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PHARMACOKINETIC MODELS FOR THE ELIMINATION OF DRINKING WATER CONTAMINANTS FROM THE BODY

Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency
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AUTHORS:

Allan Marcus, Ph.D.1
Sorell L. Schwartz, Ph.D.2
Nancy J. Balter, Ph.D.2
Nicolas P. Hajjar, Ph.D.3

PROJECT OFFICER:

Krishan Khanna, Ph.D.
Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC 20460

1Battelle Memorial Institute, P.O. Box 13750, Research Triangle Park, NC.

2Toxicology and Applied Pharmacokinetics Program, Department of Pharmacology, Georgetown University School of Medicine, Washington, DC.

3Dynamac Corporation, Department of Health Assessment, 11140 Rockville Pike, Rockville, MD.

PREFACE

This report was prepared in accordance with the Memorandum of Understanding between the Department of the Army, Deputy for Environment Safety and Occupational Health (OASA(I&L)), and the U.S. Environmental Protection Agency (EPA), Office of Drinking Water (ODW), Criteria and Standards Division, for the purpose of developing risk assessment methology.

Humans are exposed to a variety of chemicals in drinking water. These chemicals or their toxic metabolites could elicit adverse biological effects in target tissues if present at sufficient concentrations and exposure durations. Understanding the metabolism and pharmacokinetics of these chemicals thus can provide a better evaluation of biological effects associated with environmental exposure. In this research project, an attempt is made to understand the pharmacokinetic behavior of representative chemicals and to identify those models most suitable in estimating the time period required to excrete drinking water contaminants at concentrations specified by One-day, Ten-day, Longer-term, and Lifetime exposure Health Advisories. In addition, available pharmacokinetic models are critically evaluated for their strengths and weaknesses in achieving the objective specified.

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Krishan Khanna, Ph.D.
Project Officer
Office of Drinking Water

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LIST OF ABBREVIATIONS

$a_1,...a_n$	=	Time constants
A_1, A_2, A_3	=	Coefficients of the distinctive components of the elimination curve
$A_1,...A_n$	=	Coefficients of the nth exponential component in the elimination curve
ADH	=	Alcohol dehydrogenase enzyme
ALDH	=	Aldehyde dehydrogenase
AUBC	=	Area under the blood curve
AUC	=	Area under the plasma concentration vs. time curve
AUC_{liv}	=	Area under the curve for the liver
AUTC	=	Area under the tissue curve
BEI	=	Biological exposure index
Cmax	=	Mmax/volume of distribution
Css	=	Steady-state concentration
C(ti)	=	Concentration of toxicant at time (ti)
C(td)	=	Accumulated concentration at time (td)
d	=	Day
DBPPK	=	Data-based physiologic pharmacokinetic
DBPK	=	Data-based pharmacokinetic
dC(ti)	=	Differential concentration of toxicant at time (ti)
DCM	=	Dichloromethane
dl	=	Deciliter
dti	=	Differential time (ti)

LIST OF ABBREVIATIONS (continued)

D(ti)	=	Cumulatively biologically effective dose at time (ti)
$e_1,...e_n$	=	Limiting values
EGME	=	Ethylene glycol monomethyl ether
EPA	=	Environmental Protection Agency
exp	=	Exponential function
g	=	Gram
GSH	=	Glutathione S-transferase
F	=	Fractional absorption of contaminant from water
hr	=	Hour
iv	=	Intravenous
kg	=	Kilogram
Km	=	Michaelis-Menten constant
L	=	Toxicologically acceptable level of concern
L'	=	Cumulative dose specified level
l	=	Liter
ln	=	Natural logarithm
m	=	Meter
M	=	Maximum toxicologically acceptable level of concern
M(1)	=	Amount of contaminant absorbed daily
MA	=	Mandelic acid
MAA	=	2-Methoxy acetic acid
MC	=	Methyl chloroform
MCL	=	Maximum concentration limit
MFO	=	Mixed function oxidase

LIST OF ABBREVIATIONS (continued)

mg	=	Milligram
ml	=	Milliliter
Mmax	=	Daily peak body level reached during infinite repeated dosing intervals
MRP	=	Medical Removal Plan
Mss	=	Amount of contaminant in the body at steady-state
n	=	Number
ODW	=	Office of Drinking Water
OSHA	=	Occupational Safety and Health Administration
OTS	=	Office of Toxic Substances
Pb	=	Lead
PBPK	=	Physiologically based pharmacokinetic
PGA	=	Phenyl glyoxylic acid
Q	=	Quantity of water consumed in liters/day
r	=	First-order elimination rate constant
R	=	Maximum elimination rate, fraction per day when C = 0
R_c	=	Continuous dosing rate
S.D.	=	Standard deviation
S.E.	=	Standard error of mean
t	=	Time
$t_{1/2}$	=	Half-life
t_d	=	Interval between doses
t_e	=	Elimination time
t_i	=	Duration of dosing

LIST OF ABBREVIATIONS (continued)

T_1, T_2, T_3	=	Time constants for the mean residence time in a component of the elimination curves
TCE	=	Trichloroethane
U	=	Uptake rate of toxicant into compartment, e.g., micrograms per day, i.e., intake times absorption
UCLA	=	University of California, Los Angeles
V	=	Volume of compartment, liters or kilograms
V_d	=	Volume of distribution
Vmax	=	Maximum velocity
WC	=	Water concentration
XRF	=	X-ray fluorescence
Y(1)	=	Y intercept for fast compartment
Y(2)	=	Y intercept for slow compartment
µg	=	Microgram
µmol	=	Micromoles

EXECUTIVE SUMMARY

Humans are exposed to a variety of chemicals in drinking water. These chemicals or their toxic metabolites could elicit adverse biological effects in target tissues if present at sufficient concentrations and exposure durations. Understanding the metabolism and pharmacokinetics of these chemicals thus can provide a better evaluation of biological effects associated with environmental exposure. In this research project, an attempt is made to understand the pharmacokinetic behavior of representative chemicals and to identify those models most suitable in estimating the time period required to excrete drinking water contaminants at concentrations specified by One-day, Ten-day, Longer-term, and Lifetime exposure Health Advisories. Five chemicals with good pharmacokinetic data and representative chemicals with short to long elimination half-lives were selected for consideration in this report. These chemicals include lead, styrene, chlordane, trichloroethane, and 1,4-dioxane.

In almost all cases, the elimination pharmacokinetics of the five toxicants studied exhibited deviations from simple first-order pharmacokinetics. Most of these deviations were related to limited sites for binding or transport of the toxicant, or to saturable processes for toxicant metabolism. Nonetheless, with very few exceptions, these kinetic nonlinearities occurred at tissue concentrations well exceeding existing, proposed, or likely biological levels of concern related to adverse health effects in humans.

In most cases, the washout curves could be approximated very well

by two- or three-term exponential functions (corresponding to two- or three-compartment models). For the chemicals studied, there were human data, or useful data in nonhuman primates or in dogs that could be extrapolated to humans by simple nonphysiological methods such as allometric scaling. The parameters could be estimated statistically. These parameters are directly relevant to the goals of this project, elimination of the toxicant.

Unfortunately, specific information is needed about both the time constants (T1, T2, T3) and amplitudes (A1, A2, A3) of the elimination curves, and about the lowest (L) and maximum (M) toxicologically acceptable levels of concern. Very good information about the "fast" time scale, T1, will not help us if A1 is only 1% of the total tissue burden, and similarly for the "very slow" components T3 and A3. It is important that the biological trigger levels L and M be established so that we can ascertain whether most of the relevant elimination occurs in the "fast" tissue (blood or plasma), in the "slower" component (soft tissues such as liver, kidney, muscle), or in the "very slow" component (sequestered in bone or in adipose tissue).

Finally, much more attention must be given to differences among individuals and among potentially exposed human populations that affect toxicant distribution and elimination. Data are presented on those toxicants for which adequate information on parameter variability is available. For many toxicants in which the only information available is on homogeneous inbred strains of laboratory animals, the littermates are often treated as independent animals and the data are truly inadequate to represent variability in heterogeneous human populations. Prudence in extrapolation of animals' kinetic parameters to diverse human populations

should always be exercised.

In conclusion, the following recommendations are proposed:

1. Abandon the idea of using a universal data-based pharmacokinetic (DBPK) model equation for most or all compounds.

2. For compounds in question, develop values for pharmacokinetic parameters describing the following:

a. Water concentration (WC)/area-under-blood curve (AUBC)/area-under-tissue curve (AUTC) relationships for parent compound. AUTC applies to all target tissues.

b. Relationship of WC and AUBC for parent compound to AUTC for reactive metabolites.

3. Establish criteria for the selection and use of DBPK models and for the selection and use of physiologically based pharmacokinetic (PBPK) models. DBPK models should not be used for extrapolation across species unless data exist for both species (e.g., rat and human). Otherwise, PBPK modeling should be used to extrapolate across species. Criteria should be developed for selecting model approaches.

4. Establish criteria for using pharmacokinetic models, DBPK or PBPK, for estimating target site concentrations of parent compound and reactive metabolites.

I. INTRODUCTION

Pharmacokinetics includes the study of the absorption, distribution among body tissues, biotransformation or metabolism, and elimination of toxic substances from the body. These processes affect the magnitude and duration of exposure of target tissues or sites of toxicity to the toxicant and to its toxic metabolites. Pharmacokinetic models thus provide an essential link between environmental exposure and estimates of biological effect. Several questions have been posed by U.S. EPA's Office of Drinking Water (ODW) concerning the applicability of certain pharmacokinetic models in estimating the time period required to excrete drinking water contaminants at concentrations specified by One-day, Ten-day, Longer-term, and Lifetime exposure Health Advisories.

The initial requirements of ODW were to evaluate the use of one mathematical model and to recommend approaches for implementing this model on a select group of chemicals. If this model equation could not be used, ODW suggested recommending alternative model(s) to achieve the objective of this task. The chemicals selected were representative of chemicals with long to short half-lives and relatively high Health Advisory values. Also considered were the inorganic metals.

Based on the initial evaluation of the available information, it was determined that a review of the various pharmacokinetic models available was warranted. The advantages and disadvantages of the available pharmacokinetic models, including the EPA-proposed model, and their applicability in estimating the time for elimination of selected chemicals and metals from the human body, were discussed. In addition, the type of pharmacokinetic data needed to use these models was established to

facilitate literature searches.

Five chemicals with good pharmacokinetic data were selected for consideration in this report. The pharmacokinetic approaches for estimating the elimination times of lead, styrene, chlordane, trichloroethane, and 1,4-dioxane were thoroughly reviewed and discussed.

II. PHARMACOKINETIC MODELS FOR ELIMINATION OF TOXICANTS

A. Model Equation

EPA suggested the following equation to estimate elimination times of drinking water contaminants:

$$[M(1) = Mss \ln t_i/t_{1/2}]$$

where M(1) is the amount of contaminant absorbed daily, Mss is the amount of contaminant in the body at steady state, $t_{1/2}$ is half-life in days, and ti is the duration of dosing. The model equation suggested by EPA is an expression of the common pharmacokinetic equation:

$$Rc = Mss * r \quad (1)$$

where Rc is the continuous dosing rate, Mss is the amount of contaminant in the body at steady state (90% of which is reached within 3.3 half-lives), and r is the first-order elimination rate constant. For alternate periods of continuous dosing and no-dosing intervals,

$$Rc = Mmax * r * [1-\exp(-rt_d)]/[1-\exp(-rt_i)] \quad (2)$$

where Mmax is the maximum daily peak body level that can be reached during infinite repeated dosing intervals, t_i is the duration of dosing, and td is the interval between doses. For the purpose of this discussion, t_i = 12 hr and t_d = 24 hr.

Substituting the relationship in equation 1, equation 2 can be expressed as:

$$Mmax = Mss * [1-exp(-rt_i)]/[1-exp(-rt_d)] \quad (3)$$

When $t_{1/2}$ is small with respect to t_i and t_d, then $[1-exp(-rt_i)]/[1-exp(-rt_d)]$ approaches 1 and Mmax approximates Mss, and equation 2 reduces to equation 1, which can be expressed as

$$Rc = Mmax * r \quad (4)$$

and the total dose for any 24-hr period can be expressed as Rc * t_i, which is the relationship stated in the model equation suggested by EPA. However, when $t_{1/2}$ increases toward infinity, then when t_i = 12 hr and t_d = 24 hr, $[1-exp(-rt_i)]/[1-exp(-rt_d)]$ approaches 0.5 and Mmax approximates Mss/2. Under these conditions, the model equation suggested by EPA is not valid. Figures II-1 and II-2 demonstrate the foregoing. Figure II-1 shows the continuous and intermittent (t_i = 12 hr; t_d = 24 hr) infusions (10 units/hr) of an agent with a $t_{1/2}$ of 1 hr. Figure II-2 shows the same protocols using an agent with a $t_{1/2}$ of 1 day. It can be seen from Figure I 2 that the use of Mss will overestimate the body burden of the agent over a period of time. Consequently. equation 2 is the more universally applicable expression of intermittent exposure to agents with first-order elimination characteristics.

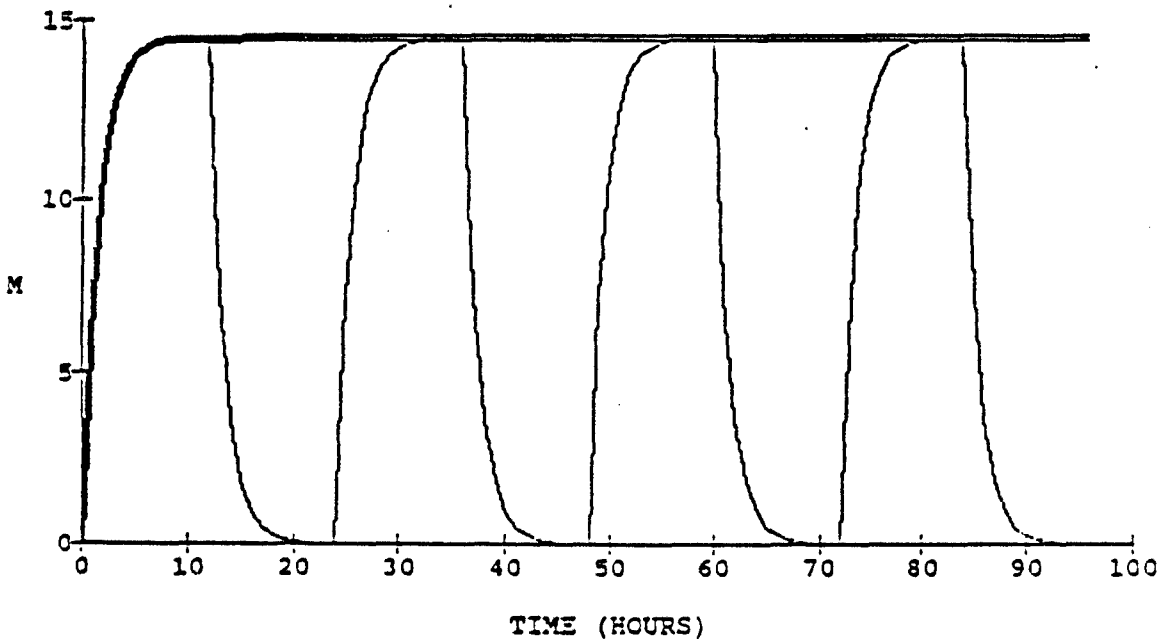


Figure II-1.Mss and Mmax for agent with $t_{1/2}$ of 1-hour infusion rate 10 units/hr.

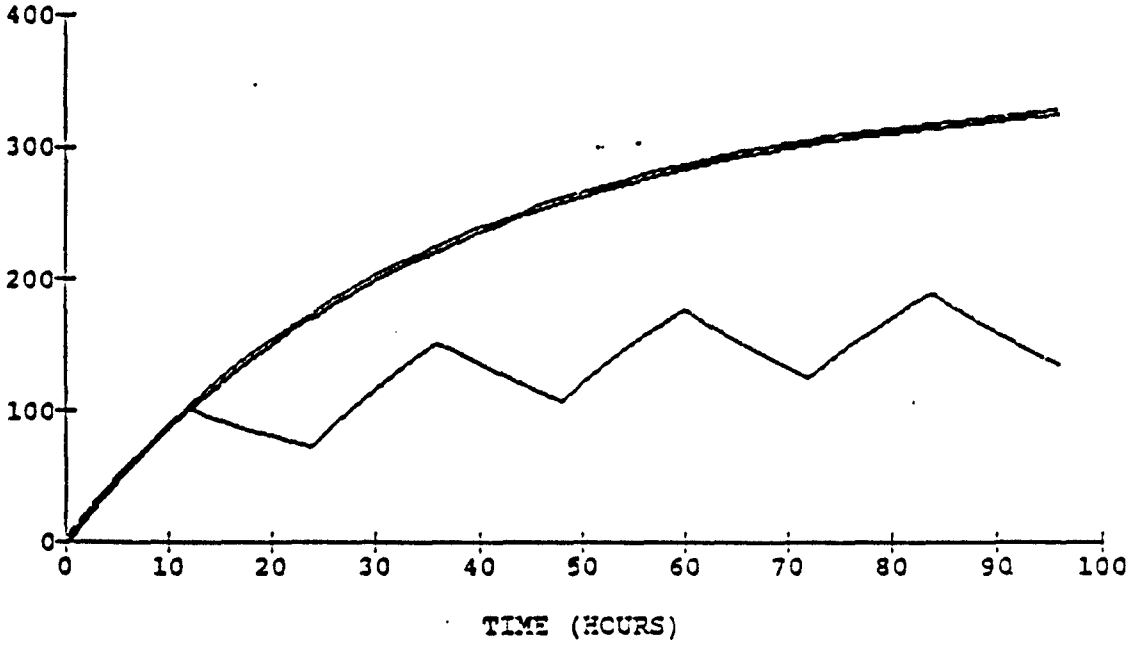


Figure II-2. Mss and Mmax for agent with $t_{1/2}$ of 1-day infusion rate 10 units/hr.

B. Compartmental Models

The separate tissues of the human body are clearly not equally available to a toxicant. It is convenient to think of the body as composed of several kinetically distinct pools or compartments, which are often, but not always, identifiable with physiological tissues, organs, or organ systems. Each compartment is thought of as internally homogeneous and well-mixed. The rate of change of toxicant concentration in each compartment is then defined by an ordinary differential equation. But, since the change of concentration in each compartment is related to concentrations in other compartments that may exchange toxicant or metabolite, we have to solve a system of coupled differential equations, one equation for each compartment.

The mathematical and computational methods of compartmental analysis have been developed in many texts, monographs, and research papers. We recommend Anderson (1983), Jacquez (1985), and Godfrey (1985) for the theory; and Wagner (1975) and O'Flaherty (1981) for practical applications of compartmental analysis. For almost all multicompartmental systems, results on concentrations and elimination times must be obtained by numerical computation. For the one-compartment model, we can sketch some of the main issues in detail and will do so in this section. In Appendix A, we present some explicit results for the two-compartment model, which show the reader some of the additional complexities in even the simplest cases.

One of the most common assumptions is that the rate of change of toxicant concentration is a linear function of concentrations in other compartments. In reality, nonlinear kinetic processes are commonly encountered and are known to significantly affect the pharmacokinetics of

most of the toxicants listed by EPA as test chemicals in the Work Assignment. Kinetic nonlinearities can arise in the following ways:

1. The toxicant is metabolized in some compartment by a saturable enzyme-limited process;

2. The rate at which the toxicant is absorbed depends on the availability of binding sites in the compartment receiving it;

3. The presence of the toxicant causes toxicity or otherwise changes the kinetics of toxicant transfer or elimination; and

4. The toxicant is co-administered with another chemical that changes the system kinetics, e.g., by competing for a metabolic pathway.

For simplicity, we will demonstrate only the one-compartment model with a constant rate of uptake of toxicant from the environment and constant kinetics. Some mathematical notation is useful to define the following quantities:

$C(t_i)$ = concentration of toxicant at time t_i.

V = volume of compartment, liters (or kilograms).

U = uptake rate of toxicant into compartment, e.g., micrograms per day, i.e., intake times absorption.

r = first-order elimination rate constant.

The differential equation for first-order elimination is thus

$$dC(t_i)/dt_i = U/V - r\ C(t_i) \qquad (5)$$

and the steady-state concentration (set $dC(t_i)/dt_i = 0$) is given by Css,

$$Css = (U/V)/r = (U/V)\ t_{1/2}/\ln(2) \qquad (6)$$

The half-life is defined by $t_{1/2} = \ln(2)/r$. The time-dependent concentration is given by an exponential approach to Css,

$$C(t_i) = Css\ [1 - \exp(-rt_i)] \qquad (7)$$

where we assume that $C(0) = 0$; exp (rt_i) is the exponential function. During washout or elimination, when uptake $U = 0$ after time, t_i, we find that

$$C(t_i) = C(t_d)\ \exp[-r\ (t_i - t_d)],\ \text{if } t_i > t_d \qquad (8)$$

Note that this model implies that the chemical is never completely eliminated from the body; some molecules always remain. In that case,

the most useful definition of the elimination time, te, is the time required to reduce the accumulated concentration, C(T), to some toxicologically acceptable level of concern, denoted L. From equation 8,

$$t_e = (1/r) \ln [C(t_d)/L] \qquad (9)$$

where $\ln[C(t_d)/L]$ is the natural logarithm of $[C(t_d)/L]$, and $C(t_d)>L$. The maximum value of te is $(1/r) \ln(Css/L)$. If exposure to the chemical is periodic, then the more complicated model in Appendix B should be used.

For many organic compounds, the primary source of elimination from the body is by metabolism to a nontoxic chemical. This usually requires the presence of an enzyme, and the rate of biotransformation is governed by the amount of enzyme present. The compartmental model may be defined in terms of:

Km = Michaelis-Menten constant.

R = maximum elimination rate, fraction per day when C = 0.

The differential equation model is

$$dC(t)/dti = U/V - R\ K_m\ C(ti)/[K_m + C(ti)] \qquad (10)$$

which can be solved explicitly for t_e, but not C(ti), as

$$t_e = (1/R) \ln[C(t_d)/L] + [C(t_d) - L]/RK_m \qquad (11)$$

Note that if we incorrectly assumed a first-order kinetic process from low-concentration studies and set r = R, we would considerably underestimate the elimination time at high concentrations.

Often both first-order and Michaelis-Menten processes are occurring, as when some of the toxicant in the body is metabolized and the rest is excreted unchanged. The differential equation formulation for both pathways is

$$dC(t_i)/dt_i = U/V - r\,C(t_i) - R\,K_m\,C(t_i)/[K_m + C(t_i)] \qquad (12)$$

which can be solved explicitly for t_e,

$$t_e = \{(R/r)\,\ln[(r+R_m+rC(td)/K_m)/(r+R+rL/K_m)] + \ln[C(td)/L]\}/(R+r) \qquad (13)$$

Multicompartment models are required when peripheral tissues store substantial quantities of toxicant that are returned only relatively slowly to the plasma or blood pool. The concept of a single "half-life" is not meaningful when significant amounts of toxicant are stored in peripheral tissues. In a system with n compartments, the elimination curve could have as many as n distinct exponential components. Many bone seeking metals such as lead and barium have at least three distinct elimination time scales, roughly one month from blood, three to six months from liver and other tissues (including new trabecular or spongy bone), and 20-30 years from cortical bone (Marcus, 1985a,b,c; Rabinowitz et al., 1976; Christoffersson et al., 1986; and Newton et al., 1977). Lipophilic organic toxicants such as DDT and hexachlorobenzene (HCB) also

show both short and long elimination time scales (Yesair et al., 1986).

Nonlinear processes may arise at the very beginning in the absorption of the chemical. Transport of many chemicals through the intestine may depend on the concentration of chemical present in the gut, and there may be other chemicals in the gut that facilitate or inhibit the transport of the chemical through the gut wall. For example, lead absorption may be only 10-15% during meals, but may increase to 40-50% when lead is ingested during a fasting condition. This is likely related to other substances in the gut during meals, including iron, calcium, lactose, and fats. Studies in everted rat intestines suggest that there is both a passive diffusion process for lead absorption, which is independent of concentration, and a saturable process that is dependent on concentration (Aungst and Fung, 1981).

Multicompartmental models with nonlinear kinetic mechanisms arise in several applications. An especially important situation is one in which the proximate toxicant is the metabolite, not the parent compound. For example, ethanol is metabolized by the alcohol dehydrogenase enzyme (ADH) to acetaldehyde, which is in turn metabolized by aldehyde dehydrogenase (ALDH) to acetic acid. The proximate fetal toxicant in fetal alcohol syndrome is now believed to be the parent compound (Blakely and Scott, 1984a,b). On the other hand, the important industrial solvent 2-methoxyethanol (ethylene glycol monomethyl ether, or EGME) is metabolized by ADH to 2-methoxyacetaldehye and by ALDH to 2-methoxy acetic acid (MAA). The fetal toxicity of EGME in mice is caused by its metabolite MAA (Sleet et al., 1985a,b).

Other nonlinear processes arise because of limited binding capacity in recipient tissues. This includes limitations in the amount of

carboxyhemoglobin that can be formed after carbon monoxide exposure (Marcus, 1985c; Muller and Barton, 1987), decreased percentages of lead taken up by erythrocytes at higher blood lead concentrations (Marcus, 1985b; Barton, 1989), and saturable accumulation of 2,4-D on the choroid plexus (Kim et al., 1983). Whereas the equilibrium or steady-state concentrations are constant at all uptake levels in ordinary linear pharmacokinetic models, the steady-state levels are different at different exposure levels in nonlinear systems. Dose-dependent pharmacokinetic models are discussed in detail in O'Flaherty (1985).

We note finally that many pharmacokinetic parameters, and the half-lives or elimination times that are derived from them, can be changed by a wide variety of exogenous factors. For example, physiological conditions such as osteoporosis (Silbergeld et al., 1988) and pregnancy (Manton, 1985) can mobilize large quantities of lead from bone, effectively reducing the half-life. Fasting or starvation can mobilize toxicants stored in adipose tissue. Competition for enzyme binding can affect the kinetics (hence, toxicity) when individuals are exposed to several chemicals at the same time. For example, large numbers of humans ingest ethanol to an extent that saturates the ADH-ALDH pathway. Because ethanol has a greater affinity for these enzymes than does EGME, the rate of metabolism of EGME to MAA is greatly reduced, thus mitigating the developmental toxicity of EGME in mice (Welsch et al., 1987; Mebus et al., 1989). The "chemical mixture" problem has pharmacokinetic aspects that have as yet received little attention (NAS, 1988).

C. Physiologically Based Pharmacokinetic (PBPK) Models

The most significant limitation of compartmental modeling for risk assessment is the lack of experimental information in humans. Even when human data are available, we often have the wrong route of exposure, the wrong doses, the wrong time intervals, or inadequate data on metabolites and on toxicant concentrations in peripheral tissues. The use of PBPK models has been recommended as a tool for extrapolating the results of animal experimental studies (NAS, 1987). PBPK models include explicit blood flow rates and tissue volumes. Tissue-blood perfusion rates can often be estimated from in vitro partition studies. Metabolic parameters such as K can also be estimated from in vitro studies. Species extrapolation of many parameters can be carried out using allometric scaling, i.e., body weight (or organ weight) ratio raised to some power (Mordenti, 1986). Surface-area scaling implies an exponent of 2/3 for rate parameters. The data needs for a PBPK model are considerable, as shown in a model for hexachlorobenzene developed for EPA's Office of Toxic Substances (OTS) (Feder et al., 1985). However, the experimental data in rodents and in the laboratory are often available.

The earliest PBPK models were developed for cancer chemotherapeutic agents such as methotraxate and cisplatin. Toxic side effects of these agents required careful consideration of dose. By far the largest number of reported (presumably, successful) applications of PBPK models have been to small organic molecules, many of which are directly relevant to this work assignment. These chemicals include methylene chloride and its structural analogs (chloroform, carbon tetrachloride), chlorinated ethanes, and ethylenes. A very brief selection of applications is listed in the references, including Andersen (1981a,b), Angelo et al.

(1984), Chen and Blancato (1987), D'Souza and Andersen (1988), D'Souza et al. (1988). Johanson (1986), Medinsky et al. (1988, 1989), Paustenbach et al. (1988), Reitz et al. (1988, 1989), and Ward et al. (1988). PBPK models for lead are currently being developed (O'Flaherty and Hamilton, 1989). PBPK modeling is impossible without the use of computer simulation programs. Because of the multiplicity of nonlinear kinetic and metabolic processes employed in such models, it is very difficult to reach general conclusions about the elimination times of the models, or about relationships of tissue level to duration of exposure. One of the most serious reservations we have is that the application of PBPK models to risk assessment is often done without adequate validation of the models.

D. Conclusions

The pharmacokinetic models that can be used to estimate the buildup and elimination of toxicants from the body have been reviewed in this chapter. The simplest model is the linear compartment model, with one or more compartments to represent the affected tissues in the body. Even in this model, the concentration of the toxicant at time t_i, $C(t_i)$, is not proportional to the duration, t_i, of exposure unless t_i is much less than the half-life, $t_{1/2}$, since from Equation 6 we have

$$C(t_i) = Css\ [1-\exp(-rt_i)]$$
$$= Css\ [rt_i - (rt_i)2/2 + - + \text{other terms}] \qquad (14)$$

In more complex models, the concept of a "half-life" may be very inadequate, if the site of toxicity is located in a peripheral compartment and if the long-term elimination kinetics is governed by storage and release from the same or another peripheral compartment. The half-life is, in fact, not a constant if the toxicant is metabolized or if nonlinear tissue binding processes occur, since the time to reduce the concentration from $C(t_d)$ to 1/2 of $C(t_d)$ depends on the value of $C(t_d)$. Equation 14 could be used only if there were very compelling evidence that nonlinear kinetic processes were negligible at levels for which these analyses were being done, and if the half-life were sufficiently long in the compartment of interest that no significant equilibration would have occurred during the exposure interval.

Data for developing an adequately predictive compartmental model in humans are not usually available. In the absence of such data, biologically and physiologically plausible extrapolations from experimental data in small mammals may be used. PBPK models for many of the simpler organic compounds are available and could probably serve as starting points for related compounds, since the blood flows and tissue volumes are the same, and since many of the tissue perfusion coefficients and metabolic parameters could be measured inexpensively, or estimated from structural similarities. At worst, this approach would be a good point of departure for studying the sensitivity of the predicted body burden and elimination times to the unknown parameters. The sensitivity analyses could also help guide experimental work into the most critical areas of uncertainty. The use of PBPK models that have not been validated experimentally should be avoided.

III. DATA REQUIREMENTS AND PHARMACOKINETIC CONSIDERATIONS FOR ESTIMATING ELIMINATION TIME

A. Data Requirements

Estimation of elimination times requires several kinds of experimental information:

1. Time pattern in change of concentration levels of the toxicant or its metabolites, internally if possible, and/or in excreta;

2. Effects of applied dose or dose rate (intake) of toxicant from the environment; and

3. Biological basis for extrapolating results from experimental animal studies to human exposures.

1. Concentration vs. Time Curves

Data on time pattern, in one form or another, are essential. While steady-state or equilibrium concentration studies can provide a great deal of supporting information, the most reliable evidence on kinetics comes from observing changes in system response to changes in toxicant intake. The concentrations of the toxicant or its metabolites are usually measured at several different times after exposure to the chemical begins ("uptake" studies) or after all external exposure ceases ("elimination" studies). The concentrations in plasma or in whole blood are the most commonly measured, and concentrations in urine, feces, or exhaled air provide information about elimination pathways. The use of radioactive

isotopes as tracers allows estimation of whole-body retention of the labeled element. Concentrations of some elements such as lead and cadmium can be tracked in specific sites, such as the long bones in vivo, by the use of x-ray fluorescence (XRF) techniques.

The study of kinetics in soft tissues in a single animal is generally not possible. More commonly, concentrations in soft tissues (especially the liver and kidney) of experimental animals are obtained by sacrificing groups of genetically similar animals at several different times, and then using the average of the concentrations within a group as the value of the tissue concentration at the time of sacrifice. However, unless the animals within the group have very similar pharmacokinetic parameters, the elimination time estimated from averages of concentrations will be systematically different from the average elimination time that could have been estimated from the elimination times of the individuals, if they had been available.

Some examples drawn from the recent research literature on haloalkanes are attached. The first two figures (Figures III-1 and III-2) show typical elimination curves for methylchloroform (1,1,1-trichloroethane, MC) following intravenous (iv) and oral (drinking water) exposures (Reitz et al., 1988). Note that the elimination curves appear biphasic on these semilog plots, with a rapid early decline followed by a much slower decline after some hours. The solid curves were estimated from a physiologically based pharmacokinetic model. Figure III-3 shows a much slower rate of decline of methylene chloride (dichloromethane, DCM) at high concentrations, attributable to saturation of the glutathione S-transferase (GSH) and mixed-function oxidase (MFO) pathways (Andersen, 1989). Note the much more rapid decline (and comparable parallel rate) at

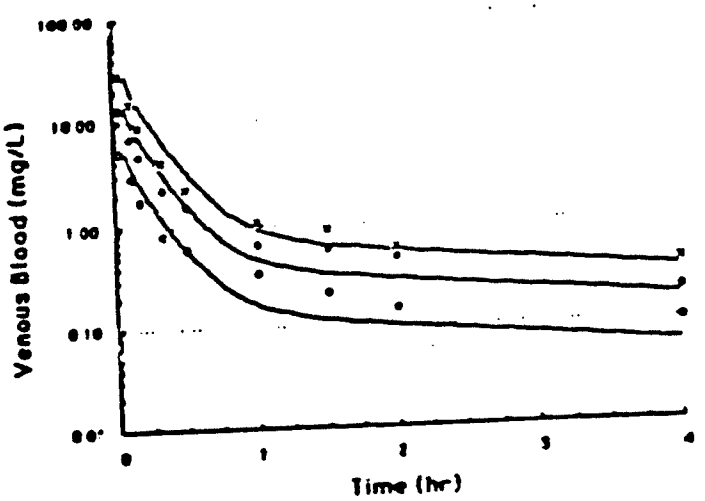


Figure III-1. Blood levels of MC in rats following intravenous injection of 8.8 mg/kg (open circles), 26 mg/kg (closed circles), or 47 mg/kg (crosses) of MC dissolved in rat plasma. MC was dissolved in heparinized plasma at concentrations calculated to give the indicated doses while maintaining a constant vehicle volume of 1 ml plasma/kg of body weight. Values predicted by computer simulations are shown as a solid line(s).

SOURCE: Reitz et al. (1988).

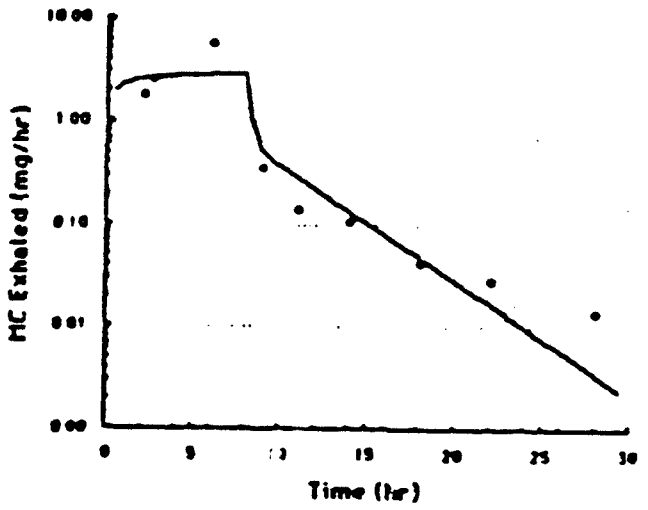


Figure III-2. Rate of elimination of [14C]MC in exhaled air (mg equivalents of MC/hr) during and following ad libitum exposure of rats to a solution of [^{14}C]MC in drinking water. The average water consumption of the rats (net weight = 250 g) during the 8 hr in which they had accepted the treated water was 8.1±3.8 ml, corresponding to an average dose of 116 mg/kg. Values predicted by computer simulations are shown as solid line(s).

SOURCE: Reitz et al. (1988).

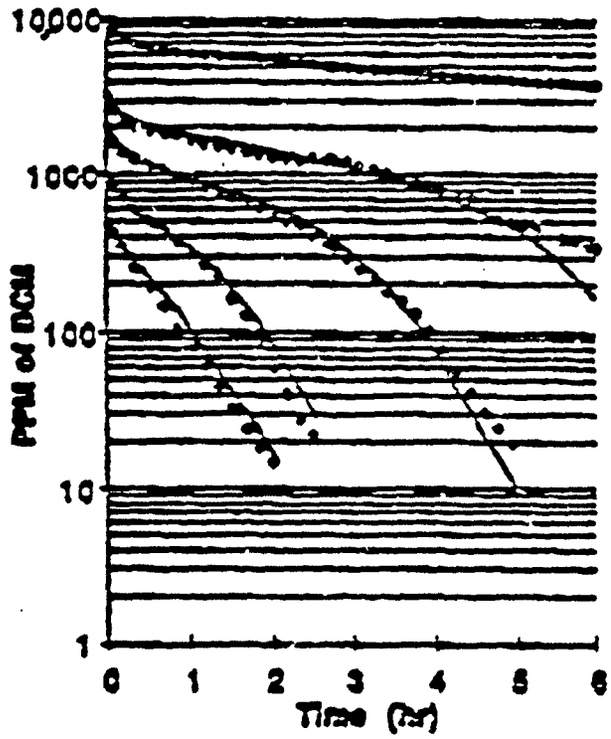


Figure III-3. Gas uptake studies utilized to estimate the kinetic constants for the MFO and GSH pathways in B6C3F1 mice. Data are ppm of DCM in the chamber atmosphere as a function of time. Experimental data are shown as symbols, while the computer simulation is presented as a solid line.

SOURCE: Andersen (1989).

low concentrations. The number of data points is unusually large and consequently permits a more precise estimation of kinetic parameters and better fit of the data. Figure III-4 shows a useful diagnostic for nonlinear or dose-dependent kinetics; it shows the estimated area under the plasma concentration vs. time curve (AUC) for trichloroethylene (TCE) (Withey et al., 1983). It is clear that AUC is not proportional to the TCE dose (log AUC vs. log dose is not a straight line with slope 1).

2. Model Fitting

The simplest situation is that of a first-order kinetic model during elimination, in which the concentration of the toxicant, $C(t_i)$, at time t_i, can be represented as combination of exponential terms,

$$C(t_i) = A_1 \exp(-a_1 t_i) + A_2 \exp(-a_2 t_i) + \ldots + A_n \exp(-a_n t_i)$$

The exponential time constants ($a_1 \ldots a_n$) should be the same for every measured compartment, although the coefficients of the distinctive components of the elimination curve (A_1, etc.) are not. The number, n, of kinetically distinct components can be estimated as the number of distinct straight-line segments on a semi-logarithmic plot of $\ln[C(t_i)]$ vs. t_i. Many computer programs for optimal estimation of the parameters A and a are available. When the data are adequate, it is even possible to estimate the parameters of the compartmental models that best fit the $C(t_i)$ vs. t_i curve. The best known of the available computer programs are NONLIN, SAAM, SIMUSOLV, and SCoP. For many toxicants, such as lead, a first-order pharmacokinetic model with several widely separated

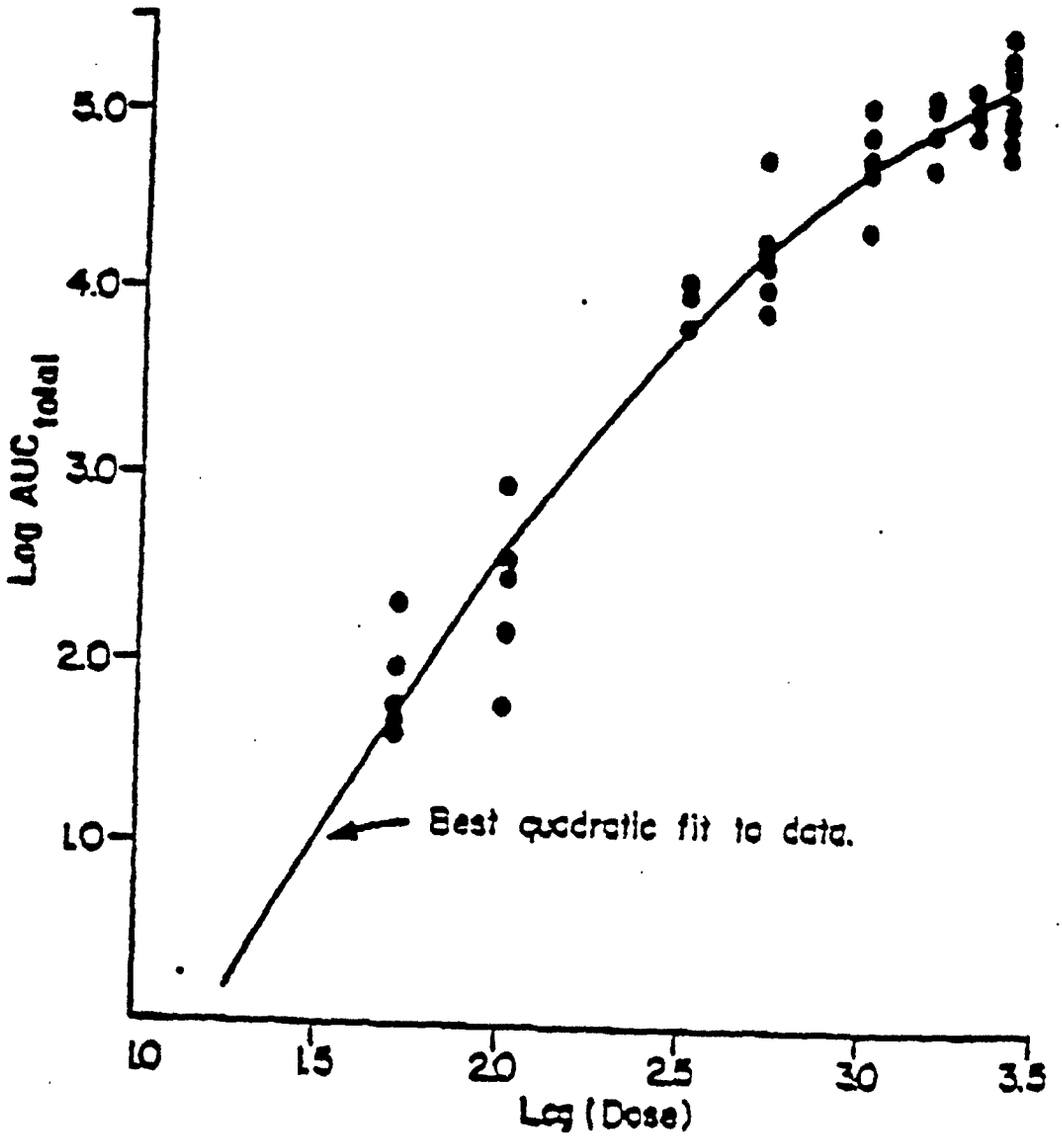


Figure III-4. Log (total area under curve) for animals dosed with trichloroethylene in oil plotted against log (dose), with quadratic line of best fit.

SOURCE: Withey et al. (1983).

components provides a very good description of the data. For many other toxicants of interest, this model fails because of dose-dependent kinetics. Nonlinear kinetic models, models with dose-dependent kinetics, and physiologically based models with adjustable parameters could be fitted with the same programs.

3. Dose Characterization

The characterization of dose is important. For chemicals that are administered intravenously or intraperitoneally, the chemical injected is almost immediately biologically available. Chemicals taken in through the gut (by gavage, or added to diet or drinking water) can be delayed for hours or even days. The effective long-term exposure to drinking water contaminants is often taken as continuous, even when episodic. This is not as satisfactory for chemicals with noncancer endpoints, since the pharmacokinetic indicator governing toxicity is more likely related to peak concentration rather than to an accumulation of damage. The justification for using "external concentration times duration of exposure" as a measure of applied dose is that, after a long period of exposure, the area under the plasma concentration vs. time curve (AUC) is approximately proportional to concentration times duration. AUC is generally regarded as the best index of total delivered dose or internal exposure.

4. Dose-Dependent Pharmacokinetics

Dose-dependent pharmacckinetic processes are commonly found in organic toxicants, chiefly due to metabolism of the parent compound by one or more mechanisms. In first-order kinetic models, the kinetic rate

coefficients do not depend on dose, so that the elimination times are independent of applied dose, and the steady-state tissue concentrations and AUC for constant continuous exposure are proportional to the concentration in the environment. If time scales are dose-dependent, or if the steady-state concentration or AUC is not proportional to the concentration, then some nonlinear or non-first-order process must be operating. If different tissues have different concentration ratios for steady-state conditions, then some non-first-order or nonlinear process must be operating. We can thus diagnose the presence of dose-dependent kinetic processes (which imply dose-dependent elimination times) without doing a kinetic study. Identification of mechanisms and estimation of parameters for elimination times require a kinetic study.

5. Cross-Species Extrapolation

The last requirement is that there be a rational biological basis for extrapolating estimates of elimination times to humans from the animal experimental studies. For many chemicals, kinetic processes at low concentrations are approximately first-order and can be extrapolated from animals to humans by allometric scaling, i.e., multiplying the parameter estimated from animal studies by the ratio of animal to human body weights raised to some exponent (Mordenti, 1986). For "surface area" scaling that has been used by some offices in EPA, the exponent is 1/3, although an empirical value of about 0.25 is often preferred in pharmaceutical studies. For example, if some substance has an elimination time scale of 1 day for a study with 300-g adult rats, the comparable estimate for a 70-kg human is

$$1 \text{ day} * (70 \text{ kg}/0.3 \text{ kg})^{1/3} = 6.16 \text{ days (surface scaling)}$$

$$1 \text{ day} * (70 \text{ kg}/0.3 \text{ kg})^{0.25} = 3.91 \text{ days (empirical)}$$

One problem is that animal toxicology studies are often carried out at high concentrations so as to provide an observable increase in toxicity. High concentrations could saturate dose-dependent processes, either those that detoxify a toxic parent compound or those that convert a nontoxic parent compound into a toxic metabolite, with a substantial change in apparent elimination time of the proximate toxicant. Extrapolation to much lower doses of interest in human risk assessment, where kinetic processes are believed to be approximately first-order, would not be justified. Reliable data on metabolic pathways and their parameters are needed for extrapolation.

B. Pharmacokinetic Considerations in Evaluating Studies

1. Absorption

One purpose of these analyses is to relate internal exposure, C(ti), to external exposure patterns. For example, it is often necessary to make inferences about routes of exposure other than those used in the experiments. This is particularly important when absorption is kinetically nonlinear, e.g., when one pathway is saturable at high concentrations. As previously mentioned (section II.B), one example is the gastrointestinal absorption of lead, which is known to be much higher when taken between meals rather than with meals (Rabinowitz et al., 1980). One possible explanation is that some active gut transport mechanism (e.g., carrier

proteins) is saturated when lead concentrations in the gut are high (Aungst and Fung, 1981). This may be particularly relevant when large quantities of other metals such as iron are also competing for the same carrier. Animal feeding studies in which there is a taste aversion to higher concentrations of the toxicant may also be difficult to interpret.

Absorption of organic drinking water contaminants may be complicated and hard to describe quantitatively. It may be difficult to estimate the true percentage absorption, since biliary excretion and enterohepatic cycling are important biological processes in many animals. Metabolites of chemicals such as 2,4-dinitrotoluene that are eliminated in the bile and into the gut are hydrolyzed and reduced by intestinal microflora, then reabsorbed from the gut and oxidized from the liver.

Absorption of volatile organics dissolved in water may not be limited to gut absorption. For example, small quantities of 1,1,1-trichloroethane, trichloroethylene, or tetrachloroethylene dissolved in water may be released during baths or showers, allowing the water contaminants to be absorbed via the inhalation or dermal route. These other absorption pathways may also be nonlinear. Formaldehyde gas is very rapidly metabolized in the human nasal mucosa and respiratory tract, greatly reducing its internal absorption into blood at low doses. Adequacy of data to assess such issues will be considered.

2. Distribution to Peripheral Tissue

If the concentration, C(ti), in blood or plasma is plotted logarithmically as a function of time, ti, after the toxicant exposure is

reduced or eliminated, it will often be approximated as a sequence of straight lines with negative slopes. This is exactly what would be predicted if the pharmacokinetics of the system could be described by a set of n ordinary first-order differential equations for concentrations in n kinetically distinct pools or compartments. The compartments in the pharmacokinetic description may or may not coincide with distinct organs or tissues. The general form of $C(t_i)$ in a washout study would then be specified as the sum of n exponential terms, with time constants $a_1 > a_2 > \ldots > a_n > 0$,

$$C(t_i) = A_1 \exp(-a_1 t_i) + A_2 \exp(-a_2 t_i) + \ldots + A_n \exp(-a_n t_i)$$

Elimination curves for the central blood or plasma compartment are log-convex, since all A_j's > 0. It is often easy to "peel" two or three exponential terms by hand, starting with the largest values of t_i, and fitting a straight line to a subset of the $\ln[\, C(t_i)\,]$ vs. t_i data points, with slope, $-a_n$, and intercept, $\ln(A_n)$. All of the other data points must fall above the straight line, which is subtracted from these values, and the process is repeated. Three components are typical for most metals (Sugita, 1978). The more realistic pharmacokinetic models may often have n = 5 to 10 compartments, but it is very difficult to discriminate more than three from elimination data with measurement variability typical of plasma concentration data (often 10% to 25% coefficient of variation). Concentration data in peripheral tissues corresponding to some of the mathematical compartments are needed to identify the model. If exponential functions are fitted to other tissue concentration data, they

must have the same set of time constants for the mean residence time in a component of the elimination curve (T_1, T_2 ... T_n) as the plasma curve.

The fastest component has a time scale, $T_1 = 1/a_1$, usually hours to days. The next fastest component has time scale, $T_2 = 1/a_2 > T_1$, and so on. The longest time scale, T_n, is usually of the order of years for toxicants that are sequestered in the bones (lead, barium), in certain soft tissues such as the kidney (cadmium), and in the adipose tissue (DDT, hexachlorobenzene). If a very high tissue burden, $C(t_i) > M$, has accumulated, and if T_n is very large and $A_n > L$, then the elimination time, t_e, may exceed the human lifespan. We will later see how the large pool of lead in bone in lead-exposed workers can maintain elevated levels of blood lead for decades after the workers have left the source of lead exposure. If two or three components are estimated from the elimination data, they are often labeled as the "alpha" (fastest), "beta" (intermediate), and "gamma" (slowest) components.

The assumption of first-order linear kinetics is not adequate for organic compounds, whose primary fate is to be removed by metabolism or biotransformation. In some cases, the parent compound is the primary toxicant (e.g., ethanol) rather than the metabolite (acetaldehyde) (Blakely and Scott, 1984a,b). In other cases, the parent compound is transformed into a much more toxic metabolite (e.g., the industrial solvent 2-methoxyethanol is metabolized into the reproductive and developmental toxicant 2-methoxy acetic acid). The removal of a parent compound by a Michaelis-Menten-type process will generally produce a log-concave washout curve at values of $C(t_i)$ comparable to and greater than the Michaelis-Menten concentration, K_m, of the substrate. Other nonlinear

kinetic processes include limited binding sites available for the toxicant, or the rapid induction of binding proteins for the toxicant as a result of toxicant exposure. Kinetic nonlinearities may be detected in several ways: (1) Concentrations in different tissues will reach equilibrium after a long period of constant exposure, as in chronic feeding studies. If all kinetic processes are linear, then the ratio of concentrations in different tissues will be the same whatever the exposure concentration. If not, some nonlinear process applies. (2) In linear kinetics, the ratio of equilibrium tissue concentration to constant external exposure concentration is the same for all exposure concentrations, which is not true in nonlinear processes. (3) The area under the plasma concentration vs. time curve is known as AUC. In linear kinetics, AUC(t_i) for large times, t_i, is approximately equal to the total external exposure dose, C(t_i). These dose assessments can often be made even in nonkinetic data sets with only a single time point, or in cross-sectional studies of populations in equilibrium exposure conditions, if the tissue concentration measurements are made at different doses or exposure concentrations. That is, kinetic nonlinearities can be recognized even when not fully identified.

In evaluating studies for estimation of t_e, we should ask the following questions:

1. Did the study have the right time points to identify the fastest ("alpha"), intermediate ("beta"), and slowest ("gamma") components?

2. Was the study administered at several external doses or dose

rates so as to facilitate identification of kinetic nonlinearities?

3. Did the exposure last long enough to create measurable tissue burdens in peripheral compartments, such that recycling from tissue to plasma could be estimated?

4. Are there data in peripheral tissues that allow identification of pharmacokinetic compartments with physiological compartments?

5. Was the experiment designed so as to actually observe the kinetic response of the system (i.e., both elimination and uptake data)?

3. Excretion

Sometimes it is difficult to obtain accurate plasma, blood, or tissue concentration data. Much can be learned from a kinetic study of excreta, provided that all routes of elimination for the parent compound and its metabolites have been identified. The exponential time scales in the excreta should be the same as in the plasma and tissues, and reasonable inferences about washout from the central plasma or blood pool can sometimes be made based on kinetics of parent compound and its metabolites in urine. The adequacy of excreta concentration kinetics for inferences about elimination time should also be considered by the criteria identified above, as if concentrations in urine, feces, hair, nails, sweat, etc., were the same as those in other compartments.

4. Effects of Toxicity on Pharmacokinetics

The definition of a toxicant requires that, at some concentrations, the toxic insult changes the biological system exposed to it. This feature is not commonly included in pharmacokinetic models for toxicants. Physiologically based pharmacokinetic models (PBPK) are more completely parameterized in terms of functional description of systemic changes. The more common responses include the following:

1. There may be changes in toxicant absorption or consumption per unit of exposure. For example, irritating air pollutants, or those with narcotic effects, may cause reduction in ventilation rate. This will effectively reduce the absorption of toxicant, unless ventilation rate is an explicitly a function of some index of external or internal concentration. In animal experiments in which the toxicant is delivered in food or in drinking water, the effects of higher concentration on the animals' consumption of food and water (i.e., on effective dose rate) are commonly monitored. This is not usually done in human exposure studies. In many observational studies, dose is characterized by the concentration of the toxicant in air or water, but changes in the amount of air inhaled or amount of water consumed may not be measured.

2. Prolonged exposure may increase/decrease the size of an organ such as the kidney or liver. Organ concentrations should be adjusted for changes in tissue volume and in cross-sectional area available for toxicant transport. We found that adjusting parameters of lead transport between plasma and red blood cells for mean erythrocyte surface area greatly improved the goodness of fit and the interpretability of a model

relating blood lead to erythrocyte protoporphyrin levels (Marcus and Schwartz, 1987). A similar adjustment for changes in blood flow could be made (but usually is not).

3. There may be changes in the efficiency of toxicant elimination processes after exposure, directly affecting t_e.

4. Prolonged exposure may induce the formation of substances that bind or sequester the toxicant, reducing acute toxicity but increasing a potentially mobilizable reservoir. The direct implication for estimation of elimination time is that there may be no changes in the short-term (nonsequestered) components of elimination but considerable increase in the longer term t_e (i.e., the "gamma" component).

5. Interactions with Other Environmental Factors

Many environmental factors may affect the pharmacokinetic processes for the toxicant. These include the age, gender, and state of health of the experimental animals or clinical subjects. There are also substantial differences in the way different strains of laboratory animals handle certain toxicants. Genetic differences among different groups of humans may be important. There is known genetic polymorphism in the inhibition of heme-synthesizing enzymes such as delta-aminolevulinic acid dehydratase (ALAD, now usually called porphobilinogen synthetase) by lead, or inhibition of uroporphyrinogen dehydratase by the insecticides Lindane and heptachlor and by the fungicide hexachlorobenzene; this

process produces observable time patterns of change in biological markers of hematotoxicity. These differences require that the strain of experimental animal or subpopulation of humans for whom te is estimated must be carefully identified.

Elimination of toxicants is often affected by exposure to or consumption of other chemicals. The absorption, distribution and storage, and elimination of many toxic metals such as lead, cadmium, and mercury, are known to be sensitive to levels of essential elements including one or more of the following: calcium, iron, zinc, and phosphorus. Nutritional status is also important in determining the rate of release of sequestered toxicants. During periods of calcium deficiency, such as during pregnancy and during the healing of bone fractures, considerable quantities of bone material including stored toxicants such as lead will be released to systemic circulation. During periods of starvation, toxicants sequestered in adipose tissue (many insecticides such as DDT) may be released.

Other toxicants also affect elimination kinetics. For example, many humans absorb significant quantities of ethyl alcohol (ethanol), with alcohol levels much larger than the K_m for the alcohol dehydrogenase metabolic pathway. Because ethanol is present in large quantities and has a high affinity for ADH, this pathway is not readily available to convert the solvent 2-methoxyethanol into 2-methoxyacetaldehyde, and subsequently by the ALDH pathway to the reproductive toxicant 2-methoxy acetic acid (MAA). Production of MAA, the proximate toxicant, is delayed. Thus, ethanol consumption is protective against reproductive toxicity by MAA (we do not recommend this as a protective strategy), in a manner in which the effects on t_e have not yet been calculated.

6. Interindividual Differences

Hazard assessments should also take into account differences in elimination kinetics among individuals. Differences among genetically inbred strains of laboratory animals under well-controlled experimental conditions are generally much smaller than in a genetically diverse human population with unknown differences in conditions of exposure and other environmental covariates. Single-subject kinetic data are clearly preferable. The common practice of fitting kinetic models to averages of tissue concentrations in a sample of subjects with identical exposures is less desirable, since it can be shown that the average of the kinetic parameters of the individuals is not equal to the kinetic parameter estimated from the average of the concentrations at different times. This is not an important problem if the individuals are highly homogeneous with respect to elimination times, but it could be important if there is much interindividual variability. There is, of course, no alternative if the data are obtained by autopsy. Where individual subject data are available, it would be desirable to estimate the variability in elimination times.

IV. PHARMACOKINETIC MODELS FOR THE ELIMINATION TIME OF SPECIFIC TOXICANTS FROM THE HUMAN BODY

Toxic substances absorbed by humans, and the metabolites formed in the body thereafter, are never completely removed from the body (in principle). Most substances are largely removed or excreted over time by one or more processes, such as urinary or fecal elimination, exhalation, perspiration, or shedding of hair, skin, nails, and teeth. The toxicant or toxic metabolite may be regarded as "eliminated" if it is biologically transformed or metabolized into nontoxic substances. Some toxicants are neither completely eliminated nor metabolized, but may be stored in inactive but potentially mobilizable pools such as bone or adipose tissue. The potential for toxicity is usually characterized by the internal body concentration, $C(t_i)$, at time, t_i, or by a cumulative biologically effective dose, $D(t_i)$, at time, t_i. The time, t_i, is important because the duration and time pattern of exposure to the parent toxicant may strongly affect $C(t_i)$ or $D(t_i)$.

A regulatory criterion for internal concentration or dose in humans is usually established on the basis of possible health effects. For example, it might be determined that if the concentration, $C(t_i)$, of some developmental toxicant could be kept less than 100 micrograms (μg) per liter of whole blood, then the risk of neurobehavioral deficits in children is negligible. This is currently the criterion level being considered for blood lead by U.S. EPA (1989a). We also note that blood lead

concentrations above 150 µg/l may carry an unacceptable risk of neurobehavioral deficits for the more vulnerable members of the population.

On the other hand, the toxicological evidence may suggest that the effects of the toxicant or its toxic metabolites are cumulative. In that case, the appropriate criterion is that the concentration in some storage compartment (e.g., tooth lead or bone lead concentrations, measured non-invasively using shed teeth or X-ray fluorescence, or adipose tissue concentration of some persistent pesticides) be less than a cumulative dose specified level, L'. If the criterion, $C(t_i) < L'$, is satisfied, then the cumulative biologically effective dose $D(t_i) < L't_i = L$, whatever the pattern of exposure.

The time to elimination of a toxicant or its metabolites can then always be calculated as the time to reduce some minimum unacceptable internal concentration, $C(t_i) = M$, to a toxicologically acceptable level of concern, L (or L' for a cumulative dose specified level). This can always be calculated from the mathematical pharmacokinetic model for the toxicant or its metabolites. The criteria values L and M may depend on observed NOAEL or LOAEL values from human clinical studies, or from animal toxicology experiments, but need not do so. In the following sections, we describe the pharmacokinetic approaches for estimating the elimination times of lead, styrene, chlordane, trichloroethane, and 1,4- dioxane. These chemicals were selected because they have a good pharmacokinetics data base, a long or short biological half-life, and relatively high Health Advisory values. We will review the adequacy of available data to establish such models, and we will then evaluate some of the models that

have been used to describe the data. If either the data or the mathematical models are inadequate to estimate a meaningful te for humans, we will suggest where additional studies could be most usefully made.

Pharmacokinetic principles are playing an increasingly important role in environmental regulation. A good review of some new approaches to biological exposure indices is given by Leung and Paustenbach (1988).

A. Lead

1. Introduction

There are abundant data in the literature to develop one- and multicompartmental models of lead in humans and in nonhuman primates, as well as in dogs and in several rodent species. A large number of multicompartmental models for lead kinetics in humans have been developed (Batschelet et al., 1979; Bert et al., 1988; Cawley et al., 1979; Chamberlain, 1985; Colombo, 1985; Harley and Kneip, 1985; Kneip et al., 1983; Marcus, 1985a,b,c,d; O'Flaherty et al., 1982; Rabinowitz, 1973; Rabinowitz et al., 1974, 1976, 1977; Schutz et al., 1987a,b; Steenhout, 1982, 1985, 1987; Steenhout and Pourtois, 1981). The extensive scientific studies on lead reflect great public concern about its widespread use and the relatively small margin of safety to protect public health.

In view of the large amount of data on the biokinetics of lead in humans, descriptive models of the multicompartmental type have proven very adequate. One-compartment models have proven inadequate, even descriptively, for exposure periods exceeding a month or two. There has

been relatively little interest in extrapolation from animal studies using PBPK models. The greatest potential use of PBPK models arises where human data are least adequate, during early growth and development (O'Flaherty, 1989) and for fetal exposure by transplacental transfer (Marcus et al., 1988). PBPK models for humans have not yet been developed from animal models.

An overall conceptual model for the biokinetics of lead is shown in Figure IV-1. It is important to recognize that the internal biokinetics of lead appear to be the same regardless of the route of administration. Since lead is not biologically transformed, no metabolic processes need be considered. However, several pharmacokinetically nonlinear processes appear to be important even at moderately elevated levels of human lead exposure (blood lead above 30 μg Pb/100 ml whole blood). The first is that at least some gastrointestinal absorption pathways appear to be partially saturable (Aungst and Fung, 1981), but the mechanisms for this process and its sensitivity to other metallic and nonmetallic components of human diet and drinking water are unknown. A second nonlinear process is that lead concentrations in human whole blood and blood plasma are not strictly proportional to each other at moderately high levels. The apparent increase of the plasma lead/blood lead ratio shown in Figure IV - 2 suggests that there may be a limited lead-binding capacity of the red blood cells or erythrocytes (Marcus, 1985b; Manton and Cook, 1984).

Even at tracer concentrations, the decrease of lead levels with time shows a second "beta" component 90-120 days after the beginning of the elimination phase. This occurs at about day 270 for Subject A (Figure IV-3), at about day 170 for Subject D (Figure IV-4), but was not observed

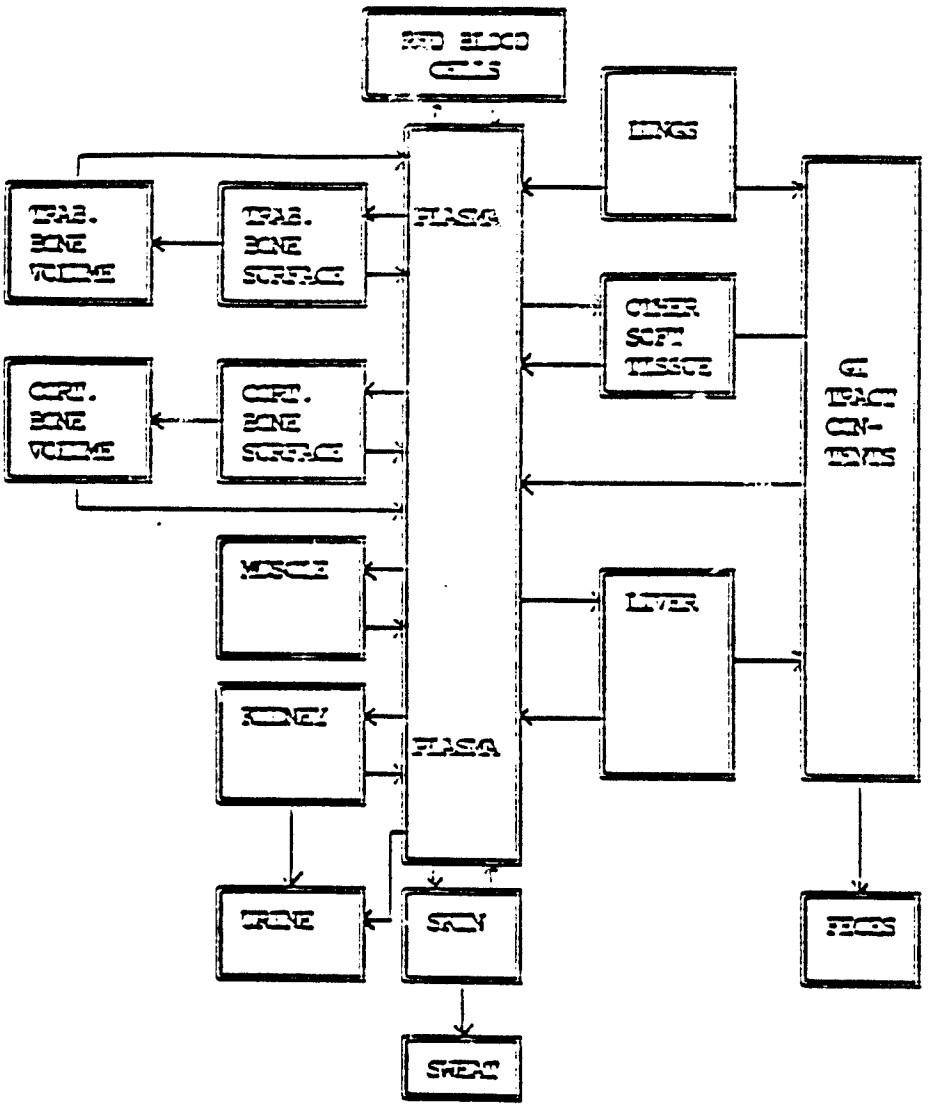


Figure IV-1. Framework for biokinetics models for lead.

SOURCE: Cristy et al. (1986).

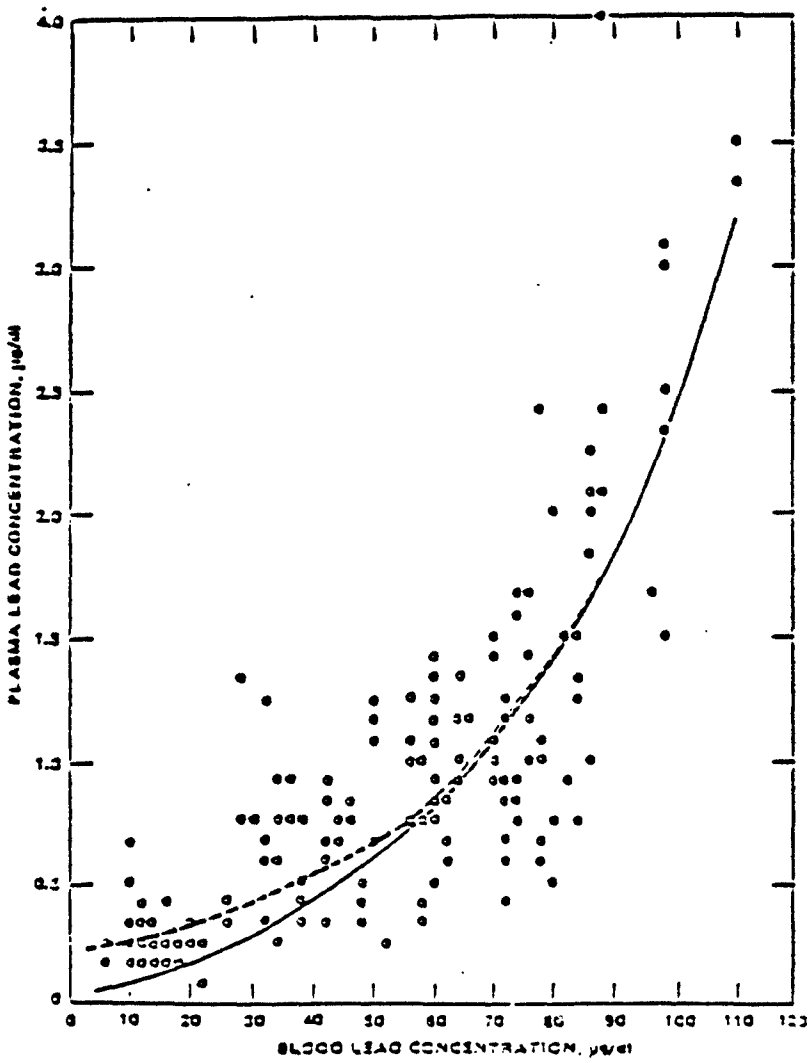


Figure IV-2. Nonlinear kinetic model fitted to data from 189 samples from 103 workers, as reported in deSilva (1981a,b). Solid curve is no-intercept model, and dashed curve is model with intercept 0.24 µg/dl.

SOURCE: Marcus (1985b).

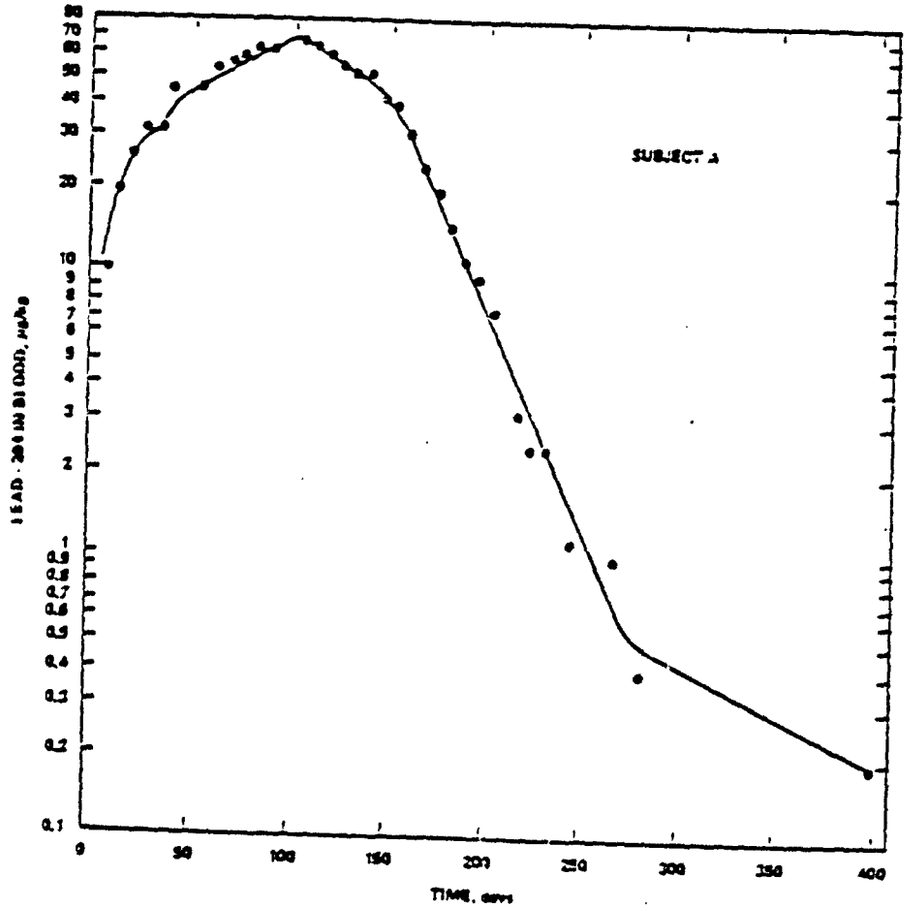


Figure IV-3. Observed and predicted blood-lead (^{204}Pb) level in Subject A.

SOURCE: Marcus (1985b).

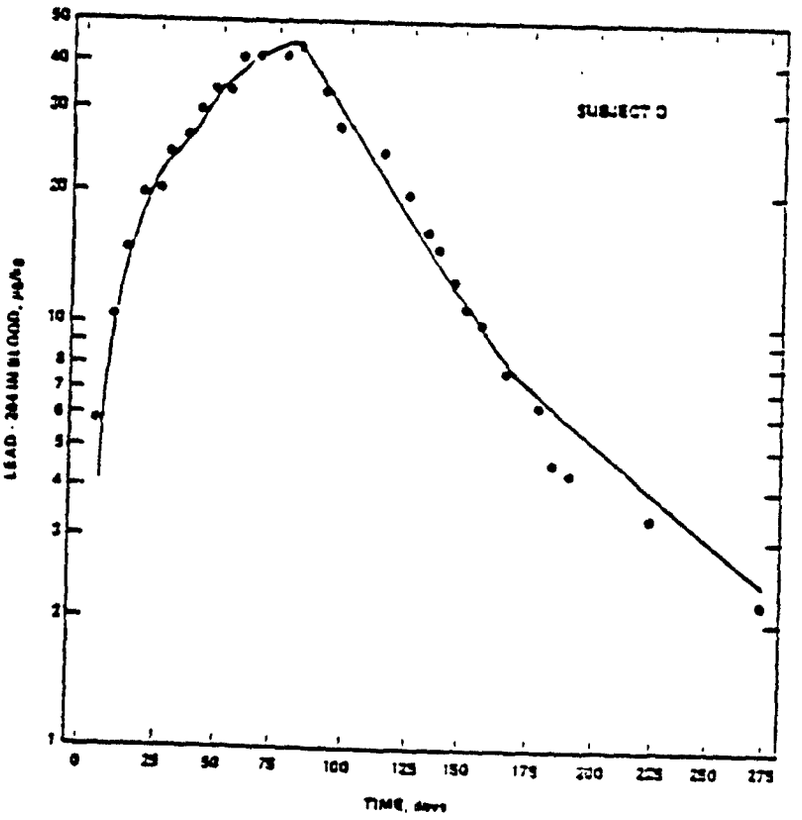


Figure IV-4. Observed and predicted blood-lead (^{204}Pb) level in Subject D.

SOURCE: Marcus (1985b).

even 50 to 60 days after cessation of exposure for Subject E (Figure IV-5) and Subject B (Figure IV-6). Figures IV-3 to IV-6 and Table IV-3 refer to the same subjects (A, B, D, and E). All subjects received a nonradioactive stable lead isotope tracer in known doses with four meals each day at various times. The usual tracer was ^{204}Pb as lead nitrate, but some subjects also received ^{204}Pb The results presented here are those for ^{204}Pb, but total blood lead levels and other isotopic tracers were also used to estimate the biokinetics parameters. For Subject A, ^{204}Pb was ingested from days 0 to 104 at a rate of 204 µg/day. For Subject B, ^{204}Pb was ingested at a rate of 185 µg/day. For Subject D, 105 µg/day was ingested for 83 days. For Subject E, ^{207}Pb and/or ^{204}Pb was ingested at a rate of 99 µg/day on days 1-2 and on days 40-50. The absence of ^{204}Pb intake at other times allowed detailed examination of elimination curves. These were almost exactly representable as one or two straight-line segments on semilog plots during the elimination phases. The elimination phases started at day 150 for Subject A, day 122 for Subject B, day 84 for Subject D, and on days 3 and 51 for Subject E.

The half-lives for brief exposure shown in Table IV-1 are shorter than those observed for longer exposures in Table IV-2 and IV-3, since the longer half-lives probably represent a mixture of the fast "alpha" and slower "beta" components. The subjects in these short-term tracer studies have not had sufficient time to add large stores of lead to their skeletal tissues, so that the "beta" component may represent return of lead from soft tissues. For subjects with many years of lead exposure, the skeletal burdens of lead are very large (90-95% of the total body burden of lead), so that the very slow release of lead from skeleton to

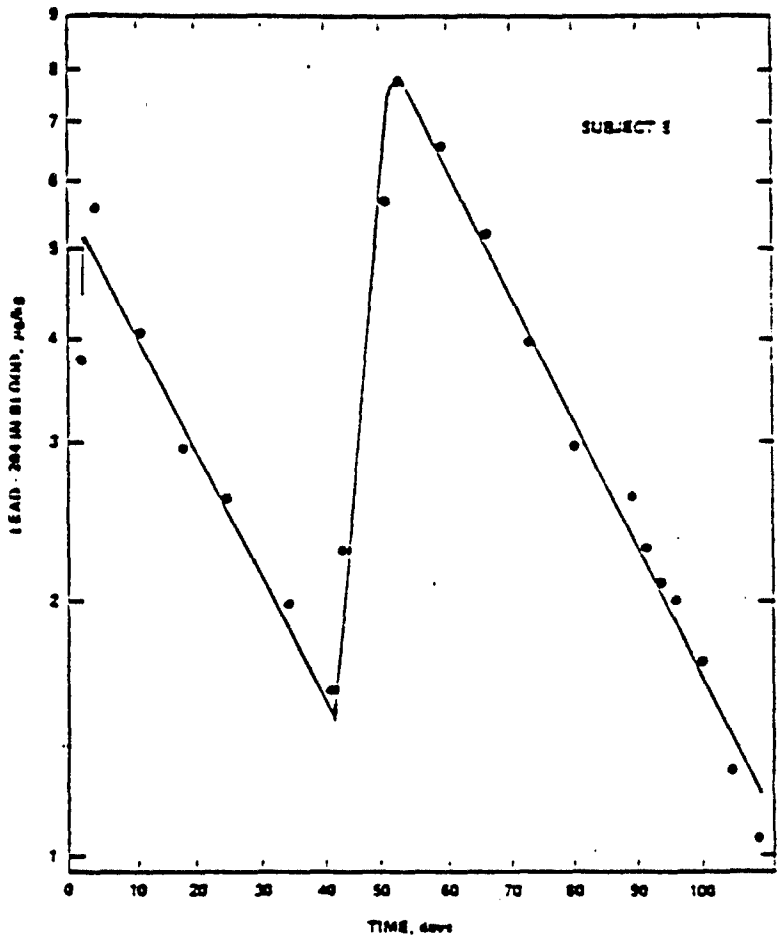


Figure IV-5. Observed and predicted blood-lead (^{204}Pb) level in Subject E.

SOURCE: Marcus (1985b).

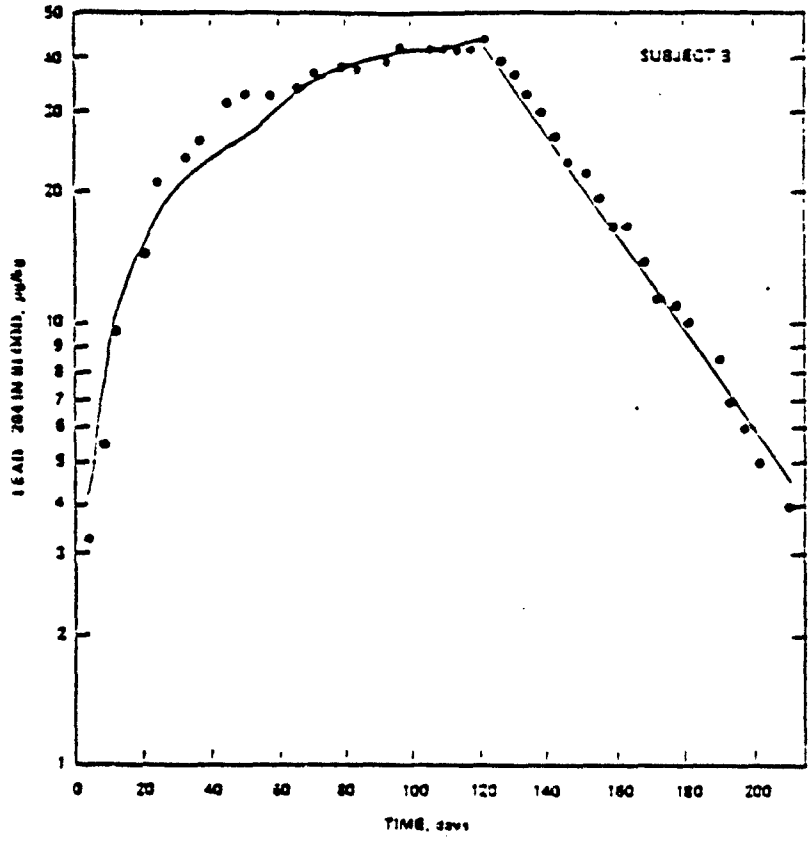


Figure IV-6. Observed and predicted blood-lead (^{204}Pb) level in Subject B.

SOURCE: Marcus (1985b).

Table IV-1. Biological Half-Lives of 203Pb in Blood Following Intravenous Saline Injection Compared With Other Modes of Intake

	Observed half-life in blood ($t_{1/2}$ in days)			
	Saline injection		All	All
Subject	1974	1977	inhalations[a]	ingestions[b]
ACC	-[c]	15.3	13.6 (3)	12.9 (2)
		15.7		
DN	22.0	20.9	20.6 (2)	22.3 (1)
		23.2		
MJH	14.9	17.4	16.1 (3)	14.0 (2)
ACW	-	21.6	-	-
PL	-	22.8	-	-
KFB	13.6	-	16.9 (1)	-
ANBS	-	13.9	-	-
Mean	18.3 ± 3.6 S.D.		16.4 ± 2.2	15.4 ± 6.0
		1.1 S.E.	0.7	3.6

[a]Subjects exposed to lead by one or more routes.

[b]Figures in brackets indicate number of experiments.

[c]No data.

SOURCE: Chamberlain et al. (1978).

Table IV-2. Experimental Mean Residence Time in Blood[a]

Group	Experiment 1	Experiment 2
Control[b]	34.6 ± 6.5 days (n = 6)	41.8 ± 9.2 days (n = 6)
Exposed[c]	40.8 ± 4.4 days (n = 14)	40.6 ± 3.6 days (n = 17)

[a]Mean blood residence time = $t_{1/2}/\ln(2)$.

[b]No known air lead exposure in either of the two experiments.

[c]Exposed to 3.2 μg/m^3 in experiment 1 and to 10.9 μg/m^3 in experiment 2.

SOURCE: U.S. EPA (1986), based on data from Griffin et al. (1975).

Table IV-3. Blood Residence Time in Five Subjects[a]

Subject	Distribution Volume (kg)	Estimated Blood Volume (kg)	Blood Residence time (days)
A	7.4 ± 0.6	4.9	34 ± 5
B	10.0 ± 0.8	6.3	40 ± 5
C	10.1 ± 1	6.3	37 ± 5
D	9.9 ± 1.2	4.6	40 ± 5
E	11.3 ± 1.4	4.6	27 ± 5

[a]Same subjects depicted in Figures IV-3 to IV-6. Mean residence time = $t_{1/2}/\ln(2)$.

SOURCE: Rabinowitz et al. (1976).nitrate or 207-Pb nitrate.

blood becomes a major source of blood lead (see Figures IV-7 and IV-8, from Christoffersen et al., 1986, and Skerfving et al., 1986). The estimated slow half-lives for active and retired lead workers is shown in Tables IV-4 and IV-5. The baseline lead level of 20 µg/dl represents all nonoccupational sources of lead exposure for these workers. The decrease of lead levels at the end of occupational exposure was decomposed into a short-term "alpha" component and a long-term "gamma" component that was added to the 20 µg/dl baseline. The baseline is not a "gamma" component. This "gamma" component becomes significant in assessing the lead burden of previously exposed children and adults, so that the one-compartment model should not be used to estimate body burden following exposure. The combination of fast and slow responses to increasing uptake is illustrated using the compartmental model of Batschelet et al. (1979) in Figure IV-9, and the combination of fast and slow responses to decreasing uptake is shown in Figure IV-10. It is clear that the short-term quasi-equilibrium achieved in a few months can differ from the true long-term steady state by 20-30%, which is not necessarily negligible in view of the very small safety margins for lead.

2. Biokinetics of Lead in Adult Males

Several of the human data sets have been very extensively analyzed. Perhaps the most useful for short-term kinetics is the stable lead isotope study performed at UCLA in the early 1970s (Rabinowitz, 1973; Rabinowitz et al., 1974, 1976). Dietary lead intakes of some relatively uncommon stable lead isotopes were carefully controlled for five adult male volunteers, and lead isotope levels were observed for up to 1 year. Their data have been extensively reanalyzed (Batschelet et al., 1979; Bert

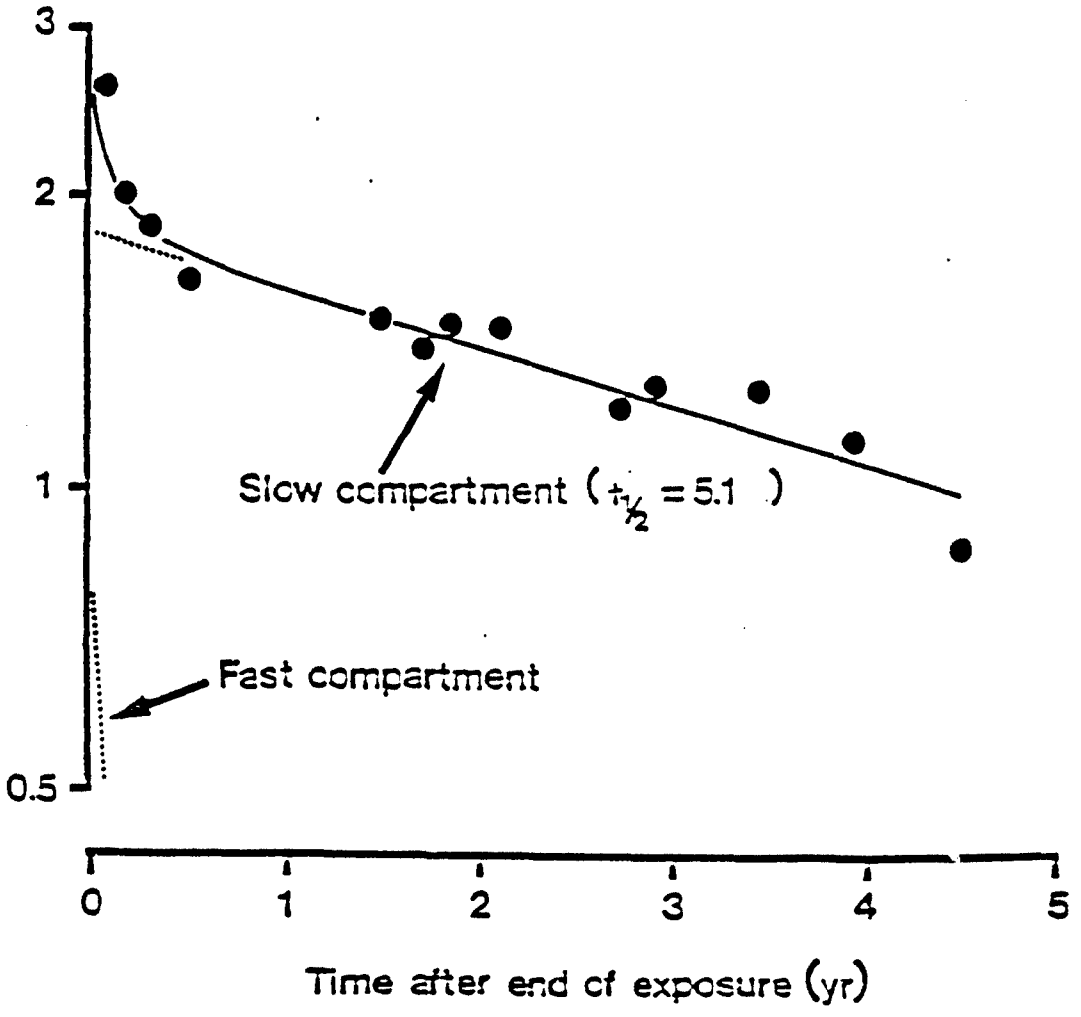


Figure IV-7. Blood-lead level on time after end of occupational lead exposure in a smelter worker (Subjects 1-6). A "background" level of 0.3 µmol/l has been subtracted from each Pb-B value. A two-compartment model was fitted to the Pb-B data. Half-time of the fast compartment was assumed to be 30 days. Half-time ($t_{1/2}$) of the slow compartment is given.

SOURCE: Christoffersson et al. (1986).

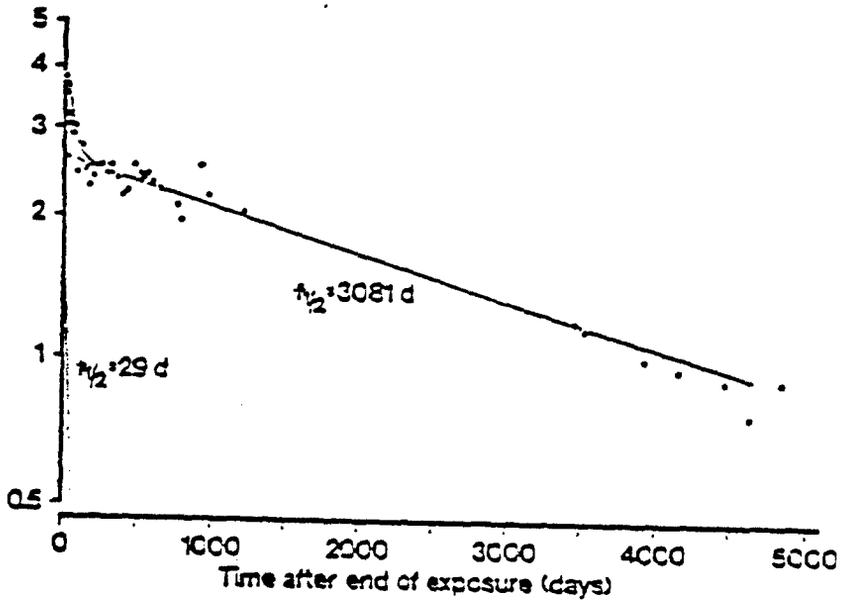


Figure IV-8. Decay of blood lead level (logarithmic) after end of exposure in an ex-lead worker. The "background" Pb-B (0.5 µmol/l) has been subtracted. Biological half-times ($t_{1/2}$) in the compartments are given.

SOURCE: Skerfving et al. (1986).

Table IV-4. Apparent Lead Half-Lives Calculated from Published Blood-Lead Levels Measured in Former Lead Workers[a]

Source	Individual or group measurement	Period of employment in lead industry (years)	Pb-B at Retirement or Removal (µg/dl)	Pb-B at Second Measurement (µg/dl)	Interval between retirement or removal and second measurement (Years)	Half-life (days)
Richer (1977)	group	>20	68.4 (mean)	55.8 (mean)	0.333	275
	group	<20	67.5 (mean)	47.1 (mean)	0.333	150
Ahlgren et al. (1976)	individual	17	68	43	2	680
	individual	23	65	41	4	1300
	individual	22	73	32	4	670
	individual	27	63	51	1	760
	individual	22	68	42	0.5	160
Chamberlain and Massey[b] (1972)	individual	11	1000[c]	450[c]	0.167	50

[a]All apparent half-lives were calculated by assuming a baseline lead level of 20 µg/dl and a one-compartment model.

[b]A single brief exposure; relatively little lead was added to the bones and soft tissue. Consequently the 50-day half-life is probably just an alpha component.

[c]Approximate.

SOURCE: O'Flaherty et al. (1982).

Table IV-5. Kinetics of the Decrease of Lead in Bone After the End of the Occupational Exposure of 23 Ex-Lead Workers Observed for More Than 1 Year

				Two Compartment Model			
				Fast Compartment		Slow Compartment	
Subject[a]	Age[b] (Years)	Exposure Time (Years)	Observation Time (Years)	t1/2 (Days)[d]	Y(1) (u mol/l)	t1/2 (Years)	Y(2) (u mol/l)
101[c]	44	45	2.9	30[b]	0.0	3.7	1.9
102	60	5	15.0	29	1.4	8.4	2.6
103	49	10	5.1	39	3.0	4.2	2.2
104	54	35	13.0	30	1.4	2.3	0.7
105	41	3	12.9	30	0.8	5.6	1.9
106	48	8	12.9	30	1.0	4.6	1.6
107	54	34	18.0	30	1.1	3.5	2.0
108	30	7	12.9	30	1.2	4.6	2.2
109	59	27	12.9	30	1.0	5.1	1.2
110	56	26	12.9	30	1.7	7.6	1.8
111	65	45	12.8	30	1.0	9.4	2.0
112	51	33	12.8	30	0.5	5.8	2.3
113	66	44	11.2	30	0.5	5.6	2.3
114	31	4	10.4	30	0.2	0.8	2.0
115	63	45	9.4	30	0.3	3.9	1.6
116	67	10	13.2	30	1.4	8.7	2.5
117[c]	59	27	4.2	30	0.1	18.0	1.6
118	58	22	4.9	30	0.4	6.5	1.2
119	65	30	4.6	30	0.8	4.7	1.8
120	65	33	4.6	30	0.6	9.5	1.3
121	65	14	4.3	30	0.4	4.3	1.0
122	61	24	3.6	30	4.8	0.0	1.4
123	65	38	1.7	7	0.3	27.0	1.5

t1/2(1) = Half-time of fast compartment; t1/2(2) = Half-time of slow compartment;

Y(1) = Y intercept for the fast compartment; Y(2) = Y intercept for the slow compartment.

[a]Subject 101 was a cast bronze founder; Subject 102, a spray painter; Subjects 103-115, storage battery workers; Subject 116, a wire lead coater; and Subjects 117-123, smeltery workers.

[b]At the end of exposure.

[c]Subjects 101 and 117 are identical with Subjects 201 and 217, respectively, in Table IV-6.

[d]When fewer than four samples were obtained during the first 2 months after the end of exposure, the t1/2(1) was assumed to be 30 days.

SOURCE: Schutz et al. (1988).

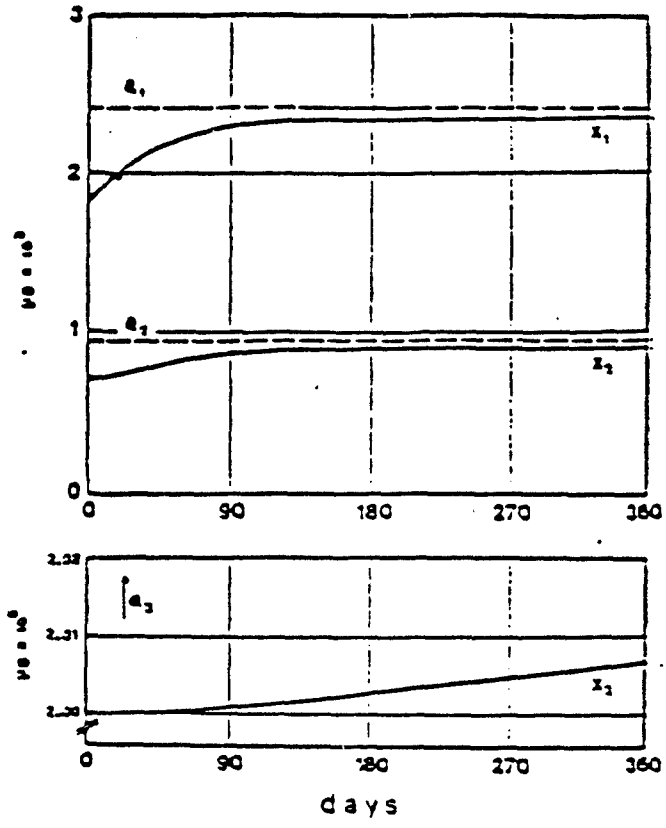


Figure IV-9. Dynamics of lead in an individual if the daily lead uptake from the air or water increases from 49 µg/d to 98 µg/d abruptly at time zero. Here, the amount of lead is x_1 in blood, x_2 in soft tissues, and x_3 in bones. Whereas x_1 and x_2 approach the limiting values e_1 and e_2 within a fraction of a year, it takes many years for x_3 to come close to e_3.

SOURCE: Batschelet et al. (1979).

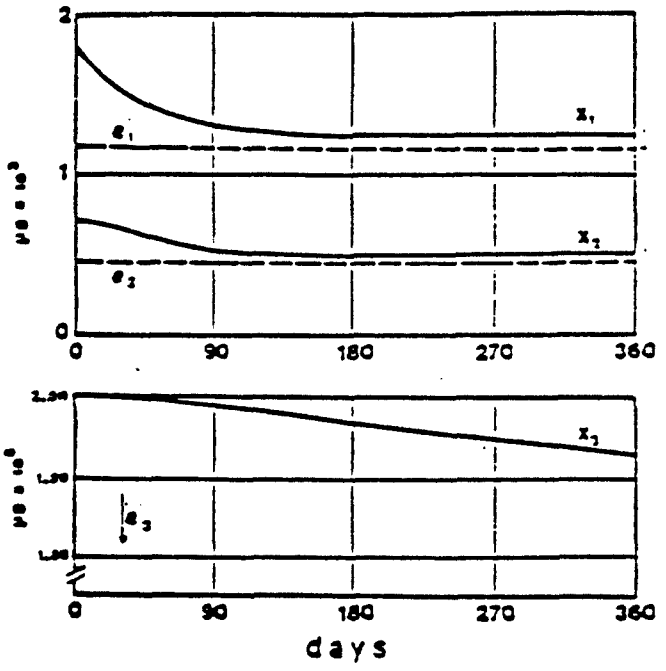


Figure IV-10. Dynamics of lead in an individual when the lead pollution of the air or water disappears abruptly at time zero. The lead in blood (x_1) and in soft tissues (x_2) adjusts to the new situation within a few months, but the lead content of the skeleton (x_3) decreases very slowly.

SOURCE: Batschelet et al. (1979).

et al., 1988; Chamberlain, 1985; Chamberlain et al., 1978; Mallon, 1983; Marcus, 1985b; O'Flaherty et al., 1982; U.S. EPA, 1986). The estimated mean residence time in blood from these studies is 27 to 40 days (S.E. = 5 days) in the five adult male subjects. This corresponds to the component T_1 in the elimination curve. A second slower component is also detectable in the data for two subjects, corresponding to T_2 = 150 days for Subject A and 100 days for Subject D. The bone lead retention was so long that it could only be inferred from balance considerations as about equal to 10,000 days (27 years).

A second widely used data set is based on adult male prisoners (Griffin et al., 1975) exposed to 3.2 or 10.9 μg Pb per cubic meter of air for periods up to 4 months. Several one- and two-compartment models have been fitted to these data (Bert et al., 1988; Chamberlain et al., 1978; O'Flaherty et al., 1982; U.S. EPA, 1986). The EPA estimates average T_1 = 41 days, but with a large range of variability (S.D. = 4 days).

A third source of useful information comes from lead industry workers, whose blood leads are routinely monitored over time. The washout of lead during an extended strike allowed O'Flaherty et al. (1982) to estimate the "blood-lead half-life", which increased from about 0.10 years (36 days) in the least exposed workers (range 20 to 60 days), to about 0.20 years (73 days) in the most exposed workers (range 20 to 130 days). This corresponds roughly to T_1 = "half-life"/ ln(2) = 52 to 105 days, much larger the other estimates, and may be attributed to some intermingling of the "alpha" and "beta" components of the elimination curves. The apparent increase in half-life with increasing duration of exposure or blood-lead increment may be attributed to the greater lead

load in the skeleton of the workers with longer exposure to lead.

A great deal of useful information is provided by the long-term Swedish studies on blood lead and skeletal lead in active and retired smelter workers (Ahlgren et al., 1980; Christoffersson et al., 1986; Schutz et al., 1987a,b; Skerfving et al., 1983, 1985). Much of the skeletal data were obtained by noninvasive X-ray fluorescence (XRF) methods. Because the subjects were followed for a very long period, the slow "gamma" component could be observed. The "half-life" of lead in finger bone averaged about 7.3 years (2700 days), but varied from 2.4 years to 62 years (one case > 100 years). The blood-lead "half-life" was sometimes longer and sometimes shorter than the phalanx half-life. The blood-lead half-life averaged about 6.8 years (2500 days), but ranged from 3.5 to 18 years (one case > 100 years). The relevance of these data on older males is uncertain, due to changes in bone structure with age. It is nonetheless clear that individuals with long exposure to lead, whatever the level, accumulate relatively large stores of lead in bone, and these skeletal lead stores are returned to the blood for many years after exposure ceases. The long residence times are consistent with the hypothesis that 20 to 60% of adult blood lead may be due to recycling of skeletal lead (Chamberlain, 1985). These analyses suggest that the long-term "half-life"/ln(2) = T_3 = 10 years approximately. This is likely to be an average or composite number combining resorption from cortical bone (20 to 50 years) with resorption from trabecular bone (4 to 8 years).

Supporting data are attached as Tables IV-1 to IV-5. The distribution of the fast "alpha" half-life may be deduced from Table IV-6, based on Schutz et al. (1988).

Table IV-6. Kinetics of the Decrease of the Blood-Lead Levels During a Temporary Cessation of Occupational Exposure Among 17 Lead Workers Observed for Less Than 1 Year and Among Two Volunteers Who Had a Short, Heavy Exposure

				Two Compartment Model		
				Fast Compartment		Slow Compartment[c]
Subject[a]	Age[b] (Years)	Exposure Time (Years)	Observation Time (Days)	t1/2 (Days)	Y(1) (u mol/1)	Y(2) (Years)
201[d]	43	3	189	26	3.6	2.6
202	59	23	209	43	1.2	2.7
203[e]	59	22	172	69	2.1	1.9
	60	23	118	49	2.8	2.3
204	53	22	239	37	1.3	2.2
205	38	14	48	14	1.2	2.2
206	60	5.5	112	28	1.1	1.5
207	52	29	218	63	0.5	2
208[e]	28	3.5	114	34	1.5	1.7
	29	4	115	24	1.2	1.6
209	48	75	171	13	1.3	1.8
210	58	3.5	160	47	1.5	1.8
211	59	13	155	8	0.6	1.9
212	49	10	238	7	0.8	2.4
213	51	1.5	120	20	1.9	1.6
214	40	1	155	50	2	1
215	50	1	147	24	1.4	1.7
216	29	0.3	83	42	2.4	0.9
217[d]	59	26	111	63	1.5	1.2
318	33	0.0001	215	27	1.4	0.1
319	37	0.0001	500	44	1.7	0.1

R = Degree of explanation.
t1/2(1) = Half-time of fast compartment.
t1/2(2) = Half-time of slow compartment.
Y(1) = Y intercept for the fast compartment.
Y(2) = Y intercept for the slow compartment.

[a]Subject 201 was a cast bronze founder; Subjects 202-205, demolition workers; Subjects 206-217, smeltery workers; and Subjects 318-319, volunteers.

[b]At the end of exposure.

[c]$t_{1/2(2)}$ is assumed to be 5 years.

[d]Subjects 201 and 217 are identical to Subjects 101 and 117, respectively, in Table IV-5.

[e]Two subjects were studied twice in the statistical calculations. The decay pattern with the best fit was used.

SOURCE: Schutz et al. (1988).

Several clinical studies on plasma lead kinetics have used radioactive lead isotopes (Campbell et al., 1984; Chamberlain et al., 1978), or ordinary lead ingestion with careful attention to determination of plasma lead levels (DeSilva, 1981a,b). Plasma lead is rapidly taken up by the red blood cells, typically within tens of minutes to a few hours transit time. Kinetic models have been developed (Marcus, 1985c,d). Because of this rapid uptake, distinction is not usually made between lead in plasma (2 to 5% of blood lead) and lead in red blood cells (95 to 98% of blood lead). However, considerable evidence indicates that the amount of lead in or on erythrocytes is proportionately much less at high concentrations than at lower concentrations (Barton, 1989; Manton and Cook, 1984; Marcus, 1985c). Thus, whole blood-lead concentration may not be an adequate index of internal lead exposure at high concentrations.

3. Biokinetics of Lead in Other Populations

The only study on biokinetics in adult women was reported by Stuik (1974). A sample of five Dutch college students consumed lead acetate in capsules for 29 days. The absorption of lead apeared to be slower than for a similar group of male subjects, but the short-term elimination of lead thereafter appeared similar. There is no reason to believe that the time constant for the mean residence time in a component of the elimination curve, T_1, is much different in women, except for the implication of the body weight scaling theory that women (who are, on average, smaller than men) should have slightly faster kinetics than men.

The literature contains even less data on direct observation of lead kinetics in children. In cases where sequential lead data are available in

circumstances in which changes in lead exposure are known, the intervals are too long to allow estimation of the more rapid blood-lead kinetics in children. An example is the Ryu et al. (1983) infant feeding study, in which blood-lead levels in infants to 6 months of age appeared to reach equilibrium so rapidly that kinetic parameters could not be estimated from 28-day interval data (Marcus, 1989). Duggan (1983) estimated a blood-lead half-life in infants of 2.4 to 4.3 days, based on lead balance estimates (mean residence time, T_1 = 4 to 6 days). The estimates for the EPA Uptake/Biokinetic Model for Lead (US EPA, 1989b, based on Harley and Kneip, 1985) implied that the blood-lead mean residence time for a 2-year -old child was about 8.8 days. The extent to which these estimates should be adjusted upward to account for recycling of stored bone is uncertain. The limitations of the concept of a single "half-life" are very evident. Using the data from the Cincinnati Lead Program Project, with blood lead sampled at intervals of 3 to 6 months, Succop et al. (1987) estimated the long-term time scale as about 1 year in children to age 3 years, i.e., T_3 = 1 year. Both these times are much less than the adult time scales, and they scale more proportionally to body weight rather than body weight to the 1/4 or 1/3 power. A simple application of allometric scaling is not recommended here until better data are available on lead kinetics in infants and young children, the most sensitive population groups. EPA is currently developing an enhanced uptake/biokinetic model for lead in young children (Cohen et al., 1990). The model extends the current model (US EPA, 1989a), based on kinetic studies in infant and juvenile baboons (Harley and Kneip, 1985). The model is similar to that in Cristy et al. (1986), shown in Figure IV-1.

4. The Distribution of Elimination Times in Real Life

The Medical Removal Plan (MRP) developed by OSHA required that excessively lead-burdened workers be removed from their high-exposure situations when blood lead Pb-B > M, and allowed to return to the same job only when Pb-B < L. The plan was gradually phased in, the first stage having M = 80 μg/dl and l = 60 μg/dl, the second stage having M = 70 μg/dl and L = 50 μg/dl, and the third stage having M = 60 μg/dl and L = 40 μg/dl. Note that all plans require a 20-μg/dl reduction in Pb-B, but the first stage requires only a 25% reduction, the second stage a 28% reduction, and the third stage a 33% reduction. Thus, we should expect that, on average, the work return times would be shortest in the first stage and longer at each successive stage. The distribution of return times for MRP M/L = 80/60, 70/50, and 60/40 are shown in Figure IV-11 (based on O'Flaherty, 1986). The median MRP removal time is about 90 days for MRP 80/60, about 150 days for MRP 70/50, and about 180 days for MRP 60/40.

Note first that the return time is greater than the elimination time, since an individual may not have been removed until Pb-B was considerably greater than M, and may not have been allowed to return to work until Pb-B was considerably less than L, owing to the spacing of intervals between blood lead samples. Even allowing for this source of variability, the range in MRP removal times is extremely large, with at least 10% returning to work in 90 days or less under the current MRP 60/40, and 25% remaining out of work longer than 540 days (18 months).

The relevant component for MRP is obviously neither the fast "alpha" phase (T1 = 40 days) nor the very slow "gamma" phase (T3 = 10+ years). It is clear that the MRP removal times are governed by the elimination of lead accumulated in solid softer tissues with residence times on the order

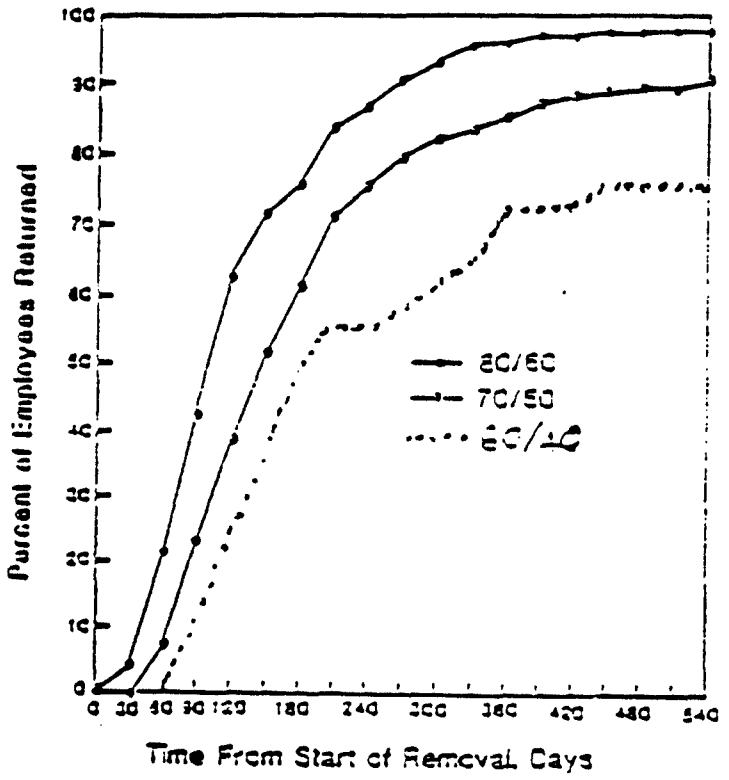


Figure IV-11. Cumulative distributions of lengths of removal under the 80/60, 70/50, and first 4 months of 60/40 triggers. Employees not yet returned are not included.

SOURCE: O'Flaherty (1986).

of 100 to 300 days, including reservoirs in liver and kidney. Detoxification of these lead-sensitive organs is undoubtedly beneficial. It is evident, from the Swedish worker data, that removal of a substantial part of the lead burden accumulated in the skeleton would be limited by the very long T_3 or "gamma" component.

5. Conclusions

Neither Equation (1) nor Equation (2) in Chapter II may be meaningful without specifying the time scale, since both the relevant steady-state level, Mss, and the approximate first-order rate coefficient, r, or half-life, $t_{1/2}$, depend on the dosing and no-dosing intervals. Indeed, since it takes years of exposure to achieve near-steady-state skeletal lead burdens, the steady-state level may never exist. A second concern is that at higher levels of exposure, the (near) steady-state tissue concentrations (even if achievable) may no longer be strictly proportional to each other, so that total exposure may no longer be an adequate index of toxicity.

More detailed compartmental models for lead uptake and biokinetics in children (ages 0-7 years) have been developed for U.S. EPA by Harley and Kneip (1985) using data on infant and juvenile baboons. These models are currently being extended and revised (Marcus et al., 1990). These models represent the best available synthesis of data on lead in animal and human tissue, with reference to children. In general, the biokinetics of lead in children is much faster than in adults, with time scales roughly proportional to the third or fourth root of body weight (the cube root represents "surface area" scaling). The models proposed by Rabinowitz et al. (1976), Marcus (1985b), or Bert et al. (1988) could be used for adults.

There is at present no completely validated model for lead transfer from mother to fetus during pregnancy. A preliminary model, without detailed compartmentalization of the fetus, was presented by Schwartz and Balter (1988). The enhanced EPA uptake/biokinetic model includes a simple proportional distribution of lead to infants' tissues based on human infant autopsy data and generalized maternal blood lead/infant blood lead ratios. This area merits additional research.

B. Styrene

1. Introduction

Styrene is extensively used in industrial processes such as the manufacture of plastics. The kinetics of styrene in adult humans is well known, and has been extensively studied in volunteer clinical subjects (Astrand et al., 1974; Engstrom, 1978; Fernandez and Caperos, 1977; Guillemin and Bauer, 1978; Ramsey et al., 1980; Stewart et al., 1968) as well as in exposed workers. Extensive animal studies are also available. The primary metabolic end-products are mandelic acid (MA) and phenylglyoxylic acid (PGA), which are useful as biological markers of exposure.

The availability of adequate data has allowed construction of a number of adequate PBPK models for styrene in humans (Droz and Guillemin, 1983; Droz et al., 1989; Johansen and Nasland, 1988; Ramsey and Andersen, 1984). These models are structurally similar to the models presented in Figure IV-12 for styrene and similar to models for 1,1,1-trichloroethane and 1,4-dioxane discussed in the following sections. The models appear to fit data well (see Figure IV-13). Additional storage of styrene in lipid-rich (especially adipose) tissues is likely to be important

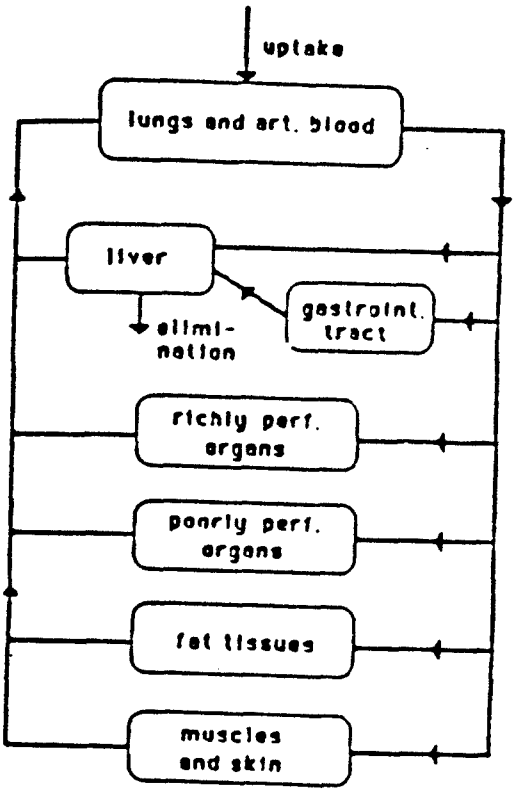


Figure IV-12. Physiological model used in the simulation of organic solvent toxicokinetics by spreadsheet programming.

SOURCE: Johanson and Nasland (1988).

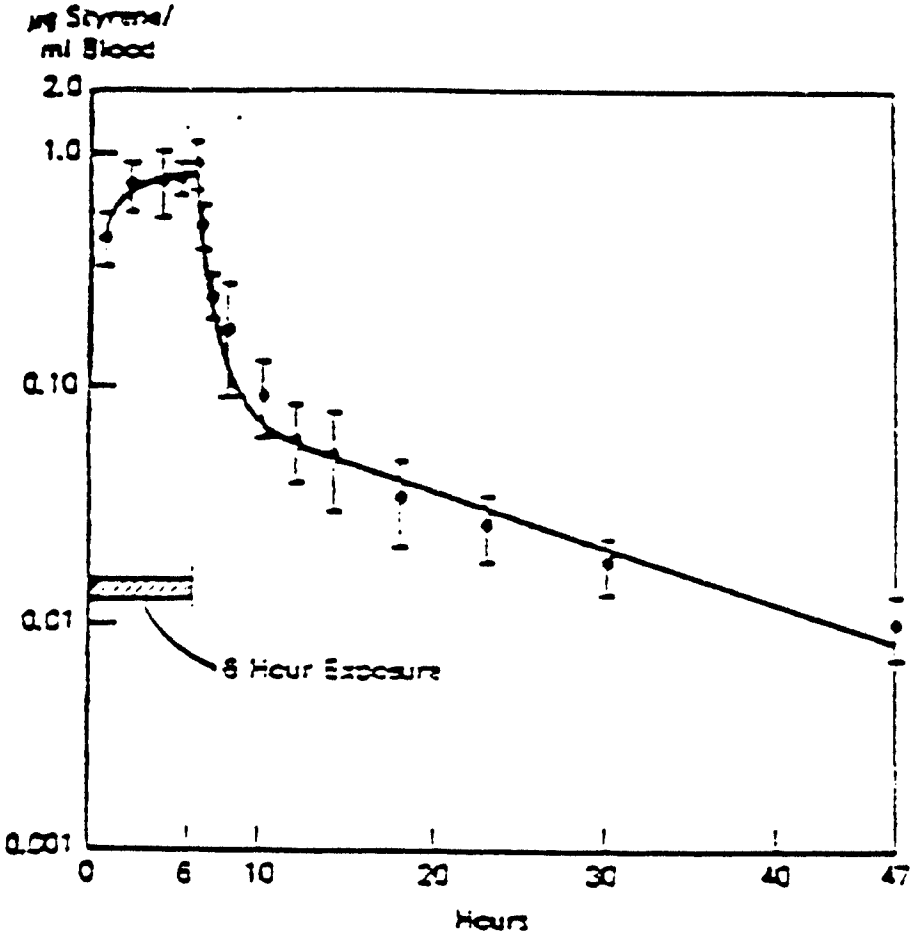


Figure IV-13. Blood styrene concentration versus time for four human volunteers exposed to 80 ppm styrene for 6 hours. Data points are mean ± S.D. (n = 4). Solid line is theoretical concentration predicted by average pharmacokinetic parameter estimates.

SOURCE: Ramsey et al. (1980).

in evaluating repeated exposures.

At lower levels of exposure, the semi-logarithmic plot of blood styrene vs. time during elimination is very nearly bi-exponential up to 24 hours, but may be tri-exponential at longer intervals. However, kinetic parameters of styrene elimination curves in rats are dependent on dose in a way that suggests Michaelis-Menten metabolism. At least some metabolic pathways appear to be saturable at higher concentrations. Thus, ordinary linear compartmental models (implying Equations 1 and 2) should not be used, especially with just one compartment.

2. Absorption

Most styrene exposure is likely to occur by inhalation. Bardodej and Bardodejova (1970) estimated that up to 61 to 66% of inspired styrene is absorbed during an extended exposure. This fraction depends on exercise level through the ventilation rate. Astrand et al. (1974) measured 14 subjects at rest and lightly exercising (50 W) exposed for 30 minutes to styrene air concentrations of 50 ppm or 150 ppm. Alveolar ventilation increased by a factor of 3 during exercise, as did the concentration of styrene in alveolar blood, but the alveolar concentration of styrene increased only slightly. The uptake of styrene by dermal absorption should also be considered in assessing chamber studies (Guillemin and Bauer, 1978). Absorbed styrene is rapidly transferred to the blood.

3. Distribution

Styrene is rapidly transferred from blood to other tissues and is known to be stored in lipid-rich or adipose tissues. Blood concentration vs. time curves in humans appear to be bi-exponential after some hours, but may be at least tri-exponential for times longer than a day. Most of

the PBPK models use 5 to 7 compartments. Since samples from humans have been limited to expired air, blood, adipose tissue, and urine, we must rely on animal studies for a more detailed look. Whole-body radiography of mice exposed to ^{14}C-labeled styrene found rapid uptake into bronchi, lungs, and liver, and at longer times mainly in bile, kidney (elimination of metabolites), and adipose tissue (storage). The distribution of styrene in rats was somewhat similar (Withey, 1976; Withey and Collins, 1977, 1979), highest in liver, kidney, and brain. The distribution in major organs appeared to be dose-dependent, suggesting saturability of at least some metabolic pathways at higher concentrations.

4. Biotransformation or Metabolism

The metabolism of styrene is complex (Figure IV-14, from WHO, 1983). The PBPK models for styrene metabolites use much more simplified models (Droz and Guillemin, 1983; Droz et al., 1989). Styrene in expired breath (Stewart et al., 1968) reflects total dose (concentration times time). In experiments with three to six subjects exposed to 51, 99, 216, or 376 ppm for 7 hours, the styrene elimination curves (semi-log scale) for the two lower concentrations were almost parallel, suggesting little metabolism of styrene at these levels. This was replicated by Guillemin and Bauer (1978) at these levels, using urinary PGA and MA, and by Ramsey et al. (1980) using expired styrene and blood styrene. At the higher levels, the elimination curves were much flatter, indicating that saturable metabolic processes are present.

The evidence for significant biotransformation of styrene in rats is very strong (Andersen et al., 1984; Withey, 1976; Withey and Collins,

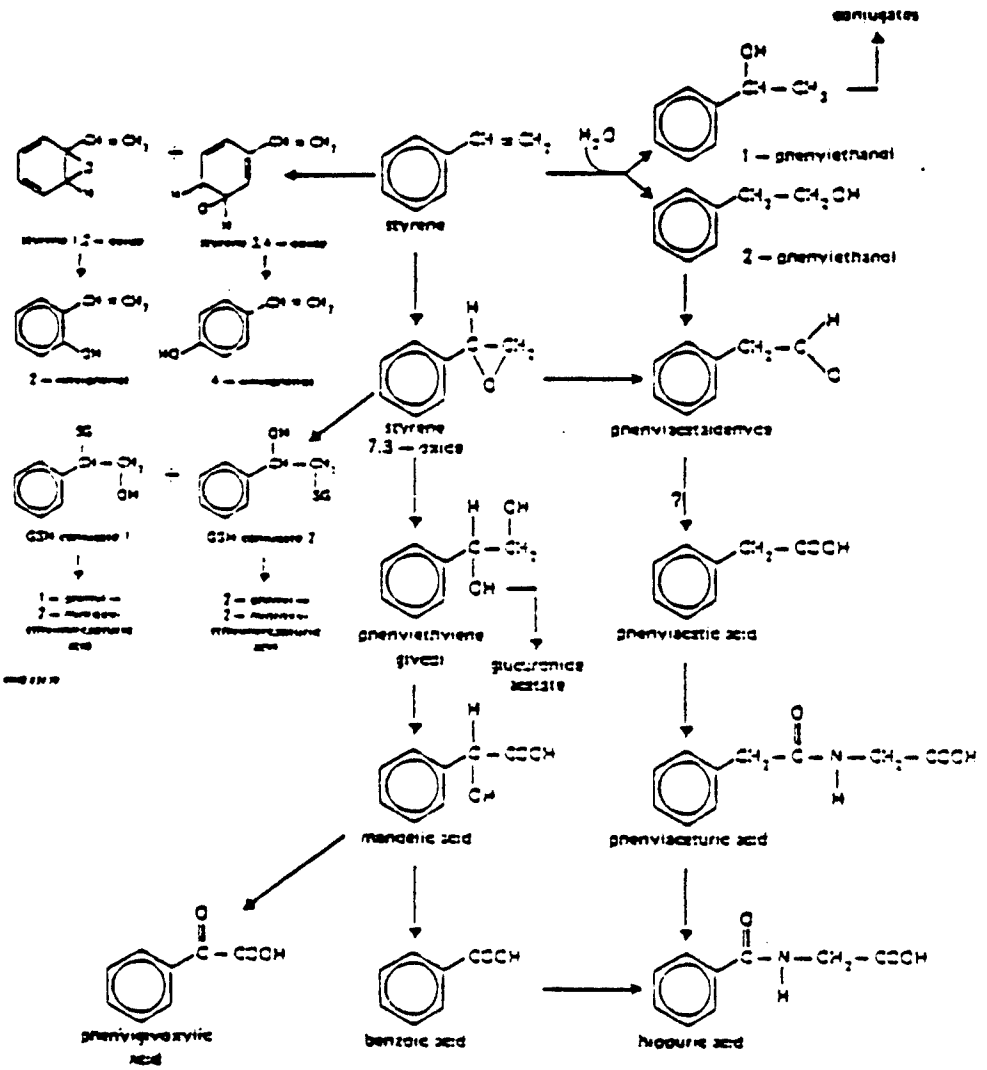


Figure IV-14. Main metabolic pathways for styrene.

SOURCE: WHO (1983).

1977, 1979). There appears to be very little styrene metabolism in naive rats, but styrene-pretreated rats have much lower blood styrene levels at a given level of styrene in the air than naive rats (Andersen et al., 1984). While the elimination curves could be fitted as the sum of two exponential components, the kinetic parameters were dose-dependent and consistent with saturable Michaelis-Menten kinetics for styrene in blood. This has been incorporated into the PBPK models.

5. Elimination Time of Styrene from Adult Males

The two-exponential elimination curves (Figure IV-13) fitted to blood styrene data by Ramsey et al. (1980) in four individuals had parameters shown in Table IV-7. The fast "alpha" component of elimination, T_1, varied from 0.72 to 0.96 hours, and the slower "beta" component, T_2, from 17.7 to 20.1 hours. The expired air styrene elimination was estimated separately from blood elimination, with somewhat different values, T_1 = 1.25 hours and T_2 = 27.8 hours. The urinary metabolites PGA and MA were eliminated very slowly, probably reflecting the slow release of styrene from adipose tissue.

The tri-exponential behavior of MA is shown clearly by Guillemin and Bauer (1978). The MA time scales were 5.6, 35.6 hours, and about 20 days, whereas PGA seemed to have just a single component with about 15 days mean transit time. Fernandez and Caperos (1977) fitted three components to expired breath styrene in six volunteers, with T_1 = 0.09 to 0.88 hours, T_2 from 1.46 to 5.4 hours, and T_3 from 14.5 to 35.7 hours. In the Engstrom (1978) study, styrene was still detectable 13 days after exposure, suggesting a much slower third pool. The overall "elimination half-time,"

Table IV-7. Two-Compartment Linear Pharmacokinetic Parameters for Four Human Volunteers Exposed to 80 ppm Styrene for 6 Hours

Half-time (hours)	Individual Values A	B	C	D	Mean ± S.D.
$t_{1/2}(a)$	0.519	0.504	0.645	0.668	0.584 ± 0.084
$t_{1/2}(b)$	12.3	13.3	14.0	12.6	13.0 ± 0.8

[a]Note that $t_{1/2}(a)$ equals T_1 x ln(2) and $t_{1/2}(b)$ equals T_2 x ln(2).

SOURCE: Ramsey et al. (1980).

based on a one-compartment fit rather than a three-compartment fit, was estimated as 2.2 to 4.0 days. Thus, the elimination time, t_e, cannot be calculated unless we specify the levels L, M of an appropriate biological indicator, e.g., mg MA per g creatinine in urine.

6. Interindividual Variability

There are very large individual variations in the clearance kinetics of styrene. Figure IV-15 shows the estimated distribution of styrene clearance in a population of styrene-exposed workers (Droz et al., 1989).

7. Conclusion

The multicompartmental nature of styrene biokinetics is clearly seen in its usual metabolites MA and PGA. The tri-exponential nature of MA elimination (Guillemin and Bauer, 1978) had distinct time scales of 5.6 hours, 35.6 hours, and 20 days. Styrene in expired breath (Fernandez and Caperos, 1977) showed much faster time scales: <1 hour, 1.5-5.4 hours, 15 36 hours. The PBPK model developed by Droz (1986) provides a serviceable prediction of MA and PGA levels in styrene-exposed workers. The slow component of MA suggests adipose tissue storage of styrene is significant. Repeated daily dosing should therefore increase blood styrene levels, but elimination over a weekend should substantially lower the body burden of styrene for most subjects.

There are several reasons why neither Equation 1 nor Equation 2 should be used to estimate the uptake and elimination of styrene. The first reason is that the body is clearly not a single pool with respect to styrene, and that there is a substantial potential for long-term styrene

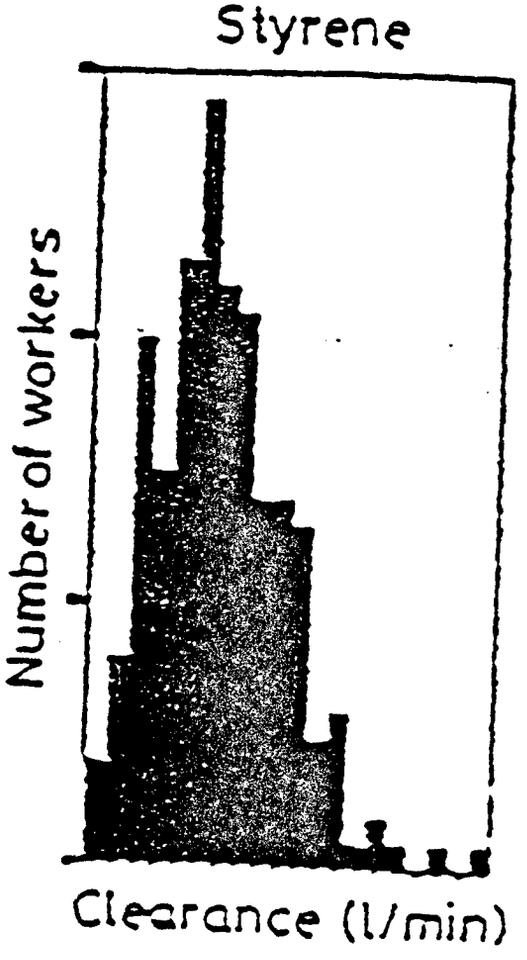


Figure IV-15. Predicted distribution of metabolic clearance in a group of 200 workers for styrene (mean 1-23, range 0-52 to 2-71).

SOURCE: Droz et al. (1989).

accumulation and storage in adipose tissue. The second reason is that some of the metabolic pathways for styrene are likely to be saturable at higher levels of potential human exposure. For these reasons, it would be prudent to use one of the available PBPK models for estimating styrene burdens from different temporal exposure patterns (e.g., Leung and Paustenbach, 1988). Whichever model is used, it should also include the very great variability in human clearance of styrene (Droz et al., 1989). This variability identifies a potentially sensitive subpopulation with slow clearance of styrene.

C. Chlordane

1. Introduction

"Pure" chlordane is the gamma- or trans-chlordane isomer of an octachlor indene compound. The "technical" grade chlordane insecticide is a mixture of more than 45 compounds, of which trans-chlordane is about 24% by weight, and the alpha- or cis-chlordane about 19%. Heptachlor, nonachlor isomers, chlordene isomers, and cyclopentadiene derivatives are the other major components of technical chlordane. While chlordane is relatively stable in environmental exposure media such as air, water, soil, and house dust, many of its components are readily metabolized in mammals. Both trans- and cis-chlordane isomers are metabolized to oxychlordane (possibly the major "proximate" toxicant) (Wariishi and Nishiyama, 1989). Trans-nonachlor is only sparingly metabolized.

The concentration vs. time relationship of chlordane has been observed in blood and excreta of chlordane-poisoned children (Aldrich and Holmes, 1969; Harrington et al., 1978). A more detailed study of the kinetics of technical chlordane components in asymptomatic human

volunteers has been reported by Wariishi and Nishiyama (1989). The serum half-life of chlordane in an acutely poisoned 20-month-old boy was estimated as about 21 days. A more detailed examination of the data (Figure IV-16, from Curley and Garrettson, 1969) show that a single elimination half-life does not adequately describe the data, and that a tri-exponential fit (implying at least a three-compartment model) is more appropriate. The case of the chlordane-intoxicated 4-year-old girl reported by Aldrich and Holmes (1969) was followed for a much longer time. They estimated a serum half-life of chlordane of 88 days, which we interpret as a "slow" third exponential component of 127 days (Figure IV-17). It is likely that this reflects storage of chlordane or its metabolites (especially oxychlordane) in adipose tissues. The long residence time of chlordane and its metabolites in adult humans is very evident in the study by Wariishi and Nishiyama (1989) shown in Figure IV-18.

We are not aware of any physiologically based pharmacokinetic models for technical chlordane in humans. The need for a multicomponent model is very clear, as several components of chlordane insecticide may have the same metabolites. If the saturation of some of the enzymes in these metabolic pathways occurs at human exposure levels of concern, then seriously non-linear relationships may be needed to model the effective dose rate and elimination kinetics. It is clear that the saturation of some metabolic processes occurs in nonhuman primates exposed to high levels of technical chlordane vapor and aerosols. The recent study by Khawasinah (1989) in cynomolgus monkeys shows that a tenfold increase in dose produces only a three- to fourfold increase in dose produces only a three- to fourfold increase in total chlordane residues in the liver. Thus, Equation 1 should not be used. Because of the

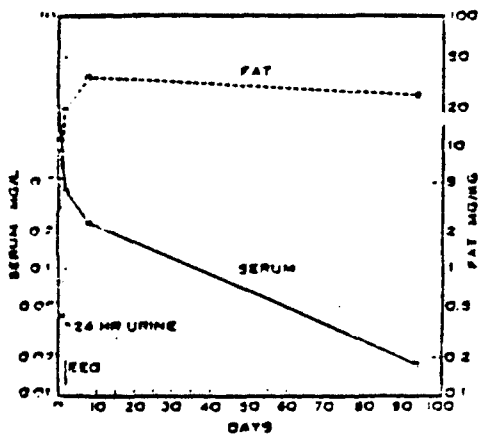


Figure IV-16. Concentration of technical chlordane in fat and serum. Time of urine sample and EEG.

SOURCE: Curley and Garrettson (1969).

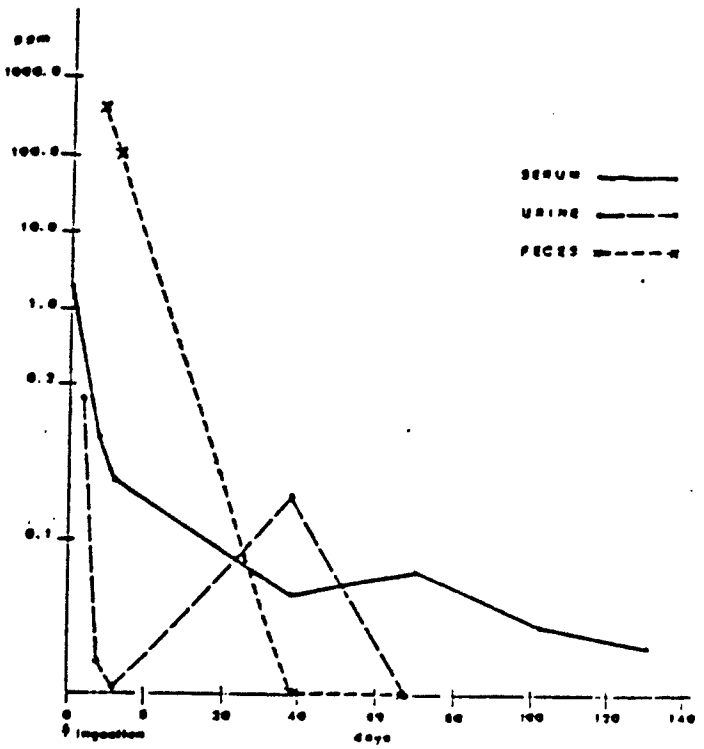
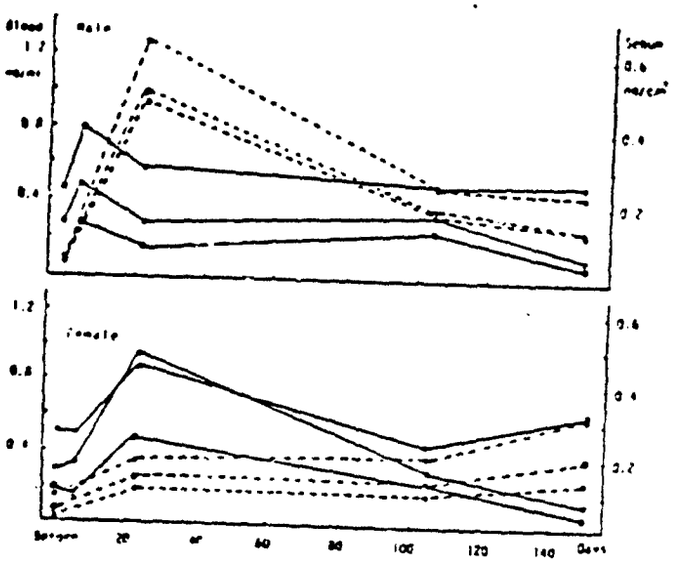


Figure IV-17. Chlordane concentration in serum, urine, and feces, plotted against time.

SOURCE: Aldrich and Holmes (1969).



Symbols: Blood ■——■ *trans*-Nonachlor; ●——● *trans*-Chlordane; ○——○ *cis*-Chlordane. Sebum ■----■ *trans*-Nonachlor, ●----● *trans*-Chlordane; ○----○ *cis*-Chlordane

Figure IV-18. Chlordane residues in blood and sebum of normal subjects resident in the house after termite control treatment.

SOURCE: Wariishi and Nishiyama (1989).

long retention time of some chlordane components in fat, a multicompartmental PBPK will be necessary, so that Equation 2 is not entirely valid even at low levels of exposure to chlordane.

The available data on humans may be adequate for the construction of a PBPK model, especially if supplemented by experimental studies in a wide variety of laboratory animals. Chlordane and chlordane by-products are known to be widely distributed in the tissues of mice (Ewing et al., 1985), rats (Barnett and Dorough, 1974), rabbits (Balba and Saha, 1978; Poonawalla and Korte, 1971), and monkeys (Khasawinah, 1989). However, it appears that the fate of chlordane is different in rats and mice, suggesting that extrapolation of metabolic parameters across species requires a more detailed assessment of the processes involved.

The kinetic parameters for chlordane uptake, metabolism, and elimination are likely to vary enormously among individuals. Impaired liver function, whether due to chlordane intoxication or to other toxic agents, may create a particularly susceptible subpopulation. The mobilization of chlordane residues in adipose tissue is also a matter of possible concern, as it is for many other organochlorine pesticides.

2. Absorption, Distribution, Elimination, and Storage

Technical chlordane is efficiently absorbed by humans, via inhalation and ingestion from contaminated water or house dust. Chlordane and chlordane by-products (using radiocarbon tracers) are known to be widely distributed in tissues of mice (Ewing et al., 1985), rats (Barnett and Dorough, 1974), rabbits (Balba and Saha, 1978; Poonawalla and Korte, 1971), and monkeys (Khasawinah, 1989). This allows plausible inference about analogously wide distribution of chlordane residues in human

tissues. Oxychlordane is avidly retained in fat. However, it appears that the fate of chlordane is different in rats and mice, suggesting that a detailed assessment of metabolism may be useful when there are important differences in metabolism of a toxicant among species.

In the case of acute chlordane poisoning in a 20-month-old boy, the serum half-life was estimated to be about 21 days. Examination of the data shows that this is a very severe simplification, and that a three-component model is the minimum required to describe serum and fat levels of chlordane. The data are shown in Figure IV-16 (Curley and Garrettson, 1969). There is a very fast component (T_1 less than a day in serum and fat), a slower component in serum that likely reflects soft tissue storage and release (T_2 of about 30 days), and a very long-lived release from fat (T_3 of months). These data are probably not adequate for a multicompartmental analysis.

The case of a 4-year-old girl reported by Aldrich and Holmes (1969) was followed for a much longer time. They estimated the serum half-life of chlordane was 88 days (we interpret this as T_3 of 127 days). They did not have levels in fat, but the long component in serum is very clear in Figure IV-17. A synthesis of these two studies may allow a useful three-compartment model, provided some approximate method for dealing with kinetic nonlinearities of metabolism can be worked out.

Much more detailed analysis of the study on chlordane-exposed adults by Wariishi and Nishiyama (1989) is recommended. They present data on the time course of six technical chlordane residues in the home environment air, house dust, in the blood, and in the sebum (skin wipe) of residents and pest control operators (PCOs). The six residues are trans-

nonachlor, trans-chlordane, cis-chlordane, heptachlor, heptachlor epoxide, and oxychlordane. Air concentrations were taken pre-exposure and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 9 days after treatment of the house for termites. Dust concentrations were measured for both chlordane and nonachlor isomers pretreatment, and 25, 105, and 148 days posttreatment. Blood and sebum levels for three residues are shown in Figure IV-18. The very long T_3 in adults is evident. These data offer an excellent opportunity to study the long-term kinetics of technical chlordane in response to persistent environmental exposure (rather than acute chlordane exposure, as in the child poisoning cases). Comparison of elimination parameters between children and adults would be of great interest.

3. Metabolism and Toxicity of Technical Chlordane

The most important mechanism affecting chlordane elimination is the metabolism of its constituents. The metabolism of chlordane has been extensively studied in mammals (Barnett and Dorough, 1974; Brimfield and Street, 1979; Ewing et al., 1985; Street and Blau, 1972; Tashirc and Matsumara, 1977). It is clear that the saturation of some metabolic processes must reduce the accumulation of chlordane residues in nonhumar primates. Table IV-8 (from Khasawinah, 1989) shows the accumulation of total chlordane residues in three groups of cynomolgus monkeys exposed to concentrations of technical chlordane vapor and aerosol for 90 days, respectively, to be 0.1, 1.0, and 10.0 µg/l. If elimination kinetics were first-order, then each tissue level would be approximately a 10:1 ratio above the preceding dose level. This 10-fold approximation is valid for plasma residues after 31 and 90 days, and is somewhat less valid for red

Table IV-8. Average Total Chlordane Residues in Monkey Blood and Tissues

Exposure (ug/l)	Interval (days)	Tissue	Av. Total Residue (ppm) Male	Female
0.1	90	A	3.4 ± 1.1	2.8 ± 0.4
1.0	90	A	23.7 ± 0.8	21.3 ± 0.5
10.0	90	A	173.5 ±20.1	122.4 ±36.1
0.1	90	L	0.75 ± 0.31	0.80± 0.27
1.0	90	L	3.43 ± 0.94	2.70± 0.69
10.0	90	L	10.80 ± 2.04	9.56± 1.96
0.1	31	R	0.001± .001	ND
1.0	31	R	0.009± .002	0.009±0.003
10.0	31	R	0.083± .018	0.095±0.055
0.1	90	R	0.003± .001	0.003±0.001
1.0	90	R	0.024± .006	0.032± .011
10.0	90	R	0.173± .038	0.200± .159
0.1	31	P	0.002± .002	0.001± .001
1.0	31	P	0.016± .005	0.015± .005
10.0	31	P	0.174± .040	0.191± .086
0.1	90	P	0.004± .001	0.006± .001
1.0	90	P	0.045± .015	0.061± .028
10.0	90	P	0.390± .050	0.358± .177

A=Adipose, L=Liver, R=Red Blood Cells, P=Plasma

SOURCE: Khasawinah (1989).

blood cells at 31 days (factor of 9) and 90 days (factor of 8) and for adipose tissue at 90 days (factor of 7). The approximation is not valid in the liver where most metabolism takes place, since the ratio of liver residues at 90 days is (3.43/0.75 = 4.6) for the 1.0 and 0.1 µg/l dose groups. The variation may also, in part, be due to the fact that one of the toxic effects of chlordane over time is an enlargement of the weight of the liver (Hart and Fouts, 1965; Yarbrough et al., 1982). Quantification of the effects of metabolism and toxicity on the elimination of chlordane residues is not yet available.

These primate chronic exposure data presented by Khasawinah (1969) could be analyzed in conjunction with the low-level human exposure data presented by Wariishi and Nishiyama (1989) to estimate a low-dose linear compartmental model for chlordane residues. This would be a basis for a nonlinear kinetic model involving metabolism at the higher exposure levels in the monkey inhalation study. Validation of the models using the acute exposure kinetics in children may be possible. It is conceivable that saturation of some metabolic pathways after high exposures could contribute to delayed elimination of toxic chlordane residues at levels encountered by humans in accidental poisoning cases. This has not yet been quantified.

4. Interindividual Variations

There is reason to suspect that very large interindividual variations in chlordane elimination exist among humans. First of all, Ewing et al. (1985) found large differences in excretion in a relatively homogeneous C57BL/6JX strain of mice, and divided their mice into "low" and "high" excretors. The differences were somewhat less pronounced in rats. Large

variations in tissue residues of chlordane in humans also suggest differences in individual metabolic rates. Wariishi and Nishiyama (1989) report "two subjects (subject A among the pest control operators and subject B among the Okinawans), who had extremely high blood chlordane ... showed impaired liver function. This impairment, however, could not be attributed with certainty to only chlordane action because both subjects were heavy drinkers. The increased amount of chlordane in the blood was probably produced as a result of the dysfunction of chlordane metabolism in the liver."

Another potential source of variability is the mobilizability of chlordane residues stored in the adipose tissues. This depends on changes in external conditions that may cause fat loss, e.g., starvation.

5. Conclusion

The multicompartmental metabolism of chlordane in humans is very clear and therefore Equations 1 and 2 should not be used. While there are adequate data to construct PBPK models for technical chlordane in humans we are not aware of such models at the present time.

D. 1-1-1 Trichloroethane (Methyl Chloroform)

1. Introduction

1,1,1-Trichloroethane (TRI, TCE), also known as methyl chloroform (MC), has been widely used as an industrial solvent and degreasing agent. The biokinetics are amenable to study by use of PBPK models, and several PBPK models have been developed (Bogan and Hall, 1989; Caperos et al., 1982; Dallas et al., 1989; Droz et al., 1989; Nolan et al., 1984; Reitz et al., 1988). The PBPK models can be fitted and validated using abundant data on

human volunteers (Humbert and Fernandez, 1977; Imbriani et al., 1988; Monster, 1979; Monster et al., 1979; Nolan et al., 1984; Seki et al., 1975; Stewart et al., 1961, 1968, 1969).

Some of the PBPK models for MC have been developed and extrapolated from experimental data on rats. These are true extrapolation models based on physiological principles. It is important to distinguish these models from data-driven physiological models in which some of the most poorly extrapolatable parameters were estimated from the human data. It would be more appropriate to denote the data-driven models as "data-based physiologic pharmacokinetic models" (DBPPK). They play an intermediate role between purely descriptive (e.g., compartmental) models and PBPK models.

2. Physiologically Based Pharmacokinetic Models

Methyl chloroform, like styrene, is eliminated by the respiratory and metabolite urinary elimination routes. It has, therefore, been the subject of numerous efforts to develop physiologically based pharmacokinetic models for uptake and elimination. Models have been presented by Bogan and Hall (1989), Caperos et al. (1982), Dallas et al. (1989), Droz et al. (1989), Nolan et al. (1984), and Reitz et al. (1988). The scheme used by Bogan and Hall (1989) is shown in Figure IV-19, and is much the same as in other studies. Goodness of fit of the model to human data may be judged from those shown by Reitz et al. (1989), here reproduced as Figures IV-20 and IV-21.

In particular, the PBPK models presented by Reitz et al. (1988) are not very satisfactory for descriptive or predictive purposes at some time scales. The inadequacies are illustrated in Figures IV-20 and IV-21.

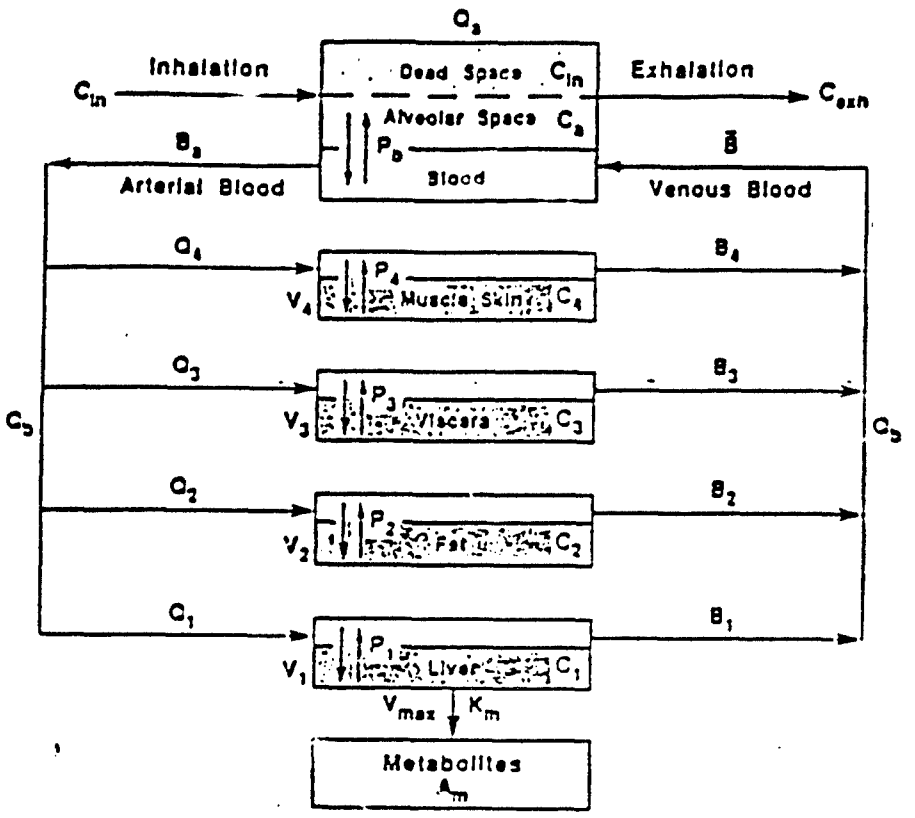


Figure IV-19. Schematic diagram of physiologically based pharmacokinetic (PBPK) model for inhalation of volatile organic compounds. The model assumes that four "well-stirred" compartments or tissue groups collected inhaled compound at rates governed by air concentration (C_{in}), air and blood flow (Q), blood concentration (B), compartment volumes (V), tissue/blood partition coefficients (P), and metabolic parameters (Vmax, Km).

SOURCE: Bogan and Hall (1989).

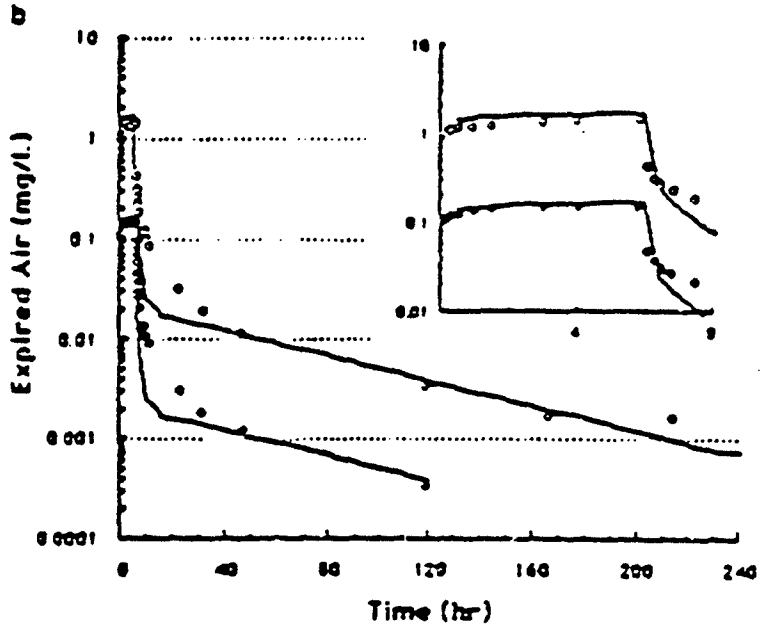


Figure IV-20. Concentration of MC in exhaled air (mg/l) during and following a 6-hr inhalation exposure of human volunteers to 35 ppm (closed circles) or 350 ppm (open circles) of MC. Values predicted by computer simulations are shown as a solid line(s).

SOURCE: Reitz et al. (1988).

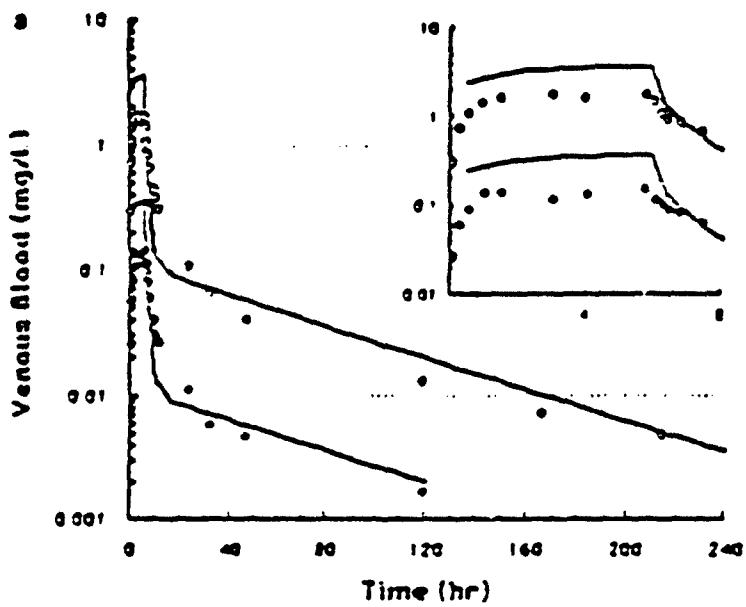
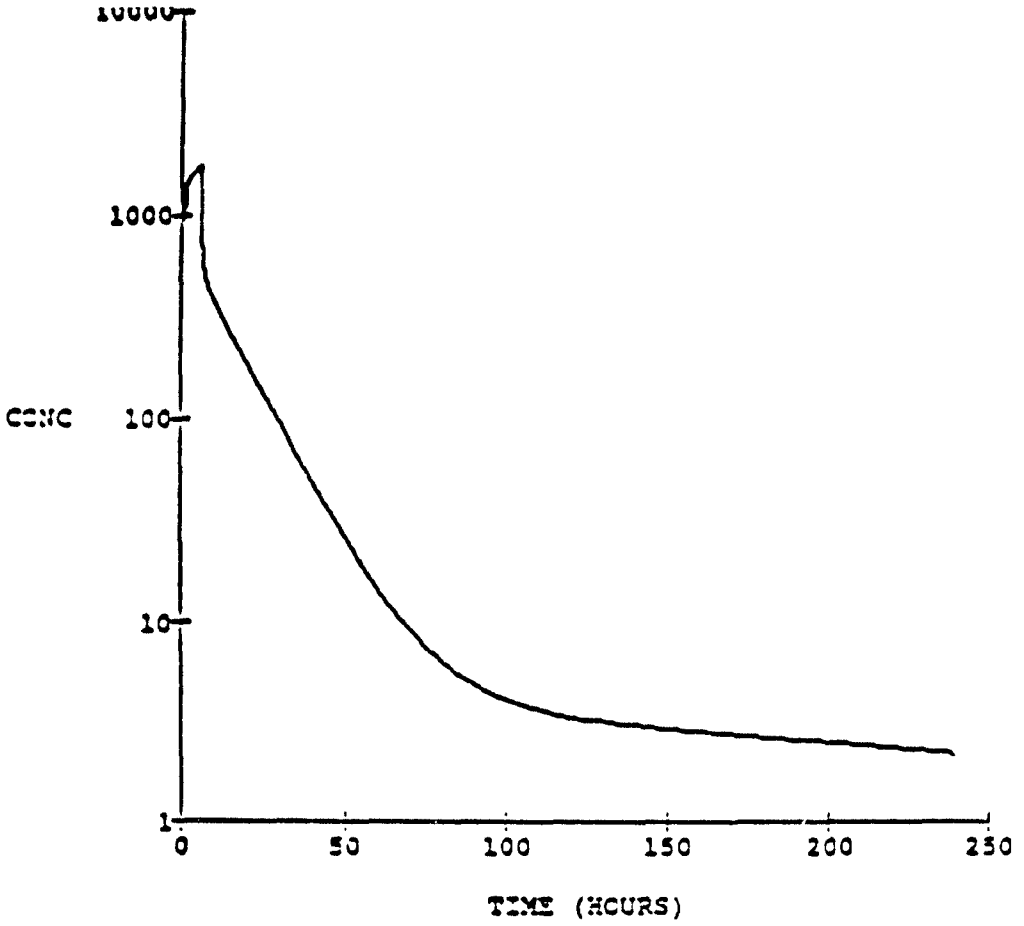


Figure IV-21. Concentration of MC in venous blood (mg/l) during and following a 6-hr inhalation exposure of human volunteers to 35 ppm (closed circles) or 350 ppm (open circles) of MC. Values predicted by computer simulations are shown as a solid line(s).

SOURCE: Reitz et al. (1988).

Venous blood concentrations of MC are greatly underestimated for times of 7 to 30 hours (1 to 24 hours in the elimination phases). The exhaled air concentration (which might be used as a biological marker of exposure) is similarly mis-estimated during this interval. The blood MC vs. time curve (semi-log scale) can be very well described by three exponential components, with rather similar time scales at both 35- and 350-ppm exposure. The fastest time scale corresponds to an initial clearance half-life of about 28 minutes, followed by a slower redistribution phase with a half-life of about 10.3 hours (this is not well described by Reitz' PBPK models), and a very slow component with a half-life of about 8 days. Since the elimination curves maintain about the same 10-fold spacing for both 35 and 350 ppm exposures, it is likely that that metabolic processes are not saturated at the higher concentration, and that multi -compartmental models will be adequate for predictive purposes. This example points out that both one-compartment models and inadequately validated PBPK models may not be useful for estimating the elimination time.

These data sets have helped us to build a pharmacokinetic model for MC using the CMATRIX program (software developed at Georgetown University). Figure IV-22 shows the venous blood concentration during and after a 6-hour inhalation period. Three successive decay components (Q_1, Q_2, Q_3) can be discerned with rate constants of 1.47 hour^{-1}, 0.067^{-1}, and 0.0035 hr^{-1}, respectively. These represent a rapid distribution phase and elimination phase influenced primarily by elimination mechanisms and distribution in vessel-rich tissues and muscle. The slowest phase is a reflection of the increased volume of distribution created by a high (>300



r_1 = 1.47 hr^{-1} T_1 = 41 min

r_2 = 0.067 hr^{-1} T_2 = 15 hr

r_3 = 0.0035 hr^{-1} T_3 = 281 hr

Figure IV-22. Blood decay of 1,1,1-trichloroethane after 6-hour inhalation of 1.9 mg/l.

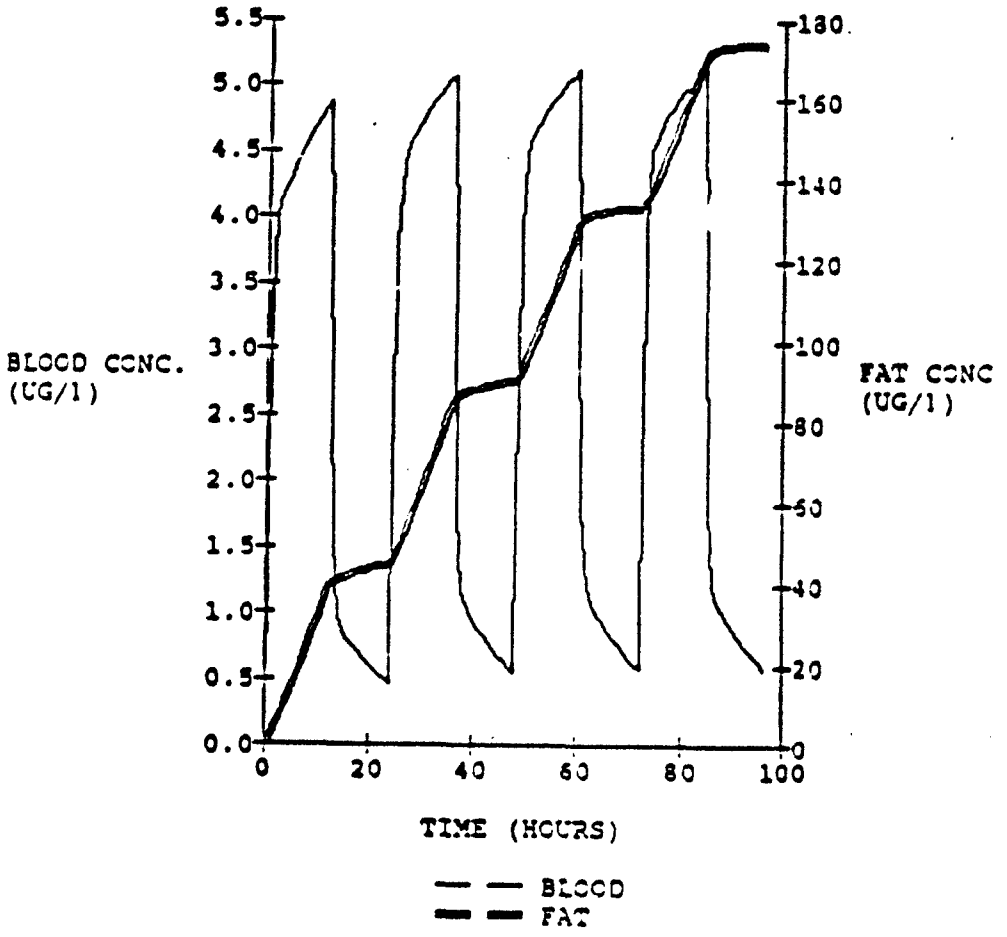
at thermodynamic equilibrium) fat/blood partition coefficient. Figure IV-23 shows the results of a four-day PBPK simulation using CMATRIX where 1 mg/hr is ingested at t_i = 12 hr, t_d = 24 hr. It is clear that the first two phases of decay predominate. It can also be seen that, though the blood appears to be over 90% Cmax (i.e., Mmax/volume of distribution), MC fat concentration continues to rise. The effects of this accumulation on target tissue levels of MC should be studied further. Figure IV-24 compares the PBPK and one-compartment model, the latter using the middle first-order elimination constant. The latter, which would be predicted by equation 2, clearly overestimates accumulation. This is a clear example of the pitfalls encountered when relying solely on one-compartment models.

3. Interindividual Variability

Elimination times for human volunteers show considerable variation. This is formally incorporated in the PBPK model developed by Droz et al. (1989). The distribution of MC clearance rates used in their model is shown in Figure IV-25. The study of model sensitivity with respect to interindividual variations in physiological and pharmacokinetic variation in parameters should be reported in any estimation of clearance times in a population exposed to the toxicant.

4. Conclusions

The multicompartmental metabolism of 1,1,1-trichloroethane in humans is very clear and therefore Equations 1 and 2 should not be used. While there are adequate data to construct PBPK models for technical ,1,1



V_D at 36 hr = 775 l

Mmax based on k_1 = 0.88 µg/l

mmax based on k_2 = 13.28 µg/l

Figure IV-23. Simulation of gastrointestinal administration of 1,1,1-trichloroethane.

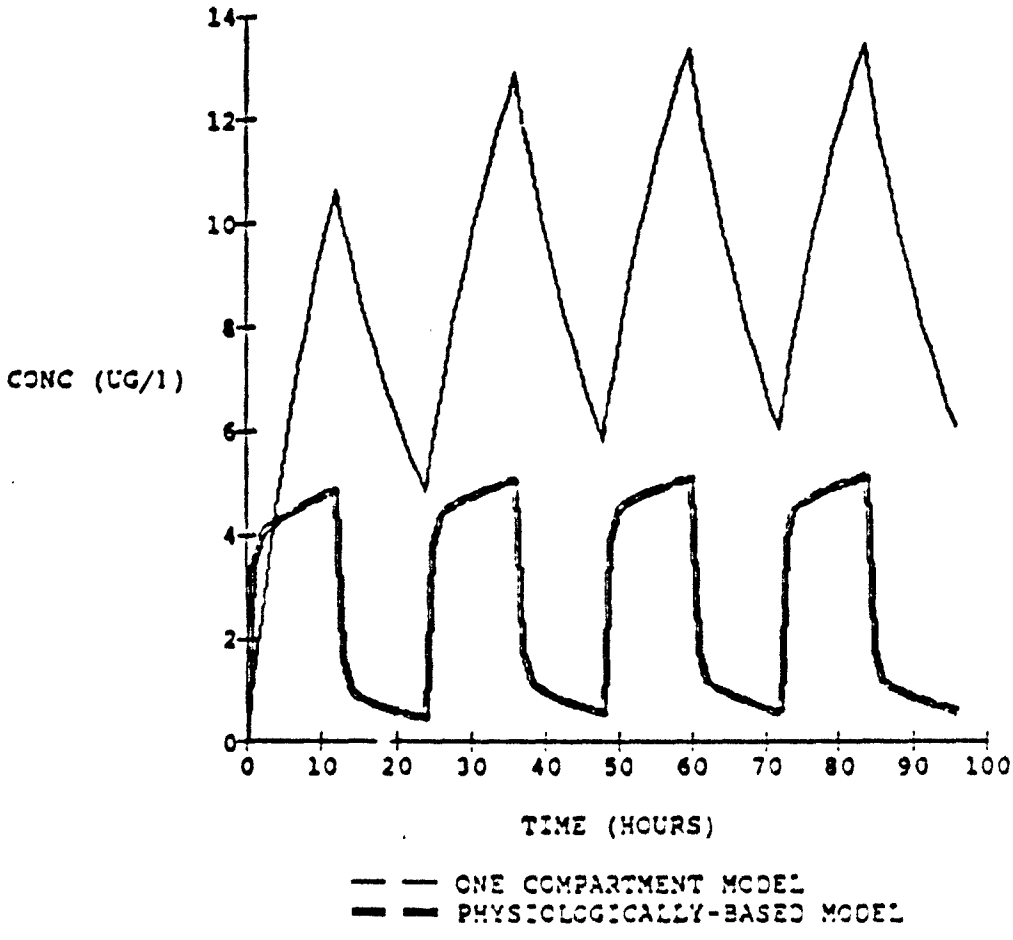


Figure IV-24. Comparison of a one-compartment model and a physiologically based model for 1,1,1-trichloroethane.

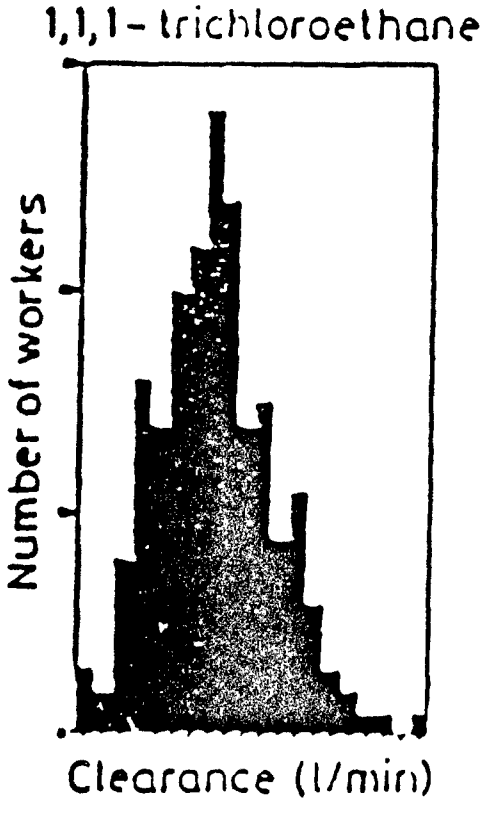


Figure IV-25. Predicted distribution of metabolic clearance in a group of 200 workers for 1,1,1-trichloroethane (mean 0.0152, range 0.0088-0.0252 l/min).

SOURCE: Droz et al. (1989).

trichloroethane in humans, we are not aware of such models at the present time. The use of PBPK models allows experimental data from inhalation exposure to be extended to water exposure in drinking water.

E. 1,4-Dioxane

Dioxane is an example of a chemical for which exte .sive pharmacokinetic data are available for rats following intravenous, oral (gavage), and inhalation exposure (Young et al., 1978). These data are significant as they relate to low-dose extrapolation of the carcinogenicity data in rats. Extrapolation to humans also presents some significant problems given the published data concerning dioxane pharmacokinetics in humans. The data reported by Young et al. (1977) on the pharmacokinetics of dioxane in humans suggest that the exposure-blood concentration-target site concentration relationship will be substantially different from that reported in rats. Specifically, the volume of distribution (V_d) of dioxane in humans was only 0.1 l/kg, 10% of that reported in rats on a body weight basis. The V_ds reported in humans and rats suggest that in rats, dioxane is distributed in total body water while in humans, dioxane remains almost completely intravascular, consistent with a high degree of macromolecular (possibly plasma protein) binding. Such a marked interspecies difference in intravascular binding is a highly unusual finding; suggests a laboratory error as much as it does a rare interspecies difference in intravascular binding. Consequently, the plausibility of this difference in V_d, and its implications for the extrapolation of carcinogenicity data from rats to humans, were further explored using PBPK modeling.

Figure IV-26, taken from Young et al. (1978), illustrates this saturation based on the administration of single iv doses of dioxane. Dioxane exposure via drinking water is carcinogenic in rats (hepatocellular carcinoma and nasal carcinoma) at daily doses resulting in metabolic saturation demonstrated when the dose is administered by gavage. These data are summarized in Table IV-9.

All of this raises a number of questions concerning the treatment of dioxane in dose-response and interspecies extrapolations. PBPK modeling has been used to provide insight into these issues and to address the usefulness of an approach-dependent, one-compartment, linear pharmacokinetic model.

Figure IV-27 shows the nonlinear pharmacokinetic behavior of dioxane doses near saturation. Drinking water exposure in rats was simulated over a 7-day period, and involved total daily doses of 10, 30, 100, 300, and 1,000 mg dioxane/kg. Total daily doses of 10, 100, and 1,000 mg/kg approximated those reported in the rat carcinogenicity study of Kociba et al. (1974) for drinking water concentrations of 0.01%, 0.1%, and 1%, respectively. Figures IV-28 and IV-29 show the results from the 1,000-mg/kg/day and 300-mg/kg/day simulations, respectively. The results of the drinking water simulations are presented in Table IV-10 in terms of the peak liver concentration, the 24-hr area under the curve for the liver (AUCLIV), and the amount of metabolite formed over a 24-hr period. Although peak and integrated (AUC) dioxane concentrations for other tissues are not reported, the relationship between the drinking water exposure concentration and organ dose (or blood level) will be the same as that reported for liver.

Considering the relatively short half-life of dioxane, a modification

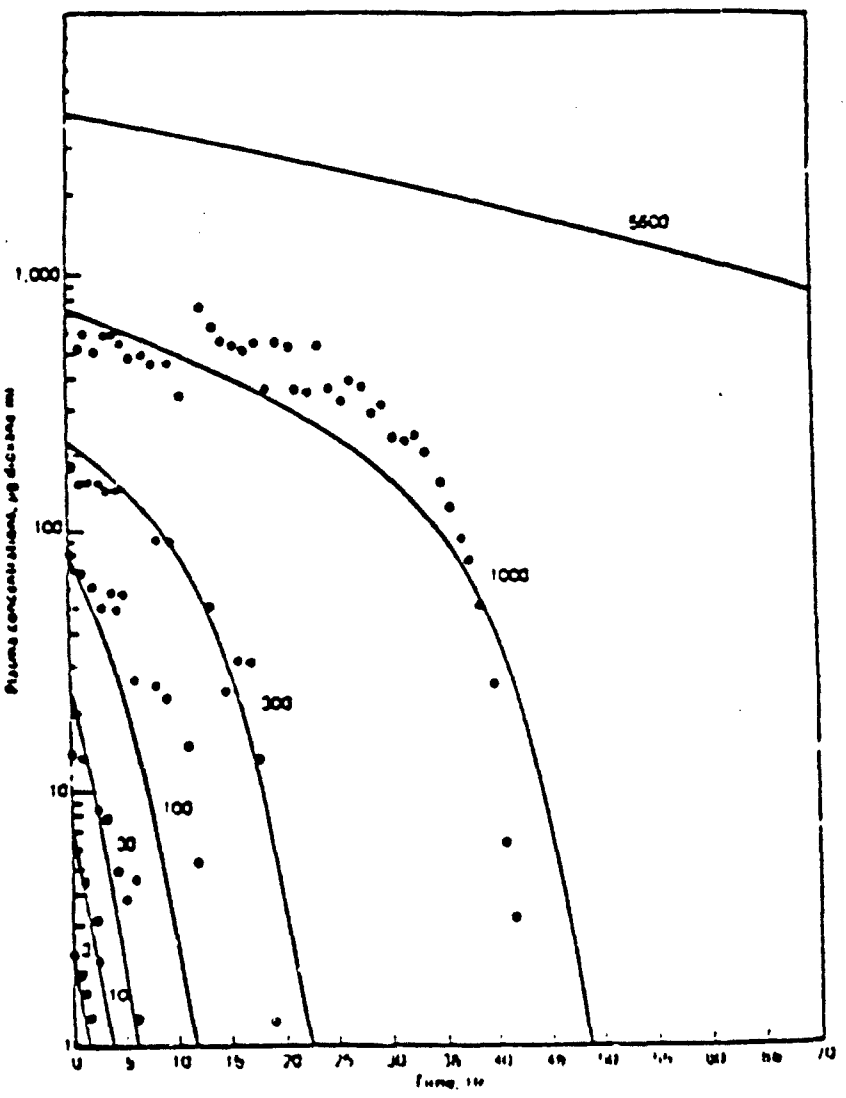


Figure IV-26. Blood plasma concentration-time curves for intravenous doses of 1,4-dioxane given to rats.

SOURCE: Young et al. (1978).

Table IV-9. Summary of Statistically Significant Tumor Responses

Tumor Type & Species	Drinking Water Concentration %	Average Daily Dose (mg/kg)	Response Ratio	%	Adj. %	Ref.
Liver Carcinoma	0	0	8/49	16.3	0	NCI (1978)
& adenoma	0.5	720	19/50	38.0	25.9	
(male mouse)	1.0	830	28/47	59.6	51.7	
Liver Carcinoma	0	0	0/50	0	0	NCI (1978)
& adenoma	0.5	380	12/48	25.0	25.0	
(female mouse)	1.0	860	29/37	78.4	78.4	
Liver Carcinoma	0	0	2/49	4.1	0	NCI (1978)
(male mouse)	0.5	720	18/50	36.0	33.3	
	1.0	830	24/47	51.1	49.0	
Nasal Carc.	0	0	0/33	0	0	NCI (1978)
(male rat)	0.5	240	12/33	36.4	36.4	
	1.0	530	16/34	47.1	47.1	
Nasal Carc.	0	0	0/34	0	0	NCI (1978)
(female rat)	0.5	350	10/35	28.6	28.6	
	1.0	640	8/35	22.9	22.9	
Liver Adenoma	0	0	0/31	0	0	NCI (1978)
(female rat)	0.5	350	10/33	30.3	30.3	
	1.0	640	11/32	34.4	34.4	
All liver tumors	0	0	2/106	1.89	0	Kociba
rats: both sexes	0.01	14.3	0/110	0	0	et al. (1974)
	0.1	121	1/106	0.94	0	
	1.0	1184	12.66	18.2	16.6	
Liver Carcinoma	0	0	1/106	0.94	0	Kociba
rats: both sexes	0.01	14.3	0/110	0	0	et al. (1974)
	0.1	121	1/106	0.94	0	
	1.0	1184	10/66	15.2	14.3	
Nasal Carcinoma	0	0	0/106	0	0	Kociba
rats: both sexes	0.01	14.3	0/110	0	0	et al. (1974)
	0.1	121	0/106	0	0	
	1.0	1184	10/66	4.5	4.5	

SOURCE: Young et al. (1978).

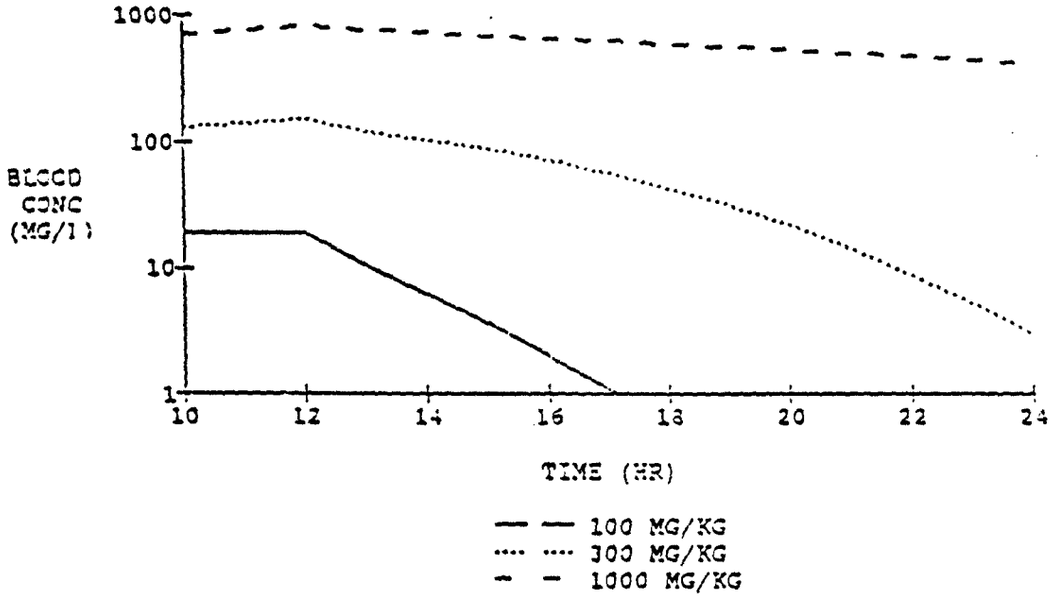


Figure IV-27. Saturation kinetics in dioxane drinking water exposure simulation of decay following 12-hr drinking water exposure at total daily doses of 100, 300, and 1,000 mg/kg dioxane given to rats.

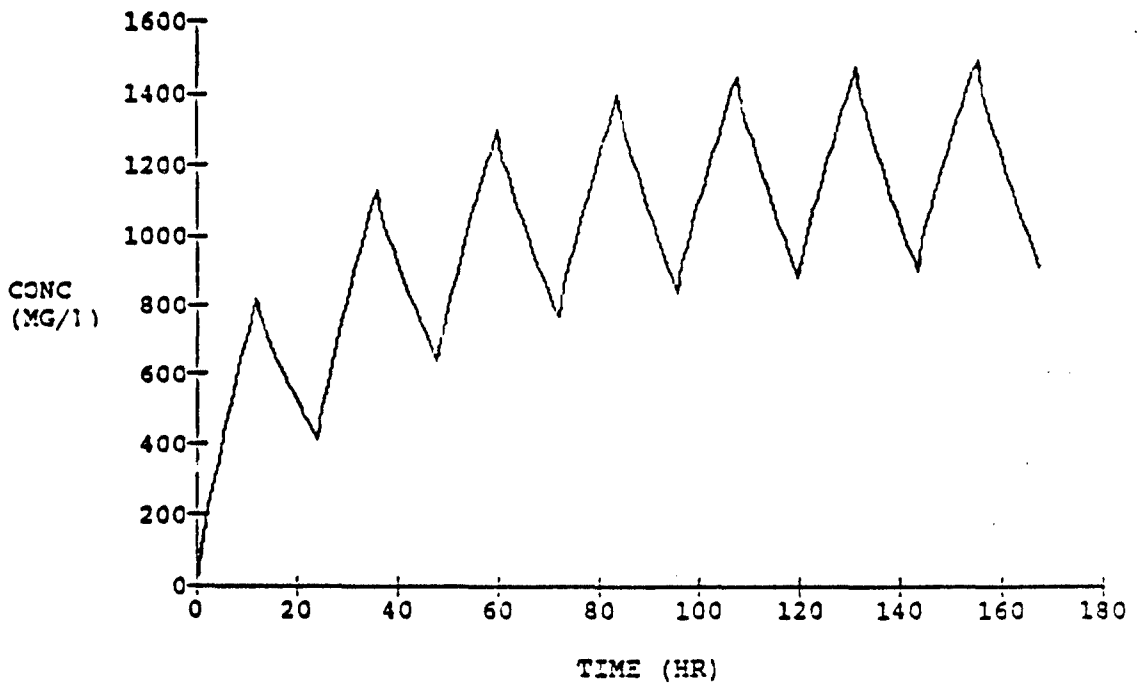


Figure IV-28. Drinking water simulation (1,000 mg/kg total daily dose given to rats).

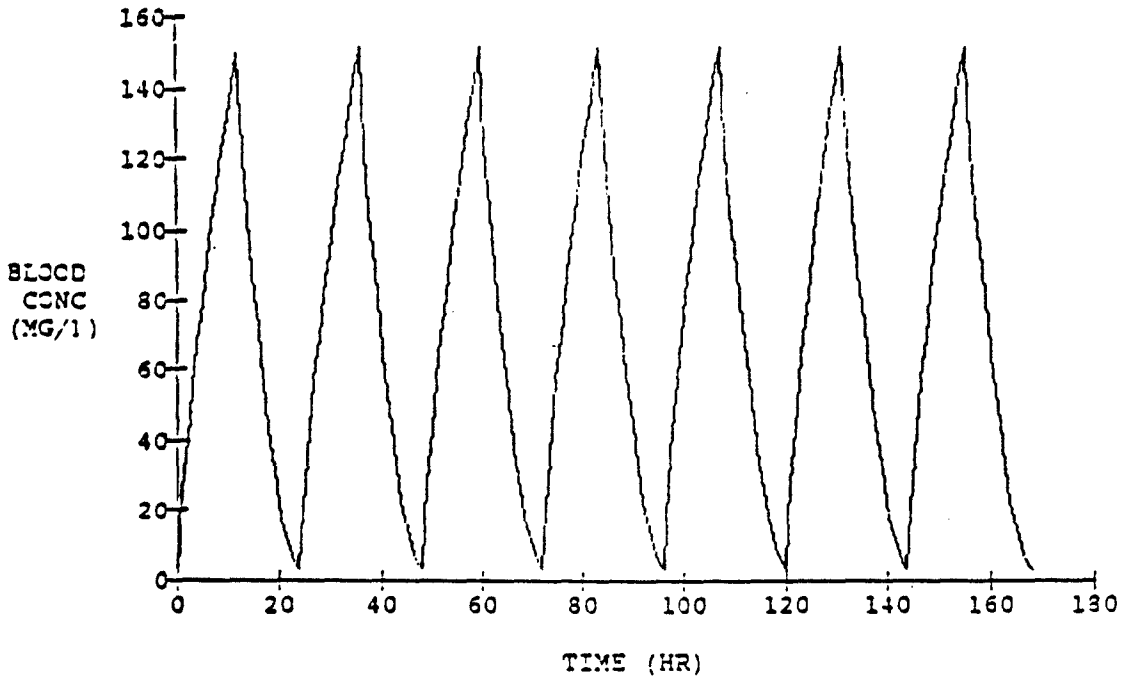


Figure IV-29. Drinking water simulation (300 mg/kg total daily dose given to rats).

Table IV-10. Drinking Water Exposure Simulation (7 days)

Parameter	Daily Dose (mg/kg)	1st 24 hours	7th 24 hours
PEAK (LIVER) (mg/l)	10	1 (0.1)*	1 (0.1)
	30	4 (0.1)	4 (0.1)
	100	20 (0.2)	20 (0.2)
	300	151 (0.5)	152 (0.5)
	1000	827 (0.8)	1498 (1.5)
24 HR LIVER AUC (mg·hr/l)	10	13 (1.3)	13 (1.3)
	30	44 (1.5)	44 (1.5)
	100	213 (2.1)	213 (2.1)
	300	1636 (5.6)	1723 (5.8)
	1000	12471 (12.5)	28793 (28.8)
24 HR EXHALATION (mg)	10	0.05 (0.005)	0.05 (0.005)
	30	0.15 (0.005)	0.15 (0.005)
	100	0.75 (0.007)	0.75 (0.007)
	300	5.9 (0.020)	6.1 (0.020)
	1000	43.7 (0.044)	101.3 (0.10)
24 HR METABOLITE (mg as dioxane)	10	2.4 (0.2)	2.4 (0.2)
	30	7.3 (0.2)	7.3 (0.2)
	100	23.9 (0.2)	23.9 (0.2)
	300	65.2 (0.2)	65.9 (0.2)
	1000	91.1 (0.1)	94.4 (0.1)

*Normalized for the daily dose

of equation 4 could apply, i.e.,

$$Rc = Mmax * r + (Vmax * Mmax)/(K_m + Mmax)$$

where r represents the rate constant for a separate first-order metabolic process. At low concentrations (and low Mmax), the equation would be

$$Rc = Mmax * [r + (Vmax/K_m)]$$

How applicable this analysis in the rat is to the human depends on the reliability of data obtained from human studies. The reports by Young et al. (1977, 1978), showing discordance of volume of distribution for dioxane between rats and humans, demonstrates the necessity of a case by case pharmacokinetic analysis for each compound and the peril inherent in attempting to establish a universally appropriate equation to the pharmacokinetic description of drinking water contaminants.

V. SOME APPLICATIONS OF ELIMINATION TIME TO RISK ASSESSMENT

The assumption that toxicant elimination is a single half-life phenomenon has been used to define a "biological exposure index" (BEI) from Threshold Limit Values (Leu] and Paustenbach, 1988). The same approach can be used for drinking water contaminants, based on an appropriate criterion such as a Maximum Concentration Limit (MCL), usually in units of micrograms per liter. It is necessary to assume a quantity of water consumed, denoted Q (liters/day), during the exposure. Then the BEI in the target tissue is related to the volume of distribution of toxicant in the body, denoted V_d (liters), and the biological half-life, $t_{1/2}$, in days. The relationship is

$$BEI = F * A * Q * MCL * t_{1/2} / Vd * \ln(2) = F * Q * MCL * t_{1/2} / Vd * \ln(2)$$

F is the fractional absorption of contaminant from water. The MCL is determined by health effects criteria. For example, for lead in drinking water, U.S. EPA is currently evaluating values on the order of 10 to 20 µg/l. For adults, we use $t_{1/2}$ = 30 days, Q = 2 liters, F = 0.35, and V_d = 10 liters (about twice the blood volume). Thus, for MCL = 10 µg Pb/l,

$$BEI = (0.35)\ (2\ l/d)\ (10\ \mu g/l)\ (30\ d)\ /(10\ l)\ 0.693$$
$$= 30\ \mu g/l = 3\ \mu g/100\ ml$$

This level is plausible as a maximum allowable average contribution of lead in drinking water to adult blood lead.

VI. REFERENCES

Ahlgren L, Haeger-Aronsen B, Mattsson S, Schutz A. 1980. In-vivo determination of lead in the skeleton after occupational exposure to lead. Br. J. Ind. Med. 37:109-113.

Aldrich FD, Holmes JH. 1969. Acute chlordane intoxication in a child. Case report with toxicological data. Arch. Environ. Health 19:129-132.

Andersen ME. 1981a. A physiologically based toxicokinetic description of the metabolism of inhaled gases and vapors: Analysis at steady state. Toxicol. Appl. Pharmacol. 60:509-526.

Andersen ME. 1981b. Saturable metabolism and its relationship to toxicity. CRC Crit. Rev. Toxicol. 105-129.

Andersen ME. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87:185-205.

Andersen ME, Gargas ML, Ramsey JC. 1984. Inhalation pharmacokinetics: Evaluating systemic extraction, total in vivo metabolism, and the time course of enzyme induction for inhaled styrene in rats based on arterial blood: Inhaled air concentration ratios. Toxicol. Appl. Pharmacol. 73:176-187.

Anderson DH. 1983. Compartmental modeling and tracer kinetics. In: Levin S. (ed) Lecture Notes in Biomathematics. Vol. 50. New York, NY: Springer-Verlag.

Angelo MJ, Bischoff KB, Pritchard AB, Presser MA. 1984. A physiological model for the pharmacokinetics of methylene chloride in B6C3F1 mice following IV administrations. J. Pharmacol. Biopharm. 12(4):413-436.

Astrand I, Kilborn A, Ovrum P, Wahlberg I, Verterberg O. 1974. Exposure to styrene. I. Concentration in alveolar air and blood at rest and during exercise and metabolism. Scand. J. Work Environ. Health 11:69-85.

Aungst BJ, Fung H. 1981. Kinetic characterization of in vitro lead transport across the rat small intestine. Toxicol. Appl. Pharmacol. 61:39-57.

Balba HM, Saha JE. 1978. Studies on the distribution, excretion, and metabolism of alpha and gamma isomers of [^{14}C]chlordane in rabbits. J. Environ. Sci. Health B. 13:211-233.

Bardodej Z, Bardodejova E. 1970. Biotransformation of ethyl benzene, styrene and alpha methyl styrene in man. Am. Ind. Hyg. Assoc. J. 31:206-209.

Barnett JR, Dorough HW. 1974. Metabolism of chlordane in rats. J. Agric. Food Chem. 22:612-619.

Barton JC. 1989. Retention of radiolead by human erythrocytes in vitro. Toxicol. Appl. Pharmacol. 99:314-322.

Batschelet E, Brand L, Steiner A. 1979. On the kinetics of lead in the human body. J. Math. Biol. 8:15-23.

Bert JL, van Dusen LJ, Grace JR. 1988. A generalized model for the prediction of lead body burdens. Environ. Res. 48:117-127.

Blakley PM, Scott WJ. 1984a. Determination of the proximate teratogen of the mouse fetal alcohol syndrome. 1. Teratogenicity of ethanol and acetaldehyde. Toxicol. Appl. Pharmacol. 72:355-363.

Blakley PM, Scott WJ. 1984b. Determination of the proximate teratogen of the mouse fetal alcohol syndrome. 2. Pharmacokinetics of the placental transfer of ethanol and acetaldehyde. Toxicol. Appl. Pharmacol. 72:364-371.

Bogan KT, Hall LC. 1989. Pharmacokinetics for regulatory risk analysis: The case of 1,1,1-trichloroethane (methyl chloroform). Reg. Toxicol. Pharmacol. 10:26-50.

Brimfield AA, Street JC. 1979. Mammalian biotransformation of chlordane: in vivo and primary hepatic comparisons. Ann. NY Acad. Sci. 320:247-256.

Campbell BC, Meredith PA, Moore MR, Watson WS. 1984. Kinetics of lead following intravenous administration in man. Toxicol. Lett. 21:231-235.

Cawley CN, Cale WG, Chehroudi MT. 1979. Simulating metabolic response of a young adult male to changing levels of atmospheric lead. Toronto: SCS.

Chamberlain AC. 1985. Prediction of response of blood lead to airborne and dietary lead from volunteer experiments with lead isotopes. Proc. Roy. Soc. London B. 224:149-182.

Chamberlain AC, Heard MJ, Newton D, Wells AC, Wiffen RD. 1978. Investigations into lead from motor vehicles. AERE Report 9198. London: HMSO.

Chen CW, Blancato JN. 1987. Role of pharmacokinetic modeling in risk assessment: Perchlorethylene as an example. In: Pharmacokinetics in Risk Assessment: Drinking Water and Health. Vol. 8. Washington, DC: National Academy Press.

Christoffersson JO, Ahlgren L, Schutz A, Skerfving S, Mattsson S. 1986. Decrease of skeletal lead levels in man after end of occupational exposure. Arch. Environ. Health 41(5):312-318.

Cohen J, Marcus A, Elias R. 1990. Estimating childhood multimedia lead exposure: expanded uptake/biokinetics model. Paper to be presented at the American Waste Management Association meeting, June 1990.

Colombo A. 1985. The underdefined nature of the blood lead-air lead relationship from biological and statistical grounds. Atmos. Environ. 19:1485-1493.

Cristy M, Leggett RW, Dunning DE, Eckerman KF. 1986. Relative age-specific radiation dose commitment factors for major radionuclides released from nuclear fuel facilities. U.S. Nuclear Regulatory Commission Report NUREG/CR-4628; Oak Ridge National Laboratory Report ORNL/TM-9890.

Curley A, Garrettson LK. 1969. Acute chlordane poisoning: clinical and chemical studies. Arch. Environ. Health 18:211-215.

Dallas CE, Ramanathan R, Muralidhara S, Gallo JM, Bruckner JV. 1989. The uptake and elimination of 1,1,1-trichloroethane during and following inhalation exposures in rats. Toxicol. Appl. Pharmacol. 98:385-397.

deSilva PE. 1981a. Lead in plasma -- its analysis and biological significance. Thesis for Master of Public Health. University of Sydney, Australia.

deSilva PE. 1981b. Determination of lead in plasma and studies on its relationship to lead in erythrocytes. Br. J. Ind. Med. 38:209-217.

Droz PO. 1986. Simultaneous models for organic solvents. In: Safety and Health Aspects of Organic Solvents. NY: Alan R. Liss, Inc.; pp. 73-87.

Droz PO, Guillemin MP. 1983. Human styrene exposure. Int. Arch. Occup. Environ. Health 53:19-36.

Droz PO, Wu MM, Cumberland WG, Berode M. 1989. Variability in biological monitoring of solvent exposure. I. Development of a population physiological model. Br. J. Ind. Med. 46:447-460.

D'Souza RW, Andersen ME. 1988. Physiologically based pharmacokinetic model for vinylidene chloride. Toxicol. Appl. Pharmacol. 95:230-240.

D'Souza RW, Francis WR, Andersen ME. 1988. Physiological model for tissue glutathione depletion and increased resynthesis after ethylene dichloride exposure. J. Pharmacol. Exper. Therap. 245(2):563-568.

Duggan MJ. 1983. The uptake and excretion of lead by young children. Arch. Environ. Health 38(4):246-247.

Engstrom J. 1978. Styrene in subcutaneous adipose tissue after experimental and industrial exposure. Scand. J. Work Environ. Health 4(Suppl. 2):119-120.

Ewing AD, Kadry AM, Dorough HW. 1985. Comparative disposition and elimination of chlordane in rats and mice. Toxicol. Lett. 26:233-239.

Feder PI, Yesair DW, Naber SJ. 1985. Pharmacokinetic applications to quantitative risk assessments. Prepared by Battelle Columbus Division for the U.S. Environmental Protection Agency, Office of Toxic Substances. Contract No. 68-01-6721.

Fernandez JG, Caperos JR. 1977. Exposition au styrene. E' Etude experimentale de l'absorption et l'excretion pulmonaires sur des sujets humains. Int. Arch. Occup. Environ. Health 40:1-12.

Godfrey KR. 1985. Compartmental Models and Their Applications. London: Academic Press.

Griffin TB, Coulston F, Wills H, Russel JC, Knelson JH. 1975. Clinical studies on men continuously exposed to air-borne particulate lead. In: Griffin TB, Knelson JH (eds) Lead. Stuttgart, Germany: Georg Thieme Publishers; pp. 221-240.

Guillemin MP, Bauer D. 1978. Biological monitoring of exposure to styrene by analysis of combined urinary mandelic and phenylglyoxylic acids. Am. Ind. Hyg. Assoc. J. 39:873-879.

Harley NH, Kneip TH. 1985. An integrated metabolic model for lead in humans of all ages. Contract No. 68-B4-4899. Prepared by the New York University Department Environmental Medicine for the U.S. Environmental Protection Agency.

Harrington JM, Baker EL, Folland DS, Saucier JW, Sandifer SH. 1978. Chlordane contamination of a municipal water system. Environ. Res. 15:155-159.

Hart LG, Fouts JR. 1965. Studies of the possible mechanisms by which chlordane stimulates hepatic microsomal drug metabolism in the rat. Biochem. Pharmacol. 14:263-272.

Humbert BE, Fernandez JG. 1977. Exposition an 1,1,1-trichloroethane, contribution a l'etude de l'absorption, de l'excretion et du metabolisme sur des sujets humains. Arch. Mal. Prof. 38:415-425.

Imbriani M. Ghittori S, Pezzagna G, Huang J, Capodaglio E. 1988. 1,1,1-Trichloroethane (methyl chloroform) in urine as a biological index of exposure. Am. J. Ind. Med. 13:211-222.

Jacquez JA. 1985. Compartmental Analysis in Biology and Medicine, 2nd Ed. Ann Arbor, MI: Univ. Michigan Press.

Johanson G. 1986. Physiologically based pharmacokinetic modeling of inhaled 2-butoxyethanol in man. Toxicol. Lett. 34:23-31.

Johanson G, Nasland F-I. 1988. Spreadsheet programming -- a new approach in physiologically based modeling of solvent toxicokinetics. Toxicol. Lett. 41:115-127.

Khasawinah AM. 1989. Chlordane residues in rat and monkey tissues following subchronic inhalation exposure to technical chlordane. Bull. Environ. Contam. Toxicol. 43:459-466.

Kim CS, O'Tuama LA, Mann JD, Roe CR. 1983. Saturable accumulation of the anionic herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D), by rabbit choriod plexus: Early developmental origin and interaction with salicylates. J. Pharmacol. Exper. Therap. 225(3):699-704.

Kneip TJ, Mallon RP, Harley NH. 1983. Biokinetic modeling for mammalian lead metabolism. Neurotoxicol. 4(3):189.192.

Kociba RJ, McCollister SB, Park C, Torkelson TR, Gehring PJ. 1974. 1,4-Dioxane. I. Results of a two-year ingestion study in rats. Toxicol. Appl. Pharmacol. 30:275-286.

Leung H-W, Paustenbach DJ. 1988. Application of pharmacokinetics to derive biological exposure indexes from threshold limit values. Am. Ind. Hyg. Assoc. J. 49:445-450.

Mallon RP. 1983. A metabolic model of lead kinetics based upon measured organ burdens during chronic exposure experiments with infant and juvenile baboons. Doctoral Thesis. Institute of Environmental Medicine, New York University Medical Center, New York, NY.

Manton WI. 1985. Total contribution of airborne lead to blood lead. Br. J. Ind. Med. 42:168-172.

Manton WI, Cook JD. 1984. High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br. J. Ind. Med. 41:313-319.

Marcus AH. 1985a. Multicompartment kinetic models for lead: I. Bone diffusion models for long-term retention. Environ. Res. 36:441-458.

Marcus AH. 1985b. Multicompartment kinetic models for lead: II. Linear kinetics and variable absorption in humans without excessive lead exposures. Environ. Res. 36:459-472.

Marcus AH. 1985c. Multicompartment kinetic model for lead: III. Lead in blood plasma and erythrocytes. Environ. Res. 36:473-489.

Marcus AH. 1985d. Testing alternative nonlinear kinetic models in compartmental analysis. In: Eisenfeld J, Delisi C (eds) Mathematics and Computers in Biomedical Applications. Amsterdam, The Netherlands: Elsevier Press; pp. 259-267.

Marcus AH. 1989. Uptake of lead from formula and food by infants: reanalysis of the Ryu et al. data. Prepared by the Battelle Columbus Division, Arlington Operations for the U.S. Environmental Protection Agency, Office of Toxic Substances. Contract No. 68-02-4294.

Marcus AH, Schwartz J. 1987. Dose response curves for erythrocyte protoporphryin vs. blood lead: effects of iron status. Environ. Res. 44:221-227.

Marcus AH, Feder PI, Hobson DW. 1988. Pharmacokinetic models for fetal exposure to developmental toxicants. Toxicologist 8:462. (Abstract)

Marcus AH, Elias R, Cohen J. 1990. Multi-media lead exposure in children: Biological basis for an expanded uptake/biokinetic model. Toxicologist 79. (Abstract; in press)

Mebus CA, Welsch F, Working PK. 1989. Attenuation of 2-methoxyethanol-induced testicular toxicity in the rat by simple physiological compounds. Toxicol. Appl. Pharmacol. 99:110-121.

Medinsky MA, Bechtold WE, Birnbaum LS, et al. 1988. Uptake of vinylidene fluoride in rats simulated by a physiological model. Fund. Appl. Toxicol. 11:250-260.

Medinsky MA, Sabourin PJ, Lucier G, et al. 1989. A physiological model for simulation of benzene metabolism by rats and mice. Toxicol. Appl. Pharmacol. 99:193-206.

Monster AC. 1979. Difference in uptake, elimination, and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. Int. Arch. Occup. Environ. Health 42:311-317.

Monster AC, Boersma G, Steenweg H. 1979. Kinetics of 1,1,1-trichloroethane in volunteers: influence of exposure concentration and work load. Int. Arch. Occup. Environ. Health 42:293-301.

Mordenti J. 1986. Man versus beast: Pharmacokinetic scaling in mammals. J. Pharm. Sci. 75(11):1028-1040.

Muller KE, Barton CN. 1987. A nonlinear version of the Coburn, Forster and Kane model of blood carboxyhemoglobin. Atmos. Environ. 21(9):1963-1967.

NAS. 1987. National Academy of Sciences. Pharmacokinetics in Risk Assessment: Drinking Water and Health, Vol 8. Workshop proceedings. Subcommittee on Pharmacokinetics in Risk Assessment, Safe Drinking Water Committee, Board on Environmental Studies and Toxicology, Commission on Life Sciences. Washington, DC: National Acedemy Press.

NAS. 1988. National Academy of Sciences. Complex Mixtures - Methods for In Vivo Toxicity Testing. Committee on Methods for the In Vivo Toxicity Testing of Complex Mixtures. Board on Environmental Studies and Toxicology, Commission on Life Sciences. Washington, DC: National Academy Press.

Newton D, Rundo J, Harrison GE. 1977. The retention of alkaline earth elements in man with special reference to barium. Health Phys. 33:45.

Nolan RJ, Freshour NL, Rick DL, McCarty LP, Saunders JH. 1984. Kinetics and metabolism of inhaled methyl chloroform (1,1,1-trichloroethane) in male volunteers. Fund. Appl. Toxicol. 4:654-662.

O'Flaherty EJ. 1981. Toxicants and Drugs: Kinetics and Dynamics. New York, NY: John Wiley and Sons, Inc.

O'Flaherty EJ. 1985. Differences in metabolism at different dose levels. In: Clayson DB, Krewski D, Munro I (eds). Toxicological Risk Assessment. Vol. I. Boca Raton, FL: CRC Press.

O'Flaherty EJ. 1986. The rate of decline of blood lead in lead industry workers during medical removal: The effect of job tenure. Fund. Appl. Toxicol. 6:372-380.

O'Flaherty EJ. 1989. A physiologically-based toxicokinetic model for incorporation of lead into the growing rat skeleton. Toxicologist 9:221. (Abstract)

O'Flaherty EJ, Hamilton JD. 1989. Lead experiments and skeletal development. Toxicologist 8:90.

O'Flaherty EJ, Hammond PB, Lerner SI. 1982. Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fund. Appl. Toxicol. 2:49-55.

Paustenbach DJ, Clewell HJ, Gargas ML, Andersen ME. 1988. A physiologically based pharmacokinetic model for inhaled carbon tetrachloride. Toxicol. Appl. Pharmacol. 96:191-211.

Poonawalla NH, Korte F. 1971. Metabolism of trans-chlordane-^{14}C isolation and identification of its metabolites from the urine of rabbits. J. Agric. Food Chem. 19:467-470.

Rabinowitz MB. 1973. Lead metabolism in the normal human: stable isotope studies. Science 182:725-727.

Rabinowitz MB, Wetherill GW, Kopple JD. 1974. Studies of human lead metabolism by use of stable isotope tracers. Environ. Health Perspect. 7:145-153.

Rabinowitz MB, Wetherill GW, Kopple JD. 1976. Kinetic analysis of lead metabolism in healthy humans. J. Clin. Invest. 58:260-270.

Rabinowitz MB, Wetherill GW, Kopple JD. 1977. Magnitude of lead intake from respiration by normal man. J. Lab. Clin. Med. 90(2):238-248.

Rabinowitz MB, Kopple JD, Wetherill GW. 1980. Effect of food intake and fasting on gastrointestinal lead absorption in humans. Am. J. Clin. Nutr. 33:1784-1788.

Ramsey JC, Andersen ME. 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol. 73:159-175.

Ramsey JC, Young JD, Karbowski RJ, et al. 1980. Pharmacokinetics of inhaled styrene in human volunteers. Toxicol. Appl. Pharmacol. 53:54-63.

Reitz RH, McDougal JN, Himmelstein MW, Nolan RJ, Schumann AM. 1988. Physiologically based pharmacokinetic modeling with methylchloroform: Implications for interspecies, high dose/low dose, and dose route extrapolations. Toxicol. Appl. Pharmacol. 95:185-199.

Reitz RH, Mendrala AL, Guengerich FP. 1989. In vitro metabolism of methylene chloride in human and animal tissues: Use in physiologically based pharmacokinetic models. Toxicol. Appl. Pharmacol. 97:230-246.

Ryu JE, Ziegler EE, Nelson SE, Fomon SJ. 1983. Dietary intake of lead and blood lead concentration in early infancy. Am. J. Dis. Child. 137:886-891.

Schutz A, Skerfving S, Christoffersson JO, Tell I. 1987a. Chelatable lead versus lead in human trabecular and compact bone. Sci. Tot. Environ. 61:201-209.

Schutz A, Skerfving S, Mattson S, Christoffersson J-O, Ahlgren L. 1987b. Lead in vertebral bone biopsies from active and retired lead workers. Arch. Environ. Health 42(6):340-346.

Schwartz SL, Balter NJ. 1988. Physiological pharmacokinetic modeling to estimate human fetal dose for quantitative risk assessment. Abstract WAM-C2. Risk Analysis: Prospects and Opportunities. 1988 Annual Conference, Society for Risk Analysis. Washington, DC.

Seki Y, Urashima Y, Aikawa H, Matsumura H, et al. 1975. Trichloro-compounds in the urine of humans exposed to methyl chloroform at sub-threshold levels. Int. Arch. Arbeitsmed. 34:34-49.

Skerfving S, Ahlgren L, Christoffersson J-O, Haeger-Aronsen B, Mattsson S, Schutz A. 1983. Metabolism of inorganic lead in occupationally exposed humans. Arh. Hig. Rada. Toksikol. 34:341-350.

Skerfving S, Ahlgren L, Christoffersson J-O, Haeger-Aronsen B, Mattsson S, Schutz A, Lindberg G. 1985. Metabolism of inorganic lead in man. Nutr. Res. Suppl. I:601-607.

Skerfving S, Christoffersson JO, Haeger-Aronsen L, Mattson S, Schutz A. 1986. Biological monitoring by in vivo XRF measurements, of occupational exposure to lead, cadmium, and mercury. Biol. Trace Elements Res.

Silbergeld EK, Schwartz J, Mahaffey K. 1988. Lead and osteoporosis: Mobilization of lead from bone in postmenopausal women. Environ. Res. 47:79-94.

Sleet RB, John-Greene JA, Welsche F. 1985a. Paw dysmorphogenesis in CD 1 mice treated with 2-methoxyethanol and methoxyacetic acid in combination with ethanol. Teratol. 31:48A.

Sleet RB, John-Greene JA, Welsch F. 1985b. Exposure of CD-1 mouse maternal and conceptus tissues to radioactivity from a single dose of 2-methoxyethanol. Teratol. 31:48A.

Steenhout A. 1982. Kinetics of lead storage in teeth and bones: An epidemiologic approach. Arch. Environ. Health 37(4):224-231.

Steenhout A. 1985. Cumulative children Pb exposure in coordinated study: Right interpretation of tooth lead data for age, tooth type and resorption process. In: Heavy Metals in the Environment. Vol. I; pp. 426-429.

Steenhout A. 1987. Kinetic and epidemiologic approaches of the human organism responses to lead exposure. A solution for the pb-blood/Pb-air, or Pb-water, Pb-dust...relationships. In: Heavy Metals in the Environment. Vol 2; pp. 280-282.

Steenhout A, Pourtois M. 1981. Lead accumulation in teeth as a function of age with different exposures. Br. J. Ind. Med. 38:297-303.

Stewart RD, Gay HH, Erley DS, Hake CL, Schaffer AW. 1961. Human exposure to 1,1,1-trichloroethane vapor. Relationship of expired air and blood concentrations to exposure and toxicity. Am. Ind. Hyg. Assoc. J. 22:252-262.

Stewart RD, Dodd HC, Baretta ED, Schaffer AW. 1968. Human exposure to styrene vapor. Arch. Environ. Health 18:656-662.

Stewart RD, Gay HH, Schaffer A, Erley D, Rowe VK. 1969. Experimental human exposure to methyl chloroform vapor. Arch. Environ. Health 19:467-472.

Street JC, Blau SE. 1972. Oxychlordane: Accumulation in rat adipose tissue on feeding chlordane isomers or technical chlordane. J. Agric. Food Chem. 20:395-397.

Stuik EJ. 1974. Biological response of male and female volunteers to inorganic lead. Int. Arch. Arbeitsmed. 33:83-97.

Succop PA, O'Flaherty EJ, Bornschein RL, et al. 1987. A kinetic model for estimating changes in the concentration of lead in the blood of young children. In: Lindberg SE, Hutchinson TC (eds) Internal Conference: Heavy Metals in the Environment. Edinburgh, Scotland: EP Consultants Ltd.; pp. 289-291.

Sugita M. 1978. The biological half-time of heavy metals. Int. Arch. Occup. Environ. Health 41:25-40.

Tashiro S, Matsumura F. 1977. Metabolic routes of cis- and trans-chlordane in rats. J. Agric. Food Chem. 25:872-880.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Air Quality Criteria for Lead Volume I - IV. Environmental Criteria and Assessment Office, Office of Research and Development, Research Triangle Park, NC. EPA 600/8-83-028.

U.S. EPA. 1989a. U.S. Environmental Protection Agency. Review of the National Ambient Air Quality Standards for Lead: Assessment of Scientific and Technical Information. OAQPS Staff Report, Research Triangle Park, NC.

U.S. EPA. 1989b. U.S. Environmental Protection Agency. Review of the National Ambient Air Quality Standards for Lead: Exposure Analysis Methodology and Validation. OAQPS Staff Report, Research Triangle Park, NC. EPA-450/2-89-011.

Wagner JG. 1975. Fundamentals of Clinical Pharmacokinetics. Hamilton, IL: Drug Intelligence Publications.

Wariishi M, Nishiyama K. 1989. Observations on the progress of chlordane contamination in humans by blood and sebum analysis. Arch. Environ. Contam. Toxicol. 18:501-507.

Ward RC, Travis CC, Hetrick DM, Andersen ME, Gargas ML. 1988. Pharmacokinetics of tetrachloroethylene. Toxicol. Appl. Pharmacol. 93:108-117.

Welsch F, Sleet RB, Greene JA. 1987. Attenuation of 2-methoxyethanol and methoxyacetic acid-induced digit malformations in mice by simple physiological compounds: Implications for the role of further metabolism of methoxyacetic acid in developmental toxicity. J. Biochem. Toxicol. 2:225-240.

WHO. 1983. World Health Organization. Environmental Health Criteria 26. Styrene. Published under the joint sponsorship of the United Nations Environmental Programme, the International Labor Organization, and the World Health Organization.

Withey JR. 1976. Quantitative analysis of styrene monomer in polystyrene in foods including some preliminary studies of the uptake and pharmacodynamics of the monomer in rats. Environ. Health Perspect. 17:125-133.

Withey JR, Collins PG. 1977. Pharmacokinetics and distribution of styrene monomer in rats after intravenous administration. J. Toxicol. Environ. Health. 3:1011-1022.

Withey JR, Collins PG. 1979. The distribution and pharmacokinetics of styrene monomer in rats by the pulmonary route. J. Environ. Pathol. Toxicol. 2:1329-1342.

Withey JR, Collins BT, Collins PG. 1983. Effect of vehicle on the pharmacokinetics and uptake of four halogenated hydrocarbons from the gastrointestinal tract of the rat. J. Appl. Toxicol. 3(5):249-253.

Yarbrough JD, Chambers JE, Robinson KM. 1982. Alterations in liver structure and function resulting from chronic insecticide exposure. In: Yarbrough JD, Chambers JE (eds) Effects of Chronic Exposures to Pesticides on Animal Systems. New York, NY: Raven Press.

Yesair DW, Feder PI, Chin AE, et al. 1986. Development, evaluation, and use of a pharmacokinetic model for hexachlorobenzene. In: Morris DR, Cabral FRP (eds) Hexachlorobenzene: Proceedings of an International Symposium. IARC Sci. Publ. 77:297-318.

Young JD, Braun WH, Rampy LW, Chenoweth MB, Blau GE. 1977. Pharmacokinetics of 1,4-dioxane in humans. J. Toxicol. Environ. Health 3:507-520.

Young JD, Braun WH, Gehring PJ. 1978. The dose-dependent fate of 1,4-dioxane in rats. J. Toxicol. Environ. Health 4:709-726.

APPENDICES

APPENDIX 1

A Two-Compartment Linear Compartmental Model

Assume that uptake and elimination occur only from compartment 1. Define the following variables:

$C_j(t)$ = concentration in compartment j, where j = 1,2.

V_j = volume of compartment j

r_{10} = rate of elimination of toxicant from comp. 1.

r_{12} = rate of movement from comp. 1 to comp. 2.

r_{21} = rate of movement from comp. 2 to comp. 1.

$a = (r_{12}+r_{21}+r_{10} + [(r_{12}+r_{21}+r_{10})^{2-}4r_{21}r_{10}]^{0\cdot5})_2$

$b = (r_{12}+r_{21}+r_{10} - [(r_{12}+r_{21}+r_{10})^{2-}4r_{21}r_{10}]60\cdot5)_2$

The derived parameters, a and b, are the faster and slower rates for the coupled system. The differential equations are:

$$dC_1(t)/dt = U/V_1 + r_{21}\,C_2(t) - (r_{12} + r_{10})\,C_1(t)$$

$$dC_2(t)/dt = r_{12}\,C_1(t) - r_{21}\,C_2(t)$$

The solution during uptake, starting at $C_j(0) = 0$, are:

$$C_1(t) = U[a-b+(r_{10}-a)\exp(-bt)+(r_{10}-b)\exp(-at)]/V_1 r\pm10(a-b)$$

$$C_2(t) = U\,r_{12}[ab(a-b)+b\,\exp(-at) - a\,\exp(-bt)]/V_2\,ab(a-b)$$

with similarly complex two-component solutions during the elimination phase.

APPENDIX 2

One-Compartment Model with Periodic Exposures

Define the periodic exposure pattern as follows:

P = period, days, between successive exposures.

T = duration of exposure, days, where T < P

f = T/P = fraction of period when exposure occurs.

For example, for non-occupational exposures for 16 hours per day, P = 1 and T = 2/3 day, so that f = 2/3. Then, assuming exposure starts at time t = 0, the concentrations in period i = 1, 2,...:

$$C(t) = (U/Vrf)\ [1 - \exp[-r(t-(i-1)P)] +$$

$$[\exp(rfP)-1]\ (\exp[(i-1)rP]1)\ \exp(-rt)/[\exp(rP)-1]$$

during uptake, when $(i-1)P < t < (i-1+f)P$

$$C(t) = (U/Vrf)\ (\exp(rfP)-1[\exp(irP]-1)\ \exp(-rt)/[\exp(rP)-1]$$

during elimination, when $(i-1+f)P < t < iP$