46 | 0.18 | 0.05 |
| Resting reference man | Bogen [31] | 6.2 | 0.26 | 0.44 | 0.23 | 0.05 |
| | EPA [26] | 6.2 | 0.26 | 0.44 | 0.25 | 0.05 |
| | Eq. (20) | 5.98 | | | | |
| Mouse | Bogen [31] | 0.021 | 0.24 | 0.53 | 0.21 | 0.02 |
| | EPA [26] | 0.017 | 0.25 | 0.51 | 0.15 | 0.09 |
| | | | (0.21) | (0.48) | | |
| | | | (0.25) | (0.54) | | |
| | Eqs. (24) and (26) | 0.0094 | 0.23 | | | |
| Rat | Bogen [31] | 0.085 | 0.24 | 0.53 | 0.18 | 0.05 |
| | EPA [26] | 0.083 | 0.25 | 0.51 | 0.15 | 0.09 |
| | | | (0.17) | (0.48) | | |
| | | | (0.20) | (0.48) | | |
| | Eqs. (24) and (26) | 0.061 | 0.22 | | | |

[a]Eger [1] includes liver in the VRG compartment.
Values in parentheses are cited in the EPA document [26] and are based on measurements by different authors. The nhysical activity is not specified.

$$\text{Renal flow (l/min)}: = 0.0391 \times BW^{0.802} \quad (27)$$

$$\text{Muscle flow (l/min)}: = 0.040 \times BW^{0.81} \quad (28)$$

$$\text{Spleen flow (ml/min)}: = 3.949 \times BW^{1.028} \quad (29)$$

There are indications that brain perfusion of all mammals (including humans) is about 0.50 ml/min per g of brain tissue [16]. Combining this information with Eqs. (2) and (3) results in the following equations for scaling of brain perfusion of mammals:

$$\text{Non-human primates (ml/min)}: = 13.45 \times BW^{0.68} \quad (30)$$

$$\text{Non-primate mammals (ml/min)}: = 3.36 \times BW^{0.72} \quad (31)$$

### 4.2. Scaling of perfusion rates of compartments

*Resting conditions.* The first estimates of distribution of cardiac output among compartments were published in anesthesia literature [1–3]. Typical examples of fractions of cardiac output perfusing the major compartments of an anesthetized or resting man are shown in Table 5. A more complete summary of the distribution of cardiac output among compartments used by various investigators can be found in the EPA document [26]. There seems to be good agreement among authors on the distribution of cardiac output. The validity of estimates is strongly supported by the agreement between simulation and experimental data on pulmonary uptake and elimination of a number of solvents and anesthetic agents. However, the simulation of pulmonary desaturation of anesthetized men suggests that the fit to experimental data improves if inner adipose tissue, which is three times more perfused than subcutaneous adipose tissue [32], is treated as a separate *FG* compartment [33].

In the absence of a suitable database, scaling for resting mammals can be based on the assumption that the distribution of cardiac output among compartments (i.e. the fraction of cardiac output perfusing individual compartments) is species independent. Simulation of controlled exposure studies using the PBPK model and comparison of predicted and measured data in mice and rats

suggest that the assumption is plausible. However perfusion rates of compartments based on experimental data obtained for mice and humans exposed to tetrachloroethylene do not support this suggestion [34].

*Scaling for physical activity.* During physical activity, the excess of oxygen consumption correlates with the increased energy expenditure. Physical activity has a negligible effect on perfusion of the viscera **(VRG)** [27], so that the increase in cardiac output is distributed according to the increased oxygen demand by tissues included in the MG and **FG** compartments. Based on these assumptions, Droz et al. [19] recommend the following increments for perfusion rates (in l/min) of compartments due to physical activity:

Liver: perfusion rate is reduced by a small fraction of the basal perfusion rate. The decrease $= -0.000182 \times W \times F^*$
VRG: perfusion rate is unchanged
**MG:** perfusion rate increases by $0.0745 \times W$
FG: perfusion rate increases by $0.0095 \times W$

where $F^*$ is the perfusion rate of livers at rest ($F^* = 0.25 \times Q^*$) and $W$ is the energy expenditure in watts. The energy expenditure for the same task increases with body weight [24].

## 5. Csnsiderations in risk assessment

Species differences in physiological and biochemical parameters are of concern in the extrapolation of human toxicity from animal data. The physiological parameters determine the availability of the inhaled compound for pulmonary absorption and the capacity of the body and organs to store the compound. However, the actual absorbed dose and the biological levels of the inhaled compound are further affected by the biochemical parameters which define the interactions between the compound and tissues (metabolism and binding) and the excretion (pulmonary, ciliary and renal clearances).

### 5.1. Availability for pulmonary absorption

The availability of compounds for pulmonary absorption is predetermined by the parameters defining their transportation rates from the environment to the alveoli. Thus, the relative dose (expressed per kg of body weight) available for pulmonary absorption of a hydrophobic, &&reactive compound is calculated by multiplying the alveolar ventilation — body weight ratio by the exposure concentration and exposure duration. The exceptions are reactive and hydrophilic compounds, in which retention in the respiratory airways reduces their availability for pulmonary uptake [35–37].

Fig. 1 shows the relative dose calculated for a reference man **(70** kg, 170 *cm)* and a reference woman (58 kg, 160 *cm)* with energy expenditures shown on the abscissa in watts. The relative dose available for a man performing light or strenuous

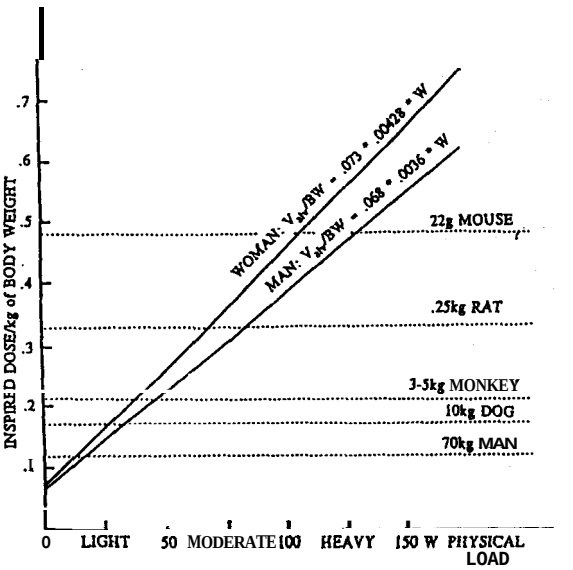



**Fig. 1. Effect of workload on inspired dose. Using Eqs. (22) and (23), inspired doses (expressed as the inspired dose per kilo of body weight assuming the inspired concentration equals 1) were calculated for a reference man (70 kg, 170 cm) and reference woman (58 kg, 160 cm) performing physical activity with energy expenditure shown in watts on the abscissa. The dashed lines indicate the inspired dose for a reference man and laboratory animals calculated by using Eq. (16), which is based on scaling for body weight but not for physical activity. The ratio of alveolar ventilation to body weight indicates that the doses available for a mouse, a rat and a dog are comparable with the doses available for a human performing strenuous, light to moderate and little activity, respectively.**

physical activity increases three or eight times, respectively, above the dose at rest. Fig. 1 shows that the doses available for a human performing activities classified as strenuous, light to moderate and very light are comparable with the doses available for a mouse, rat and dog, respectively.

### 5.2. Storage capacity of solvents

Based on Fick's law, the amount of vapor in tissues is determined by the mass of the tissues and by the solubility of the vapor in the tissues. At equilibrium, the tissue-air concentration ratios equal the tissue-gas partition coefficients at body temperature. However, if the compound is metabolized or excreted, steady state is established before equilibrium can be reached and before the capacity to store the compound is filled. Therefore, tissue-air concentration ratios remain smaller than partition coefficients regardless of the duration of exposure.

Blood-gas and lean tissue-gas partition coefficients are similar. However, the fat-gas partition coefficients of lipophilic compounds and hydrophilic compounds are, respectively, much larger and much smaller, than the partition coefficient for lean tissues [38,39]. Therefore, the capacity of the body to retain the compound depends on the body build.

Fig. 2 shows how body height affects the fat and lean body mass of a 70 kg man. Lean body mass (determined by using Eqs. **(4)** and (6)) and body fat (determined by using Eq. (8)) were calculated for 70 kg men of different body build. The lean/fatty tissue ratio increases from 2.14 in an obese man (150 cm tall) to 3.6 in the reference man and 8.7 in a slim man (200 cm tall).

The storage capacity, **SC,** available per kilogram of body weight can be calculated by using Eq. (32):

$$SC = C_{exp} \times (0.69 \times LBM \times \lambda_{lean/gas} + BF \times \lambda_{fat/gas})/BW \quad (32)$$

where $C_{exp}$ is the concentration of the compound in the inhaled air, $\lambda$ denotes the partition coefficient for the media indicated by the subscripts and the coefficient 0.69 indicates the fraction of LBM in which the compound is distributed.

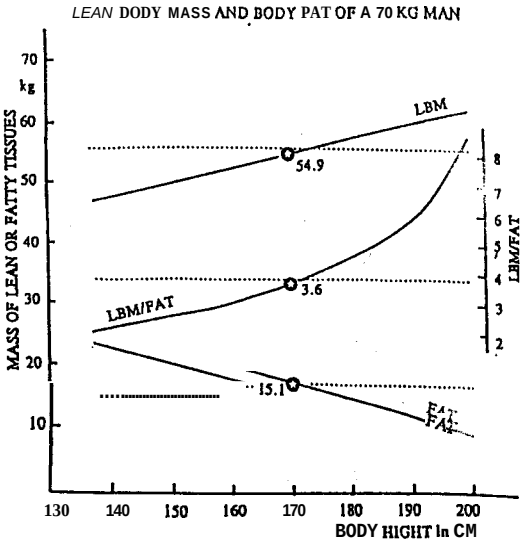


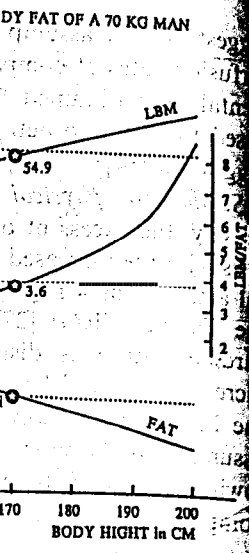

**Fig.** 2. Effect of body build on lean body mass and body fat of man. Lean body mass (LBM) and body fat of 70 kg men of body height shown on the abscissa were calculated using Eqs. (4), (5), *(6)* and (8). The shown numbers are values calculated for a reference man (170 cm tall). LBM/fat ratio is also shown. The dotted lines show values derived for a 70 kg man based on the assumption that the LBM of any mammal accounts for 78% of body weight (no adjustment for body build).

## 6. Conclusions

Simple power equations using body weight were used for scaling of basic physiological parameters across animal species. The estimates, which apply only to resting young adults, do not take into account the effect of body build on the mass of individual tissues, nor the profound effect of physical activity on pulmonary ventilation and tissue perfusion.

Organ mass estimates based on lean body mass are more realistic than those based on body weight. In humans, the effect of body build on lean body mass can be estimated from body weight and body height.

At rest, heat dissipation (and thus the body surface area) is the most decisive factor in determining pulmonary ventilation and cardiac output and its distribution. Physical stress (work, exercise) increases the demand for oxygen and the increases in pulmonary ventilation and cardiac output correlate with the energy expended in performing the task. During physical activity, the

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a were calculated using Eqs.
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perfusion rates of muscles and skin progressively increase, but the changes in perfusion rates of visceral organs' are barely 'apparent. Ergonomic data for adjustment of physiological parameters to physical activities are available for humans but are scarce for .animals.

Since relative pulmonary ventilation (l/min per kg of body weight) in small laboratory animals is larger than in resting humans, the amounts of vapors and gases inhaled per kg of body weight are also larger in small animals than in resting humans. The values of pulmonary ventilation and perfusion adjusted to activity of humans are in the range of values obtained by scaling across laboratory animals (Fig. 1). The consequences of interspecies differences in ph'ysiological parameters of humans and experimental animals for risk assessment appear negligible compared with the qualitative and quantitative differences in the biochemical interactions of the compound with tissue component! These differences in the biochemical interactions appear to be the main factors to be dealt with in extrapolating from animals to humans.

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**Abstract**

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## 1. Introduction

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