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Project Summary

Reference Physiological Parameters in Pharmacokinetic Modeling

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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 distribution, and 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.

The Project Summary presents an introduction to pharmacokinetics, discusses pharmacokinetic modeling, and diagrams a typical pharmacokinetic model with an accompanying table defining the nomenclature used.

The Project Summary concludes with a brief overview of animal scale-up (body weight scaling). Scaling is discussed in detail in the final report.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Washington, DC to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

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, tissues volumes, etc., to describe the metabolic process, the PBPK models can relate exposure concentrations to organ concentrations over a range of exposure conditions. The final report provides a literature review of the physiological parameters used in PBPK models, and recommends

reference physiological parameters for use in risk assessment.

Pharmacokinetic Modeling

A pharmacokinetic model is a set of equations 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. 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 *same* species. However, since the parameters in these data-based models generally correspond to physiologically-identifiable entities, they do not allow for extrapolation *across* 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 physiological-based approach rests on 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 different administration pathways.

The authors emphasize 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 1 and Table 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,

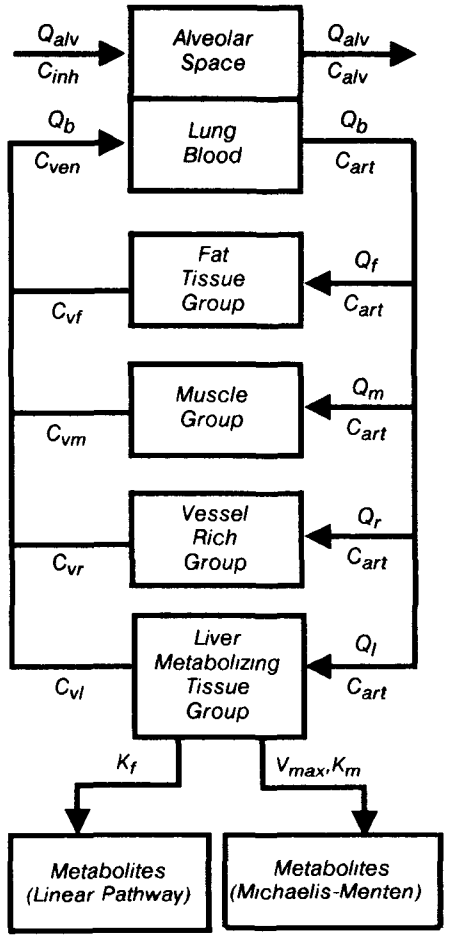

Figure 1. *Diagram of a typical pharmacokinetic model used to simulate the behavior of inhaled volatile organics. The model divides the body into four physiological groups, all connected by blood flow pathways. The symbols are defined in Table 1.*

(MG). The third group is composed adipose (fat) tissue. The fourth gro contains organs with a high capacity metabolize (principally liver). Each tiss group is described mathematically by set of differential equations whi calculate the rate of change of t amount of chemical in ea compartment. Metabolism, occurri chiefly in the liver, is described by combination of a linear metabol component and a Michaelis-Ment component accounting for saturab metabolism. Again, we stress that oth model descriptions are possible, but th will, in general, have the san physiological parameters.

Physiological Parameters

The physiological parameters typica used in pharmacokinetic modeling a listed in Table 2. Measured values these parameters in mice and rats a age, sex, and strain-dependent. F example, female rats tend to have high mass-specific ventilation rates th males, and young rats have values high than mature rats. In addition, the status the animals during measurement (bo position, conditioning, etc.,) and t measurement technique can ha substantial influences. Lack of data many physiological parameters, howev limits attempts to account for the factors. The reference parameters are a generic mouse or rat, without regard sex or strain. Differences between sex are accounted for by scaling t reference parameters within species the basis of body weight. Referen physiological values for humans are fo resting 70 kg man. For rodents, t reference physiological parameters a for a 0.025 kg mouse and a 0.25 kg rat rest.

Scope of the Final Report

The final report summarized here reviews the measured values physiological parameters found in t literature. The specific paramete detailed in the final report ar respectively, body weights, tiss volumes, cardiac output distribution a respiration parameters. The concludi chapter in the final report discuss scaling which is defined as the orde variation of anatomic and physiolo properties with body weights. Scaling possible because both large and sm animals are physiologically similar in species of animals, including humans.

Many of the physiological paramet used in pharmacokinetic modeling a directly correlated to the body weight

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. 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 1949 classical paper by E. F. Adolph* 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.

Each section of the final report is organized as follows. A summary table of the recommended reference values is presented; a literature review supports the recommended values, and the actual parameter values used in the various pharmacokinetic models are summarized. (Table 3 summarizes the reference physiological parameters which are fully discussed in the final report).

The full report also presents a complete list of references and an appendix consisting of a table of partition coefficients. Finally, the text of the full report is augmented by 45 tables.

*Quantitative relations in the physiological constituents of mammals. *Science* 109: 579-585

Table 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}	*Concentrtion 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	*Amound 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*

Table 2. *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

Table 3. *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

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***Richard Walentowicz** is the EPA Project Officer (see below).*
The complete report, entitled "Reference Physiological Parameters in Pharmacokinetic Modeling," (Order No. PB 88-196 019/AS; Cost: $19.95, subject to change) will be available only from:
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Telephone: 703-487-4650
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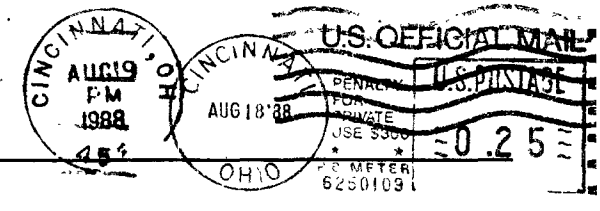

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