PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

Science and Applications

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PREFACE

In recent years, there has been an enormous expansion of uses of physiologically based pharmacokinetic (PBPK) modeling in areas related to environmental chemicals and drugs. For individuals interested in PBPK modeling, it is relatively easy to locate and use the contributions of previous authors on a specific chemical of interest. However, it is more difficult to locate broader sets of contributions containing useful modeling techniques and applications. Our purpose was to provide a broad review of the PBPK modeling literature, before the size of the body of work grew large enough to make such an effort prohibitive, and to provide a resource to contain comprehensive coverage of the PBPK modeling literature from its beginnings in the mid-1900s through the first few years of the twenty-first century. This monograph is meant to be a useful reference and educational tool for those professionals and graduate students in toxicology, pharmacology, computational biology, and risk assessment interested in PBPK modeling as a tool for quantifying tissue doses and for describing the response of organisms to chemical exposures.

Our initial literature search in 2001 and updated in 2002, conducted using the Web of Science, Medline, and Toxline databases and incorporating keywords such as physiologically based pharmacokinetic/PBPK model, physiologically based toxicokinetic/PBTK model, and physiologically based pharmacodynamic/PBPD model, uncovered over 1000 references. As the term PBPK model did not become popular until the 1980s, for earlier contributions we relied on literature searches using the names of authors known by the editors to have made early contributions in the field, followed up by searches on other authors and articles cited in these articles. We chose to organize this diverse body of work based on classes of chemicals (e.g., volatile organics and environmental contaminants) and modeling purposes (e.g., perinatal transfer models and dermal absorption models). Our goal was to be fairly comprehensive, but to stress primary contributions in PBPK model development and in applications of these models to investigate factors that regulate chemical distribution within the body. We have also attempted to include articles that appeared over the past few years during completion of this volume. While we have made attempts to be inclusive in our coverage of the PBPK modeling literature, some important contributions may have been missed in our review process. We apologize to authors whose work may have been inadvertently overlooked in these various chapters and not captured by the editorial review.

This monograph describes the development of PBPK modeling for toxic compounds over the past eight decades and their current uses, providing background on the basics of PBPK modeling for understanding the physical, chemical, and biological properties that determine absorption, distribution, metabolism, and elimination of xenobiotics. Early PBPK modeling applications with volatile anesthetics and

chemotherapeutics paved the way for applying these techniques to a wide range of volatile compounds of occupational and environmental significance. The past 15 years have witnessed extensive application with many other classes of chemicals: metals, inorganic chemicals, pesticides, persistent organics pollutants, drugs, and the metabolites of these classes of chemicals. PBPK models have played important roles in unraveling dose–response behaviors based on estimates of tissue dose and have revolutionized low dose and interspecies extrapolations in risk assessment. Following an introductory chapter on PBPK modeling, a series of chapters reviews PBPK model results for various classes of compounds with coverage of historical development, modeling challenges specific to classes of chemicals, and current practices. Comments are also provided regarding the use of these PBPK models to support pharmacodynamic modeling for various toxic responses and future directions where modeling approaches will be helpful.

This monograph arose through efforts of graduate students, postdoctoral fellows, and professors at Colorado State University to review literature in specific areas and produce a series of chapters. These individuals worked in the Quantitative and Computational Toxicology Program at the Center for Environmental Toxicology and Technology in the Department of Environmental and Radiological Health Sciences. Many of these individuals have graduated from Colorado State and left for other positions. The editors wish to express their sincere appreciation for all the assistance provided by these individuals in developing this monograph. Each of these individuals is cited as the authors on the chapters where they contributed.

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Several individuals made important contributions in this project. We thank Dr. Ying Ou, who initiated the project. The authors also thank Mr. Roger Paxton, Miss Christina Barinque, Miss Lisa Casuto, and Mrs. Linda Monum for their valuable assistance with the monograph.

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CHAPTER 1

INTRODUCTION: A HISTORICAL PERSPECTIVE OF THE DEVELOPMENT AND APPLICATIONS OF PBPK MODELS

Melvin E. Andersen, Raymond S. H. Yang, Harvey J. Clewell III, and Micaela B. Reddy

1.1 INTRODUCTION

Pharmacokinetics is the quantitative study of factors that control the time course for absorption, distribution, metabolism, and excretion of chemicals within the body. Pharmacokinetic (PK) models provide sets of equations that simulate the time courses of chemicals and their metabolites in various tissues throughout the body. The interest in PK modeling in toxicology and pharmacology arose from the need to relate internal concentrations of active compounds at their target sites with the doses of chemical given to an animal or human subject. The reason, of course, is the fundamental tenet in pharmacology or toxicology that both beneficial and adverse responses to compounds are related to the concentrations of active chemicals reaching target tissues rather than the amounts of chemical at the site of absorption.

Physiologically Based Pharmacokinetic Modeling, edited by Micaela B. Reddy, Raymond S. H. Yang, Harvey J. Clewell III, and Melvin E. Andersen.

The relationships between tissue dose and administered dose can be complex, especially in high-dose toxicity testing studies, with multiple, repeated daily dosing, or when metabolism or toxicity at routes of entry alter uptake processes for various routes of exposure. PK models of all kinds are primarily a tool to assess chemical dosimetry at target tissues for a wide range of exposure situations.

In physiologically based pharmacokinetic (PBPK) modeling, compartments correspond to discrete tissues or to groupings of tissues with appropriate volumes, blood flows, and pathways for metabolism of test chemicals (Bischoff and Brown 1966). These PBPK models include pertinent biochemical and physicochemical constants for metabolism and solubility in each compartment. Routes of dosing (routes of administration) are included in their proper relationship to the overall physiology. For instance, dermally absorbed compounds penetrate the skin, enter the mixed venous blood, and then travel through the heart and lungs to the arterial blood for distribution. Orally absorbed compounds move through intestinal tissues and portal blood to the liver before moving to the mixed venous blood for distribution to the remainder of the body. The equations that form the basis of the PBPK model also account for the time sequence of dose input into test subjects and permit input by multiple routes, if necessary, for specific exposure situations. Each compartment in the model is described with a mass-balance differential equation (MB-DE) whose terms mathematically represent biological processes. The set of equations is solved by numerical integration to simulate tissue time-course concentrations of chemicals and their metabolites.

Some PBPK models account for interactions of circulating compounds with specific receptors or the covalent interactions of chemicals with tissue constituents. Modeling these reversible and irreversible molecular interactions with cell constituents is the initial step in developing physiologically based pharmacodynamic (PBPD) models for effects of chemicals on biological processes. This monograph emphasizes progress in PBPK rather than PBPD modeling. A number of short reviews are available that focus on earlier stages of the development of PBPK modeling approaches (e.g., Himmelstein and Lutz 1979; Gerlowski and Jain 1983; Leung 1991), including a volume on PBPK modeling in chemical risk assessment (National Research Council 1987). More recent progress in PBPK modeling has not yet been thoroughly reviewed. Some of the aims of this volume are to provide an overview of the range of applications of PBPK modeling, the classes of compounds evaluated with these tools, and the insights derived from the application of PBPK models to the distribution of chemicals in intact animals. This first chapter traces the history and background of PBPK modeling over the last century, providing the background that places in perspective the rather astonishing expansion of PBPK modeling in toxicology and risk assessment over the past decade. The subsequent chapters focus either on specific chemical classes or on specific model applications.

1.2 A HISTORICAL PERSPECTIVE

The history of PBPK modeling for drugs and environmental compounds provides an interesting look at the interface between posing scientific questions and the tech-

nologies necessary to solve them. It also highlights the interdisciplinary contributions—from medicine, engineering, toxicology, pharmaceutics, and risk assessment—that made the present-day use of these PBPK modeling tools a reality. The scientific question posed almost from the earliest PK studies was, What physiological processes are important in creating and maintaining sufficient tissue concentrations of a test compound to ensure a biological effect? This question, in one form or another, motivates almost all PBPK modeling contributions whether in pharmacology or toxicology.

1.2.1 Responses to Inhaled Compounds

Inhalation anesthesiologists have maintained a long tradition of understanding the role of ventilation rates, blood flow rates, and tissue solubility on the uptake and distribution of volatile anesthetics to the central nervous system. In the 1920s, Haggard (1924a,b) quantitatively described the importance of physiological factors for the uptake of ethyl ether into the body during the first few breaths. Accomplishing this analysis required writing an equation for the relationship between inhaled ether and the concentration of ether in blood. Tools for solving this equation over time were not available, so the mathematical analysis was limited to the first few breaths when venous concentrations remained small. The American Chemical Society Monograph Series, Vol. 35 by Henderson and Haggard (1942) represents, to the authors of this chapter, the first detailed discussion of toxicology of inhaled compounds in the context of the principles that control exposure, absorption, and physiological actions. It is the first articulation of a PBPK modeling strategy in occupational and environmental toxicology.

More complete PBPK models for inhalation were provided by Kety (1951), Mapleson (1963), and Riggs (1963). In these models, body tissues were lumped together based on blood perfusion rates, giving sets of tissues referred to as richly perfused or poorly perfused. Mapleson (1963) solved the set of equations using an analog computer to give solutions to the complete time course within the various tissue groups. These analog computer PBPK models for inhaled gases and vapors were extended by Fiserova-Bergerova and colleagues (1975, 1979, 1980) to focus on compounds in the occupational environment and to describe metabolism of these compounds in liver. The extension to include metabolism was particularly important for subsequent work in toxicology because most compounds of interest in occupational toxicology are metabolized and metabolites are often involved in toxic responses.

1.2.2 Pharmaceutical Applications

In the 1930s, Teorell (1937a,b) provided a set of equations for uptake, distribution, and elimination of drugs from the body. These articles are rightly regarded as providing the first physiological model for drug distribution. However, computational methods were not available to solve the sets of equations at this time. Exact mathematical solutions for distribution of compounds in the body could only be obtained for simplified models in which the body was reduced to a small number of com-

partments that did not correspond directly with specific physiological compartments. Over the next 30 years, PK modeling focused on these simpler descriptions with exact solutions rather than on developing models more concordant with the structure and content of the biological system itself. These approaches are sometimes referred to as "data-based" compartmental modeling since the work generally took the form of a detailed collection of time-course blood/excreta concentrations at various doses (Fig. 1.1). Time-course curves were analyzed by assuming particular model structures and estimating a small number of model parameters by curve-fitting. In the earliest of these models, all processes for metabolism, distribution, and elimination were treated as first-order (i.e., they increased in direct proportion to the concentration of the chemical species). Two areas of concern that particularly affected data-based compartmental PK modeling arose in the 1960s and early 1970s: (1) the saturation of elimination pathways and (2) the possibility that blood flow rather than metabolic capacity of an organ might limit clearance. Saturation led to models that were not first-order, making it difficult to derive exact solutions to the sets of equations. Blood-flow-limited metabolism in an organ meant that the removal rate constant (k_{out}) from a central compartment (Fig. 1.1) could not increase indefinitely as the metabolic capacity increased.

1.2.3 Occupational and Environmental Applications

Data-based compartmental models were brought to toxicology and risk assessment in a series of innovative studies by the late Dr. Perry Gehring (1938–2003) and his colleagues at the Dow Chemical Company in Midland, MI, in order to examine PK behavior where specific elimination pathways, both metabolic and excretory, become saturated at high doses (Gehring *et al*. 1976, 1977, 1978). In the hands of the Dow research team, nonlinear-data-based compartmental models were ingen-

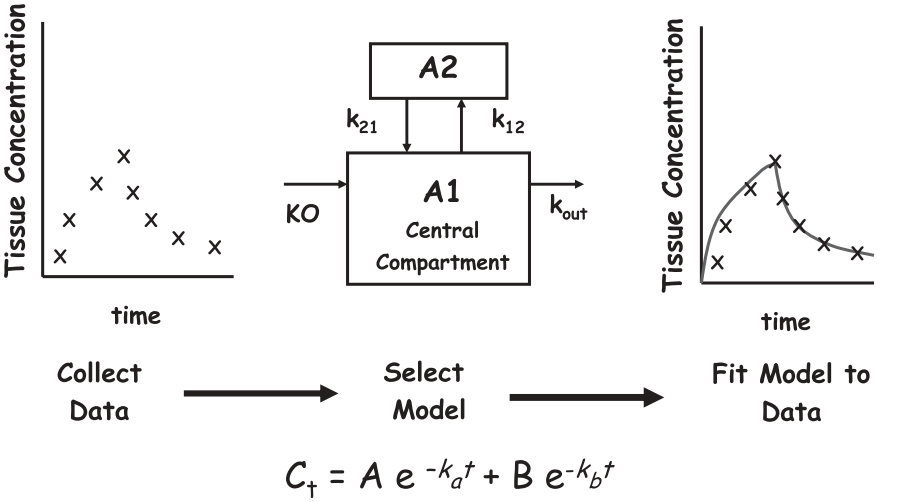

Figure 1.1 Schematic diagram depicting a method for developing data-based compartmental PK models.

iously applied to a series of compounds of toxicological and commercial importance including herbicides (Sauerhoff *et al*. 1976; 1977), solvents (McKenna *et al*. 1982), plastic monomers (McKenna *et al*. 1978a, 1978b), and hydrocarbons (Young *et al*. 1979; Ramsey *et al*. 1980). The final piece of technology needed to bring a full PBPK approach to studying factors that determine chemical disposition came with the rapid development of digital computation by the engineering community and the availability of these tools within the research laboratory at the Dow Chemical Company.

1.2.4 Digital Computation and PBPK Modeling

Scientists trained in chemical engineering and computational methods developed PBPK models for chemotherapeutic compounds—that is, chemicals used in cancer therapy (Bischoff *et al*. 1971). Many of these compounds are highly toxic and have therapeutic efficacy by being slightly more toxic to rapidly growing cells (the cancer cells) than to normal tissues. Initial successes with methotrexate (Bischoff *et al*. 1971) led to PBPK models for other compounds, including 5-fluorouracil (Collins *et al*. 1982) and cisplatin (Farris *et al*. 1988). These seminal contributions showed the ease with which realistic descriptions of physiology and relevant pathways of metabolism could be incorporated into PBPK models for chemical disposition and paved the way for more extensive use of PBPK modeling in toxicology and chemical risk assessment. These models took advantage of the increasing availability of digital computation on main frame computers for solving sets of MB-DEs.

Ramsey and Andersen (1984) applied a PBPK modeling approach to describe the disposition of styrene in rats and humans for a range of concentrations and for several routes of administration. One of these two scientists (J. C. Ramsey) was a member of the PK group developing nonlinear PK models for chemicals at Dow Chemical Company and solving these models with a modern software package for solving sets of MB-DEs by numerical integration. The other (M. E. Andersen) had worked in inhalation toxicology laboratories at the Wright-Patterson Air Force Base, OH, and developed a steady-state analysis of PBPK models for inhalation of metabolized vapors (Andersen 1981). This interinstitutional collaboration with styrene (Ramsey and Andersen 1984; Andersen *et al*. 1984) relied on advances from inhalation anesthesia, data-based compartmental modeling, pharmaceutics, chemical engineering, and digital computation, to create PBPK models that would support extrapolation across species, between exposure routes, and from high to low doses. Using scale-up methods common for engineering models (Dedrick 1973), the interspecies PBPK model for styrene (Fig. 1.2) was able to predict blood and exhaled air time-course curves for oral and intravenous dosing in the rat and for inhalation exposures in human volunteers. This ability to support extrapolation to untested (and sometimes untestable) conditions is an essential part of risk assessment and has made these PBPK models attractive tools in human health risk assessments of various kinds (Clewell and Andersen 1985; National Research Council 1987). In the styrene PBPK model, the liver was split off as a separate compartment (i.e., rather than embedded in a central compartment), metabolism in the liver was saturable (i.e., fol-

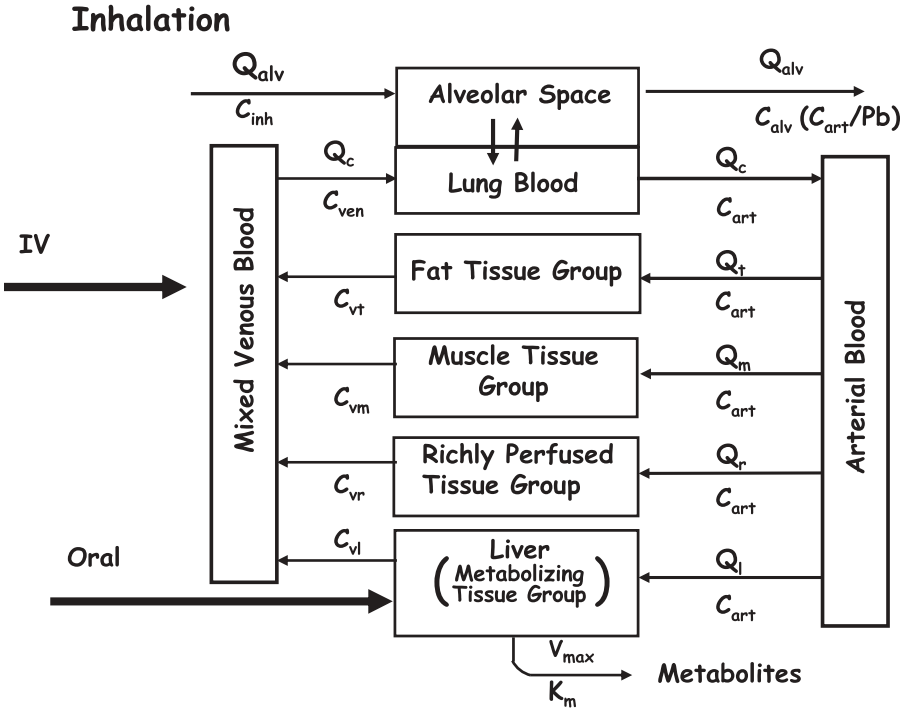

Figure 1.2 Schematic diagram of a multidose route PBPK model for a volatile compound.

lowed Michaelis–Menten kinetics), and styrene clearance from tissues was directly based on blood flow and metabolic characteristics of tissues.

1.3 EXPANSION OF PBPK MODEL APPLICATIONS

Even though the primary developments in PBPK approaches by the chemical engineering community were with pharmaceutical, primarily antineoplastic, compounds, the real expansion of the application of digital computation to create PBPK models of increasing complexity since the 1980s occurred when these methods were applied to environmental compounds and to chemical risk assessment. In pharmaceutical arenas, some of the inertia to developing PBPK models was due to the idea that extrapolations were unnecessary since PK data would eventually be developed in clinical studies. Some inappropriate "myths" which hampered the development of PBPK modeling in pharmaceutical industry and elsewhere have been discussed in a recent review on PBPK/PD modeling (Yang *et al.* 2004). This viewpoint neglects other attributes inherent in PBPK approaches. Among the opportunities offered by PBPK approaches are: (1) creating models from physiological, biochemical, and anatomical information, entirely separate from collection of detailed concentration time-course curves; (2) evaluating mechanisms by which biological processes govern disposition of a wide range of compounds by comparison of PK results with

model predictions; (3) using chemicals as probes of the biological processes to gain more general information on the way chemical characteristics govern the importance of various transport pathways in the body; (4) applying the models in risk assessments for setting exposure standards; and (5) using annotation of a modeling database as a repository of information on toxicity and kinetics of specific compounds. Each of these is discussed in turn.

1.3.1. PBPK Models for Tissue Dosimetry from Secondary Data

The advent of biologically structured PBPK models had a dramatic influence on the nature of the experiments conducted to determine PK behavior and to estimate tissue dosimetry. In PBPK descriptions, time-course behavior is not an intrinsic property of the organism accessible only by direct experimentation. Instead, it is a composite behavior, governed by more fundamental physiological and biochemical processes. More importantly, these fundamental processes can be studied in simpler systems to obtain the necessary PBPK model parameters in experiments separate from collection of time-course concentration curves (Fig. 1.3). Based on these parameters and an appropriate model structure, tissue time-course behaviors can be predicted by computer simulation with PBPK models and compared to data as a test of model performance.

Volatile chemicals have provided a good test bed for examining this approach to PBPK modeling. The disposition of volatiles in the body is related to breathing rates, tissue volumes, tissue blood flow rates, tissue partition coefficients, and kinetic constants for metabolism of the chemical in particular tissues. Physiological factors important in developing an appropriate and useful PBPK model have been discussed

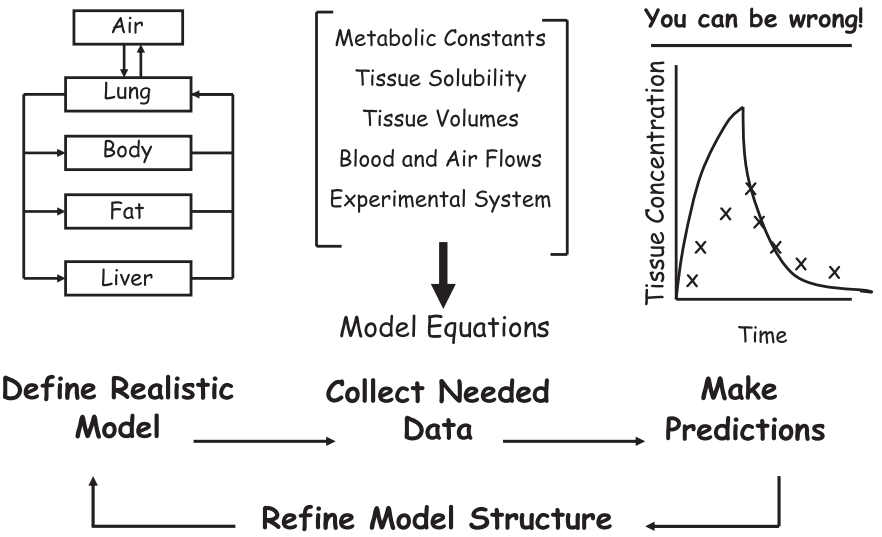

Figure 1.3 Schematic diagram depicting a method for developing PBPK models.

by Krishnan and Andersen (2001). Physiological parameters can be found in the biomedical literature, and they were recently compiled by Brown *et al*. (1997). Partition coefficients can be measured by equilibrating tissue homogenates in a vial with an atmosphere containing the test chemical (Sato and Nakajima 1979a; Gargas *et al*. 1989). Constants for metabolism (enzyme kinetic constants for saturable, first-order or second-order reactions) can be determined *in vitro* with tissue homogenates, microsomal preparations, liver slices, and so on, by supplementing these preparations with reactants to promote metabolic reactions (Sato and Nakajima 1979b; Hilderbrand *et al*. 1981; Kedderis *et al*. 1993). Another method for assessing metabolic parameters *in vivo* relies on closed chamber inhalation techniques. Here, a small numbers of live animals are placed in a closed chamber to measure the rate of loss of chemical at a variety of chamber concentrations (Hefner *et al*. 1975; Filser and Bolt 1979; Gargas *et al*. 1986). These *in vitro* and *in vivo* experiments can provide all the parameters necessary for constructing a PBPK model for the parent chemical; also, time-course behavior is now "predictable," based on results of these ancillary studies. Other approaches for developing predictive PBPK models include using structure–activity relationships (SARs) to estimate model parameters for classes of compounds (Parham *et al*. 1997; Parham and Portier 1998; Poulin and Krishnan 1996, 1999). While these approaches to parameterizing PBPK models by *in vitro*/simple *in vivo* studies are attractive for reducing the number of animals required for model development, some *in vivo* experimentation will nearly always be required to test the accuracy of the predicted behavior.

1.3.2 Biological Mechanisms Underlying Pharmacokinetic Behaviors

Predictions from PBPK models have a very useful property: They can be wrong. The ability to predict a particular outcome is a powerful tool for enhancing the information content of an experiment. In effect, PBPK models, based on proposed mechanisms of disposition, make predictions that become testable (Fig. 1.3). *Trans*-1,2-dichloroethylene (*t*DCE) provided a good example of a fairly spectacular, but enlightening, failure of a PBPK model. A simple PBPK model structure worked well in predicting the disappearance of a diverse group of volatile chemicals from a closed chamber (Gargas *et al*. 1986, 1990). This closed chamber study uses a small animal inhalation system with a recirculated atmosphere where carbon dioxide is removed by chemical adsorption and oxygen added back as it is utilized by respiration during the study. Chemical is added at time zero at various initial concentrations, and the diminution of chamber chemical is evaluated over time. The PBPK model for volatiles had time-invariant metabolic constants (maximum velocity and affinity constant, V_{max} and K_m, respectively) in liver and regarded the chamber atmosphere as another compartment. This model successfully described the behavior of many gases and vapors.

When applied to loss of *t*DCE from the chamber, the PBPK model was unable to fit the uptake curves (Gargas and Andersen 1988; Gargas *et al*. 1990). *t*DCE, or, more accurately, metabolites of *t*DCE, appeared to rapidly react with and inactivate the enzyme(s) responsible for *t*DCE metabolism (Lilly *et al*. 1999). A successful PBPK description for *t*DCE accounted for loss of *t*DCE metabolizing capacity over