PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

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Science and Applications

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CONTENTS

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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