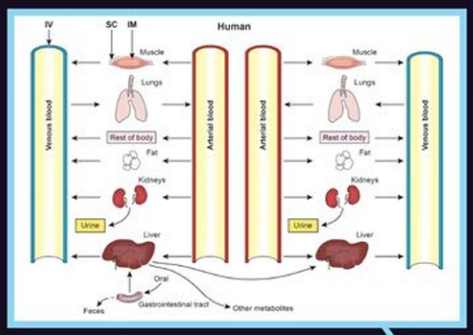
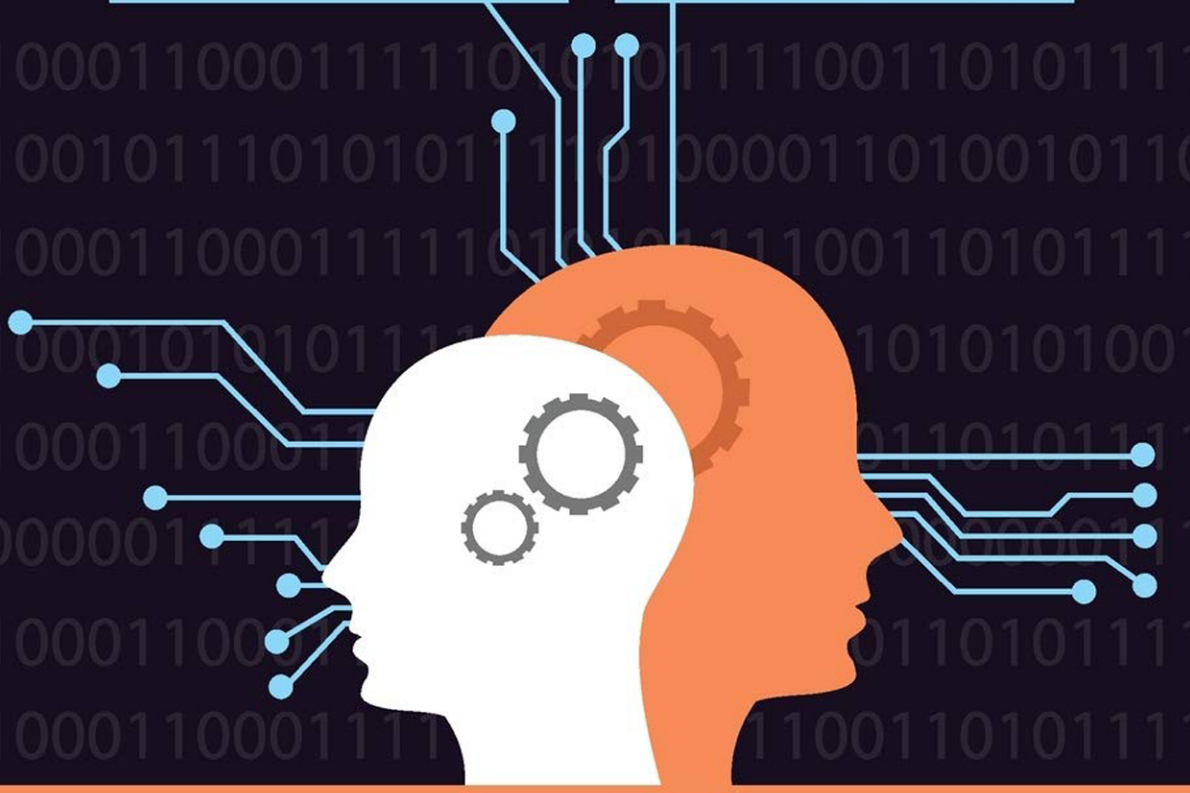
Physiologically Based Pharmacokinetic (PBPK) Modeling

Methods and Applications in Toxicology and Risk Assessment





Edited by
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ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
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British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-818596-4

Publisher: Andre Wolff
Acquisitions Editor: Kattie Washington
Editorial Project Manager: Timothy Bennett
Production Project Manager: Niranjan Bhaskaran
Cover Designer: Matthew Limbert

Typeset by MPS Limited, Chennai, India

Contents

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https://www.elsevier.com/books-and-journals/book-companion/9780128185964

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Foreword

It is a distinct pleasure to recommend this timely book, *Physiologically Based Pharmacokinetic (PBPK) Modeling: Methods and Applications in Toxicology and Risk Assessment*. My introduction to PBPK modeling took place 40 years ago while writing a review article, *Saturable Metabolism and its Relationship to Toxicity*. In doing the literature review for this paper, I discovered the work of pioneering chemical engineers in developing PBPK models to examine the tissue disposition of antineoplastic compounds used in human medicine. At that time, my interests were in understanding the kinetics, toxicology, and likely risks posed by inhalation of compounds in occupational environments. This work required kinetic models for parent compounds and rates of formation of various metabolites. With a collaborative team from Wright-Patterson Air Force Base, Dayton, OH, United States and the Toxicology Research Laboratory, Dow Chemical, Midland, MI, United States, we developed tools for collecting time course data on chemicals and metabolites and for developing PBPK models for these compounds. The process was slowed because we had to learn while we went along. There were neither textbooks discussing methods and approaches for using PBPK modeling to understand disposition of chemicals in animals and people nor clear protocols showing how to use these models in chemical risk assessment.

It became clear almost immediately that there were many potential applications of PBPK modeling in toxicology—understanding the relationship of external, applied doses, and relevant tissue dose at sites of action; clarifying interactions between chemicals that would affect tissue dose; predicting amounts of metabolites produced by various metabolic pathways; applying knowledge of tissue dosimetry in test species to infer tissue dosimetry in humans; looking at tissue dosimetry changes that would accompany different life stages; accounting for variability expected in human populations; and applying PBPK models in formal human health risk assessments. The Wright-Patterson group pursued research in all these areas in the 1980s and 1990s. Two of the editors of this book were integral parts of the collaborative team at Wright-Patterson AFB.

My research interests were relatively narrow, to understand the chemical moieties that caused toxicity and develop PBPK tools to predict tissue exposures to these moieties for various exposure modalities and in various species. The late Dr. Jim Gillette, an accomplished and productive pioneer in PK modeling with drugs, once told me that the only reason for doing pharmacokinetics is that it is impossible to do pharmacodynamics until the PK is understood. This simple concept has been the focus of most of my efforts with PBPK modeling. Another and arguably a more significant

thread in PBPK modeling is its application to improve human health risk assessment. The key contributor at Wright-Patterson in using PBPK methods for these purposes was Dr. Harvey Clewell who provided a more practical appreciation of the use of this new tool in chemical risk assessment.

The next challenge was to spread the technology for PBPK modeling to a larger audience. There were short courses offered at various institutions, especially those as Colorado State University, under the leadership of Dr. Raymond Yang. Two books appeared, *Physiologically Based Pharmacokinetics: Science and Applications* and *Quantitative Modeling in Toxicology*, published in 2005 and 2010, respectively. The first was a review of the field focused on PBPK models for various classes of chemicals. The second, although it provided examples with model code for various applications, was not organized to facilitate its use as a teaching resource. In the last 10 years since publication of this second book, the field of PBPK modeling and its use in risk assessment has grown and witnessed the introduction of new modeling software and new platforms allowing computationally intensive PBPK analyses. Our field badly needs a text to serve as a hands-on guide to PBPK modeling and provide materials for courses in PBPK modeling geared both toward beginners and to more advanced users.

The editors and authors have produced a clear, comprehensive contribution that will serve both as a textbook and as a reference text. I am pleased to see the appearance of this overdue guide to our field and the admirable efforts of these three accomplished investigators—Drs. Jeffrey Fisher, Jeffery Gearhart, and Zhoumeng Lin—in shepherding its completion. My congratulations to all who worked to make this book a reality and their efforts to provide materials to make introduction to PBPK modeling a more structured process for the next generation of practitioners.

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Preface

The question, "Do we need a physiologically based pharmacokinetic (PBPK) modeling book for toxicology?" was discussed by Jeffery Gearhart, Zhoumeng Lin, and Jeffrey Fisher for several months. Two of us, Zhoumeng Lin and Jeffrey Fisher, each taught a graduate class in PBPK modeling for chemical toxicology. We knew that students, usually from a wide range of backgrounds, had trouble learning the basics of PBPK modeling because reading published PBPK modeling papers is very difficult without some understanding of basic kinetic and modeling principles. In our graduate classes we did not have a textbook to teach the fundamental principles for PBPK model construction. We created lectures and exercises for the students. Therefore we decided to create a book with exercises, that is a textbook with PBPK model examples, so students and professionals can learn basic principles of PBPK modeling. A portion of this textbook represents experimental and computational methods that initially were created by a group of researchers at Wright-Patterson AFB, OH from the late 1980s through the 1990s. A time period when PBPK modeling ideas were translated into accomplishments. This helped set the stage for the use of computational methods in toxicology. Jeffery Gearhart and Jeffrey Fisher were thrilled to be part of this group led by Dr. Melvin E. Andersen.

The Chapter 1, "A history and recent efforts of selected PBPK modeling topics," provides a very basic introduction to the field of PBPK modeling, including historical information and more recent modeling activities. Over the last several decades, PBPK models have been increasingly used in various applications. We tried our best to cover relevant topics by discussing representative publications for selected applications. However, due to the large number of excellent PBPK studies, some may have been missed in this chapter. We apologize to authors whose work may have been unintentionally overlooked. This chapter is for readers who have no experience with PBPK models. If you have some background in PBPK modeling you may want to breeze through this chapter.

In Chapter 2, "Introduction to classical pharmacokinetics," the readers are introduced to classical pharmacokinetics. The authors review the basic principles of pharmacokinetics and the derivation of equations. Knowledge of noncompartmental and compartmental pharmacokinetic analyses is helpful for the reader to understand better the details of PBPK modeling.

In Chapter 3, "Fundamentals of PBPK modeling," various aspects of classical PBPK modeling principles are introduced to the reader. If you are new to PBPK

modeling, spend some time in this chapter to learn basic concepts and coding methods. Find a software platform to run the simulation exercises.

Chapter 4, "PBPK modeling software," is a current review of software available for readers. The readers who are new to PBPK modeling have several options for software. This chapter provides an evaluation of software options that may fit your needs, ranging from open-source software to software that requires annual fees.

Chapter 5, "Chemical absorption and writing code for portals of entry," provides examples for how to write code to mimic dosing or exposures to chemicals, including uptake of chemicals in contact with skin. Writing code to administer a chemical requires programming and there are several methods used because the coding maybe software-dependent.

Chapter 6, "PBPK model: distribution processes," addresses the fundamental principles for distribution of chemicals in the body. Understanding how chemicals enter through the exposure portal, transport throughout the circulatory system, and move across membranes to achieve concentrations within tissue compartments is the whole purpose and intent of building and exercising PBPK models for chemical exposure assessment. This chapter covers chemical thermodynamics as it relates to tissue distribution, addresses flow-limited and permeability-limited PBPK distribution models, as well as key issues of tissue binding, predictive models for partition coefficients, and lastly when protein transporters should be added to the PBPK model description for a chemical or drug.

Chapter 7, "Metabolism and PBPK models," provides a brief introduction into a complex topic. Historically, metabolism was an important aspect of PBPK models for assessing dose–response relationships. In this chapter we do not review the metabolic pathways. Examples of PBPK models are provided that describe metabolism, so the reader can learn how to write code for metabolic pathways in a PBPK model. Only a few examples are presented; thus the readers may need to search the published literature to find examples more relevant to their interests.

Chapter 8, "PBPK model: excretion via urine, feces, and breath," introduces the mechanisms of different excretion pathways, with a focus on urinary excretion, biliary excretion, and excretion via exhalation. Various PBPK modeling methods and equations describing these different excretion pathways are discussed with multiple examples.

Chapter 9, "Population PBPK analysis methods," addresses one of the common applications for fully developed PBPK models. That is, "How does one expand the "validated" model that is invariably based on point estimate values for all the model parameters, to populations, with consideration of variability in model parameters?" The answer is using Monte Carlo methods. In this chapter the origins of the Monte Carlo method are briefly discussed, the fundamental principles are reviewed, and then finally a detailed step-by-step description is given for how to use this method in a

PBPK model. The result is a distribution of model predictions. The exercises emphasize the basic construction of a Monte Carlo analysis, from model selection, model modifications, parameter setting and defining distributions, to lastly running and completing the Monte Carlo analysis for the PBPK model.

Chapter 10, "PBPK model calibration, evaluation, and performance assessment," introduces the processes of parameterization, calibration, evaluation, and performance assessment of PBPK models. This is an important aspect of model development and reporting. Enacting these methods requires experience and judgment. Several PBPK model examples are given, including two environmental chemicals, a drug, and a nanoparticle. Additionally, different software programs are illustrated for the reader with step-by-step instructions and model codes.

Chapter 11, "PBPK modeling in risk assessment," presents applications of PBPK models to address human health risk for chemical exposures. A basic overview of toxicological risk assessment is present and then placed in the context of how PBPK models are used to advance the process. The authors discuss the regulatory history of the "Red Book" and more recent human health risk assessment methods as conveyed by the National Academies, "Using 21st Century Science to Improve Risk-Related Evaluations." Specific risk assessment nomenclature is presented as it relates to toxicological principles of "dose defines the poison," reasons for choosing to utilize the PBPK model approach, a detailed overview of the risk assessment suitability evaluation process, components of model evaluation, and lastly examples of the use of PBPK models in different risk assessments and related exercises.

Chapter 12, "Physiologically based pharmacokinetic models to support modernized chemical safety assessment," introduces the emerging new roles of PBPK modeling in support of toxicity testing and risk assessment for the 21st century. New concepts of generic PBPK modeling, rapid PBPK modeling and parameterization, and quantitative in vitro-to-in vivo extrapolation (QIVIVE) are introduced. Applications of QIVIVE-PBPK to support high-throughput toxicity testing and ranking, context-dependent risk assessment beyond prioritization, and compound-specific risk assessment are discussed.

CHAPTER 1

A history and recent efforts of selected physiologically based pharmacokinetic modeling topics

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1.1 Introduction

Pharmacokinetics is the science of studying the rate and extent of absorption, distribution, metabolism, and excretion (ADME) processes of chemicals and their metabolites within the body, as well as the factors that control the time course of these processes using experimental or mathematical modeling approaches. Pharmacokinetic modeling is the quantitative study of the time course of ADME processes of chemicals and their metabolites in the body using a set of mathematical equations. Pharmacokinetics of a chemical can be described using different quantitative approaches, including compartmental modeling (i.e., traditional or classical approach), noncompartmental approach (i.e., statistical moment approach), and physiologically based pharmacokinetic (PBPK) modeling approach. An overview of the compartmental and noncompartmental pharmacokinetic approaches is presented in Chapter 2, Introduction to classical pharmacokinetics. This first chapter covers the history and recent efforts of the development and applications of PBPK modeling. The rest of this book is devoted to the principles, methodology, and applications of PBPK models in the field of toxicology and risk assessment.

PBPK models are useful in risk assessment because they can link internal target organ concentrations of chemicals with the external doses of the chemicals that animals or humans are exposed to, and they can also be used to extrapolate the simulation results from one exposure scenario to another, from one species to another, and from in vitro to in vivo. This is important because one fundamental tenet in pharmacology and toxicology is that both the beneficial and toxic effects of chemicals are related to the concentrations of the chemicals at the target organs, rather than the concentrations of the chemicals at the site of exposure (Andersen et al., 2005). In addition, concentration-time data of different exposure regimens are often needed, whether it is

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DOI: https://doi.org/10.1016/B978-0-12-818596-4.00001-1

for clinical dose optimization of a drug or for risk assessment of an environmental chemical. Traditional pharmacokinetic approaches are empirical approaches and are limited in usefulness in extrapolation beyond the range of the experimental data, whereas PBPK modeling is a physiologically based approach that can be extrapolated across species, exposure routes, exposure durations, and doses. Overall, PBPK models require more parameters, are relatively more complex and computationally more demanding than traditional pharmacokinetic models, but PBPK models are more robust than traditional pharmacokinetic models, and their unique strengths can better meet the needs of drug dose optimization or chemical risk assessment.

1.2 A historical perspective

The concept of PBPK modeling can be traced back to approximately the beginning of the 20th century. Fig. 1.1 lists representative studies of PBPK modeling and applications in the fields of pharmacology, toxicology, risk assessment, veterinary medicine, and food safety assessment that are further discussed below.

1.2.1 Early efforts on inhaled compounds

In the 1920s, Haggard (1924a,b) developed mathematical equations to simulate the concentration of the volatile anesthetic ethyl ether in the blood after inhalation exposure. The model was limited to the first few breaths when the concentrations in the blood were still low due to lack of tools to solve the mathematical equations. According to the earlier book on PBPK modeling (Andersen et al., 2005), the American Chemical Society Monograph Series, Vol. 35 by Henderson and Haggard (1943) presents the first detailed discussion of toxicology of inhaled noxious gases in the context of the principles that control exposure, absorption, and distribution. This work is considered as the first articulation of the PBPK modeling concept in the field of occupational and environmental toxicology.

Based upon the earlier work by Haggard and Henderson (Haggard, 1924a,b; Henderson and Haggard, 1943), later studies published more comprehensive PBPK models for inhaled compounds, such as the studies by Kety (1951), Mapleson (1963), and Riggs (1963). Several new concepts described in these studies are still widely used. For example, in these models the body tissues were lumped together and divided into two groups of tissues according to the blood perfusion rates, generating two sets of tissues with different blood perfusion rates, referred to as richly perfused (also termed rapidly perfused) or poorly perfused (also termed slowly perfused) tissues. In Kety (1951), it was proposed that the kinetic behavior of the inhaled compounds in the tissue is related to three tissue characteristics: tissue volume, blood flow, and partition coefficient. This concept is still the basis of modern PBPK models. In the 1960s, Mapleson (1963) used an analog computer to solve mathematical rate equations

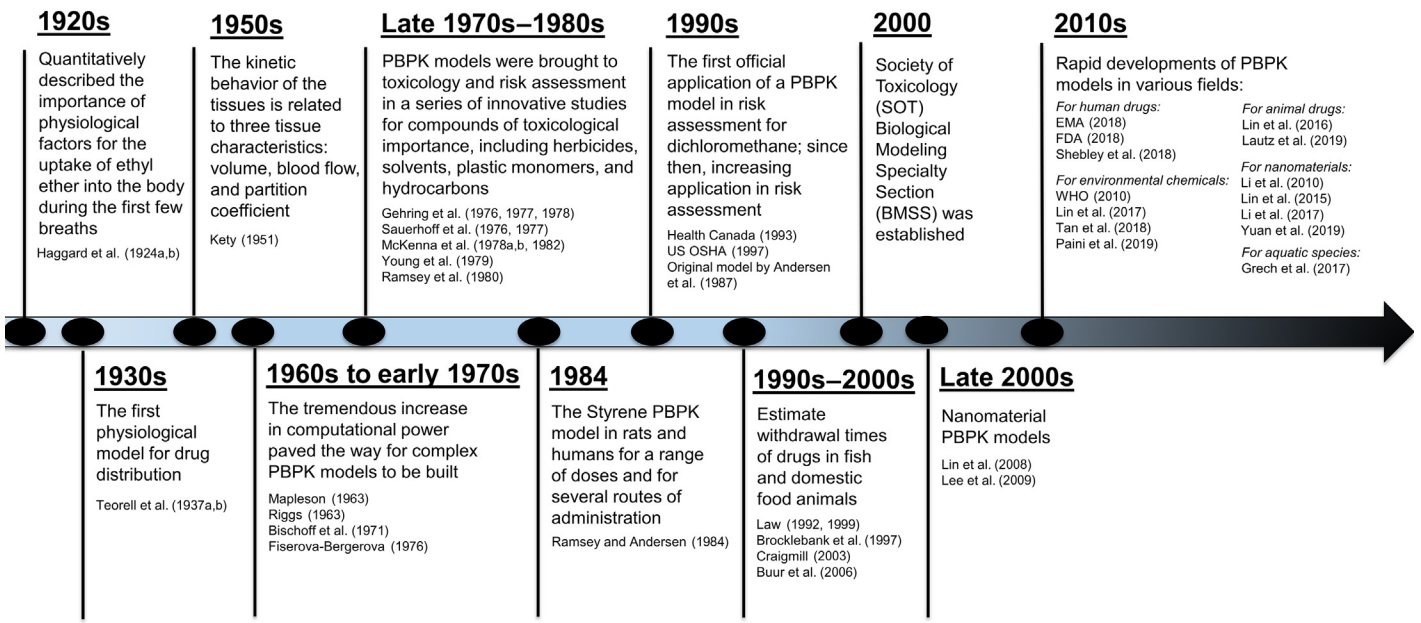

Figure 1.1 Representative studies and milestones in the history of PBPK modeling and applications.

describing the time-concentration course of inert gases in the body. This work represents a significant advancement in solving complex PBPK models using computers. Based on Mapleson's work, Fiserova-Bergerova and colleagues also used analog computers to solve PBPK models for inhaled chemicals with a consideration of metabolism of the inhaled compounds in liver (Fiserova-Bergerova, 1976; Fiserova-Bergerova and Holaday, 1979; Fiserova-Bergerova et al., 1980). The consideration of metabolism is crucial in a PBPK model because many chemicals that require risk assessment can be metabolized in the body and the metabolites are often active metabolites that can contribute to the toxic response. Nowadays, it is very common to include a metabolite submodel in a PBPK model to fully describe the pharmacokinetics of a chemical in the body.

1.2.2 History and recent efforts in the pharmaceutical industry

As early as 1930s, Teorell (1937a,b) reported a set of rate equations to simulate the ADME processes of drugs in the body. These earlier publications are generally recognized as the pioneering PBPK work that considers whole-body distribution and simulates drug concentrations in the tissues. However, computational resources were not sufficient to solve the entire set of equations at that time. As a result, the exact mathematical solutions for drug distribution were only obtained for a simplified model structure in which the body was reduced to a small number of compartments that did not correspond directly with specific physiological organ compartments (i.e., all tissues were pooled as a single tissue compartment). Nevertheless, these pioneering studies provide a basis for subsequent pharmacokinetic modeling work.

From 1930s to 1960s, pharmacokinetic modeling was focused on simpler mathematical descriptions with exact solutions instead of focusing on developing physiologically based models that correspond to the anatomical structure of the organism due to limitations in computational resources. These simpler approaches are termed "data-based" or "data-driven" compartmental modeling, empirical approaches, or traditional/classical pharmacokinetic approaches. Using these "data-based" approaches, the concentration-time data are analyzed by assuming a particular model structure (i.e., one-, two-, or three-compartment) and estimating a small number of parameters by curve-fitting methods. In these earlier simplified models, all ADME processes were described using first-order equations (i.e., a constant proportion of a drug or chemical is eliminated per unit time or in other words, the rate of elimination of drug or chemical is directly proportional to the concentration or the amount of the drug in the body). In the 1960s and early 1970s, there was a growing concern on the suitability of "data-based" compartmental modeling and whether first-order equations can be used to simulate all ADME processes because it was found that ADME processes could be saturated at higher doses. Once the ADME processes are saturated, they should be

described using nonlinear equations. The need for using more mechanism-based models and the availability of sufficient computational capacities led to the development of whole-body mechanism-based PBPK models.

In the last 10 years, PBPK models are widely used in new drug discovery, development, and regulatory approval. PBPK models are now commonly submitted as a part of Investigational New Drug and New Drug Application submissions to the US Food and Drug Administration (FDA). Between July 1, 2008 and December 31, 2013, there were 112 PBPK submissions to the US FDA (Wagner et al., 2015), and in 2014 alone there were 45 PBPK submissions to the US FDA (Wagner et al., 2015, 2016). PBPK models can be used to address a variety of clinical issues, including the evaluation of effects of intrinsic or extrinsic factors on drug pharmacokinetics (Huang et al., 2013; Zhao et al., 2011, 2012), to help decision-making on whether, when, and how to conduct a clinical pharmacology study, and to inform drug labeling (Sinha et al., 2014). Due to the rise of PBPK applications in drug development and the increasing number of PBPK submissions to regulatory agencies (Luzon et al., 2017; Sato et al., 2017; Wagner et al., 2016), both the US FDA and European Medicines Agency (EMA) have issued PBPK guidelines for industry (EMA, 2018; FDA, 2018). The FDA guideline focuses on the format and content of reporting PBPK analyses for regulatory submissions, whereas the EMA guideline has an emphasis on the "qualification" of the PBPK platform and the reporting of the PBPK modeling and simulation processes. In light of the importance of PBPK modeling and simulation in drug development, a group of PBPK modeling scientists (mainly from the industry) collaborated and published an article on the qualification and reporting procedures of PBPK models for regulatory submissions (Shebley et al., 2018). The EMA and FDA guidelines and this article from the industry's perspective on PBPK model qualification and reporting represent an important milestone in this field and are expected to facilitate an increasing application of PBPK modeling and simulation in drug discovery and development.

1.2.3 History and recent efforts of physiologically based pharmacokinetic modeling in toxicology and risk assessment

PBPK modeling was brought to the field of toxicology and risk assessment in a series of novel studies by scientists at the Dow Chemical Company (Midland, MI) in order to study the pharmacokinetics when specific elimination pathways, including metabolic and excretory processes, are saturated at relatively higher doses (Gehring et al., 1976, 1977, 1978). The Dow research team applied nonlinear equations to describe saturable elimination pathways and developed PBPK models for multiple xenobiotics, including pesticides (Sauerhoff et al., 1976, 1977), plastic monomers (McKenna et al., 1978a,b), solvents (McKenna et al., 1982), and hydrocarbons (Ramsey et al., 1980; Young et al., 1979). In addition, PBPK models for chemotherapeutic drugs were developed in the 1970s (Bischoff et al., 1971; Collins et al., 1982; Farris et al., 1988).

Many chemotherapeutic drugs are highly toxic and PBPK models are useful for risk assessment of chemotherapeutic drugs. These earlier seminal studies demonstrated the feasibility that mechanism-based descriptions of relevant ADME processes could be incorporated into PBPK models to simulate chemical pharmacokinetics and laid the foundation for more scientifically sound applications of PBPK models in toxicology and risk assessment. It is also worth mentioning that these models were successful, in part, due to the rapid development of digital computation and the availability of digital computation on mainframe computers for solving sets of mass balance differential equations.

In the 1980s, Ramsey and Andersen (1984) developed a PBPK model to describe the pharmacokinetics of styrene in rats and humans after several routes (i.e., inhalational, intravenous, and oral) of exposure to a range of concentrations. In this model, the liver was described as an individual compartment rather than embedded in a central compartment as in the traditional compartmental pharmacokinetic models. Hepatic metabolism was described as a saturable process using the Michaelis–Menten equation and the clearance of styrene from organs or tissues was directly based on the organ blood flow rates and metabolic characteristics of the specific tissues. This seminal study showed the feasibility of PBPK models to conduct extrapolations across species (e.g., from animals to humans), between exposure routes (e.g., from intravenous to oral exposure), and across doses (e.g., from high to low doses or vice versa). The ability to conduct target tissue dosimetry extrapolations to other exposure scenarios, especially to conditions in which experimental data are not available, is a pivotal part of risk assessment. As a result, the Ramsey and Andersen's (1984) PBPK model helped to usher in PBPK modeling as an attractive tool in human health risk assessment, and within a short time opened the door for using PBPK models in chemical risk assessment by regulatory agencies (Clewell and Andersen, 1985; NRC, 1987).

The first application of a PBPK model in a risk assessment was for methylene chloride (i.e., dichloromethane, DCM). The structure of the DCM PBPK model is depicted in Fig. 1.2 (Andersen et al., 1987). This model was developed to explore potential associations between various tissue dose metrics (e.g., area under the tissue concentration-time curve) and carcinogenicity of DCM in mice and humans after inhalation or ingestion (via drinking water). Tissue clearance of DCM through oxidation and glutathione (GSH) pathways was included in the model. This model can be used to estimate internal exposures to metabolites from different metabolic pathways (i.e., the oxidative and/or conjugation pathways) under different exposure scenarios in the target organs (e.g., liver and lung) for both mice and humans. This model also demonstrated the feasibility to conduct dosimetry extrapolation from mice to humans. By assuming that mouse and human tissues would be equally responsive to equivalent tissue exposures to the same reactive chemical, the results showed that the carcinogenic responses for DCM correlated well with the yield of metabolites from the GSH pathway, but not with the

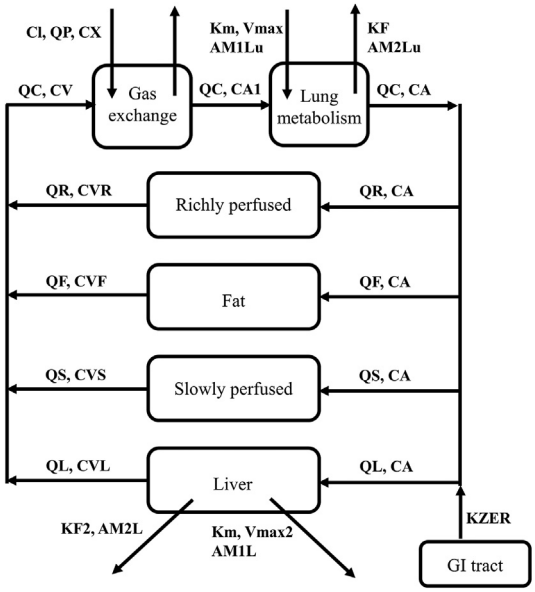

Figure 1.2 Schematic of the physiologically based pharmacokinetic model for methylene chloride (dichloromethane) in mice and humans. *Adapted from Andersen, M.E., Clewell, 3rd, H.J., Gargas, M.L., Smith, F.A., Reitz, R.H., 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87 (2), 185–205. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/3824380 with permission of the publisher. Please refer to the original publication by Andersen et al. (1987) for definitions of the model parameters.*

metabolites from the oxidative pathway, nor with the parent compound. This study represents the first use of a PBPK model for low-dose and interspecies extrapolation based on target tissue dose metrics. This study showed the capability of PBPK models to provide insight into mechanisms of toxicity and metabolism, to improve experimental designs of future studies and to strengthen the scientific basis of risk assessment of DCM. The DCM PBPK model has been applied in risk assessments by different regulatory agencies, including Health Canada (Health Canada, 1993) and the US Occupational Safety and Health Administration (OSHA) (OSHA, 1997).

Since the use of the DCM PBPK model in human health risk assessment, many PBPK models have been developed and applied to regulatory decision-making for other chemicals by various federal agencies. Tan et al. (2018) conducted a search of the US Federal Register in the repositories Regulations.gov and HeinOnline using the search term "PBPK" with options for "proposed rules, final rules, other, and supporting material" and found 314 related documents from 1988 to 2017. Among the 314 documents, 142 were directly involved in regulatory decision-making by different federal agencies, including the FDA, Environmental Protection Agency (EPA), OSHA, Agency for Toxic Substances and Disease Registry, and National Highway Traffic

Safety Administration. The study by Tan et al. (2018) suggests that public health agencies have recognized the potential benefits of PBPK modeling that is playing an increasingly important role in risk assessment for environmental chemicals, and it provides a summary of the current challenges in this field.

In order to apply PBPK models in human health risk assessment appropriately, many scientists from different organizations have published review articles and guidance documents on the development and application of PBPK models in risk assessment (Chiu et al., 2007; Clewell and Clewell, 2008; EPA, 2006; Lin et al., 2017; McLanahan et al., 2012; Mumtaz et al., 2012; Thompson et al., 2008; WHO, 2010). The documents from the EPA (2006) and WHO (2010) provide very detailed information on the rationale for using PBPK models in risk assessment, the data and model needs in risk assessment, model development and documentation, as well as different applications of PBPK models in risk assessment.

Besides human health risk assessment, PBPK models have also been applied to environmental risk assessment, mainly in terrestrial and aquatic species. According to a recent review by Grech et al. (2017), a large number of PBPK models have been published for environmental risk assessment for a number of chemical classes, such as metals, chlorinated solvents, persistent organic pollutants, and polycyclic aromatic hydrocarbons (Abbas and Hayton, 1997; Chen and Liao, 2014; Nichols et al., 1991). The majority of these models are in different fish species, with a few for mollusks (Grech et al., 2017). The same principles and applications of PBPK models in human health risk assessment, such as the target organ dosimetry prediction, interspecies extrapolation, in vitro to in vivo extrapolation, and extrapolation across exposure paradigms, are also applicable to environmental risk assessment. Furthermore, PBPK models in fish or mollusks can be used to predict the bioaccumulation of environmental contaminants, and from the food safety perspective, would provide sound tools for exposure assessment (i.e., combined with consumption factor, carryover and residue data), hazard assessment, and risk characterization of chemicals for human health risk assessment through the consumption of contaminated fish or mollusks (Law et al., 1991; Liu et al., 2014).

1.2.4 History and recent efforts of physiologically based pharmacokinetic modeling in veterinary pharmacology and animal-derived food safety assessment

Besides risk assessment and drug development, PBPK modeling has also been applied to the field of veterinary pharmacology and food safety assessment to estimate tissue residues and withdrawal intervals (or termed withdrawal times) of a drug or chemical in food-producing animals. Withdrawal interval is the time required for a drug or chemical residue in the edible tissues to deplete to be below a concentration less than the legally established tolerance or maximum residue limit, which is the drug or chemical concentration that regulatory agencies deem safe for human consumption

(Riviere et al., 2017). In the 1990s, Law's group in Canada developed a PBPK model to estimate withdrawal intervals for oxytetracycline after daily oral exposure in trout and Chinook salmon at different temperatures, and the results were similar to those calculated using an empirical statistical method (Brocklebank et al., 1997; Law, 1992, 1999). The authors concluded that population PBPK models were a more useful tool than the traditional empirical method for withdrawal interval calculation because PBPK models can be extrapolated to estimate withdrawal intervals after different exposure scenarios by incorporating treatment-specific information, such as fish weight, bioavailability, dose regimen, and water temperature.

From the early 2000s to the present, researchers from the Food Animal Residue Avoidance Databank (FARAD) program have been the main advocates in the development and applications of PBPK models to estimate withdrawal intervals of drugs in food-producing animals. The FARAD program is a university-based consortium that is focused on the development of scientifically sound quantitative tools in the prediction of withdrawal intervals of drugs in food animals, and this program is staffed by highly trained scientists at five universities: North Carolina State University, University of California-Davis, University of Florida, Kansas State University, and Virginia Tech (Riviere et al., 2017). Craigmill from the University of California-Davis first extended PBPK applications to domestic food animals. He developed a flow-limited PBPK model for oxytetracycline in sheep that well predicted tissue residues after intramuscular injection of a long-acting formulation of oxytetracycline (Craigmill, 2003). This model showed the potential of using PBPK models to predict tissue residues and withdrawal intervals of drugs in domestic food-producing animals, but it was limited in that it did not consider population variability. This limitation was soon addressed by other FARAD scientists as described below.

Riviere, Baynes, Lin, and their colleagues at North Carolina State University and Kansas State University have been in collaboration and developed many PBPK models for different drugs (e.g., sulfamethazine, flunixin, and penicillin G) in different food animal species, including swine, cattle, and goats (Buur et al., 2006; Leavens et al., 2012; Li et al., 2018; Lin et al., 2016d; Yang et al., 2019). The structure for a representative PBPK model for penicillin G in cattle is shown in Fig. 1.3 (Li et al., 2017a). It is worth mentioning that this research team has not only developed PBPK models to predict drug residue concentrations in tissues, but they have also extended their models to dairy cows to predict drug residues in milk (Li et al., 2018). These models use a Monte Carlo simulation method to account for the population variability. These models can be used to predict the time needed when the marker residue concentration of the drug in the target tissue or in the milk falls below the tolerance for the 99th percentile of the population with 95% confidence. These studies have shown that PBPK models are useful in estimating proper withdrawal intervals of drugs in food animals, thereby preventing drug residue violations in animal-derived food products. More recently, in order to facilitate the use of PBPK models in the estimation of

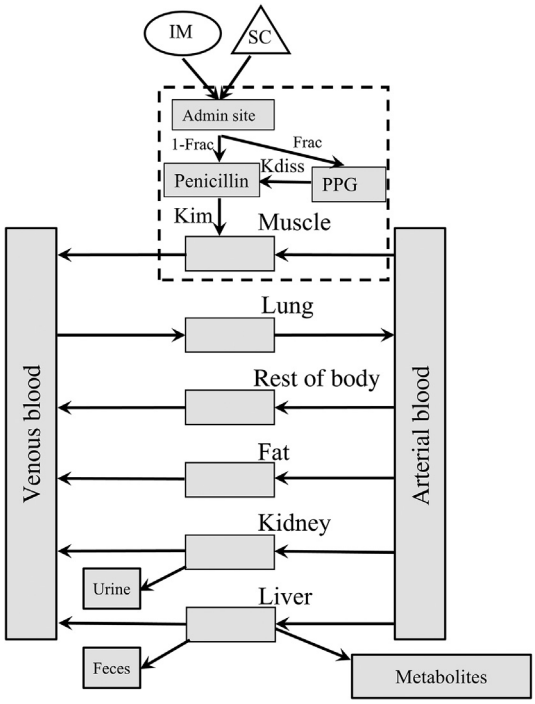

Figure 1.3 Schematic of the physiologically based pharmacokinetic model for penicillin G in cattle and swine. Compared to the model structure for environmental chemicals as presented in Fig. 1.2, PBPK models for drugs in food animals focus on edible tissues (i.e., muscle, liver, kidney, and fat) and the therapeutic target tissue (i.e., lung for antibiotics). *Adapted from Li, M., Gehring, R., Riviere, J.E., Lin, Z., 2017a. Development and application of a population physiologically based pharmacokinetic model for penicillin G in swine and cattle for food safety assessment. Food Chem. Toxicol.107 (Pt A), 74–87. Available from: https://doi.org/10.1016/j.fct.2017.06.023 with permission of the publisher. Please refer to the original publication by Li et al. (2017a) for definitions of the model parameters.*

withdrawal intervals by the FARAD responders who are often nonmodelers, the FARAD team has started to convert some of their PBPK models to a web-based user-friendly interface (Li et al., 2019). While this PBPK interface prototype remains to be improved further, it demonstrates the potential of using PBPK models that are convenient and easy to use to support real-time drug residue and withdrawal interval estimation, which can be potentially accepted by regulatory agencies.

Besides the United States and Canada, scientists from other countries, including China and European countries have also started to build PBPK models for veterinary drugs in food animals with the goal of predicting proper withdrawal intervals after different therapeutic regimens (Henri et al., 2017; Yang et al., 2012; Zhu et al., 2017). In light of the increasing applications of PBPK models in food animals, Lin et al. (2016a) published a review article on the principles, methods, and applications of

PBPK models in veterinary medicine and food safety assessment. The majority of PBPK models for drugs in food animals published prior to January 2016 were discussed in this article. One interesting finding from this study was that besides PBPK models in food animals, there were many PBPK models for environmental chemicals in the wildlife, such as PCB-153 in harbor porpoises and pilot whales, and organohalogen contaminants in polar bears (Dietz et al., 2015; Weijs et al., 2010, 2014). The common objective of these studies was to apply PBPK models to conduct animal health risk assessment or ecological risk assessment.

More recently, Lautz et al. (2019) critically reviewed published PBPK models in farm animals. Thirty-nine models were identified. Most of the available models were developed to predict tissue residues and withdrawal intervals of drugs in farm animals. Most models do not meet the criteria for applications in risk assessment set by WHO (2010). In order to facilitate the application of PBPK models for chemical risk assessment for animal health, including farm as well as companion animals, which follows the same principles as human health risk assessment (Alexander et al., 2012), Lautz et al. (2019) provided a set of specific suggestions on the development of future PBPK models for chemicals in farm animals.

1.2.5 History and recent efforts of physiologically based pharmacokinetic modeling in nanomedicine and nanotoxicology

Nanoparticles are defined as inorganic, organic, or polymeric particles with at least one size dimension in the nanoscale range (1−1000 nm) (D'Mello et al., 2017; Yuan et al., 2019). Nanoparticles are increasingly applied in disease diagnosis and therapy, as well as in consumer products (D'Mello et al., 2017; Vance et al., 2015). The increasing use of nanoparticles has led to concern on the potential adverse effects of overexposure to nanoparticles on human health. PBPK models are very helpful tools in the field of nanomedicine and nanotoxicology.

In the late 2000s, Riviere from North Carolina State University and Yang from Colorado State University and their colleagues published PBPK models to simulate the complex pharmacokinetics and tissue distribution profiles of quantum dots (Lee et al., 2009; Lin et al., 2008). To the authors' knowledge, these models are the first PBPK model for nanoparticles. Li et al. (2010) published a review article on PBPK modeling of nanoparticles. This article summarized the unique ADME features of nanoparticles and discussed the basic principles and factors that should be considered for developing PBPK models of nanoparticles. This study highlighted the great potential of PBPK models in the field of nanomedicine and nanotoxicology.

In the last 10 years, many PBPK models for different nanoparticles have been published for different applications, including risk assessment, dose−effect relationship prediction, development of nanoparticle-based drug formulations, and in vitro to in vivo correlation (Li et al., 2017b; Yuan et al., 2019). The structure of a representative