Quantitative Modeling in Toxicology

Editors
Kannan Krishnan • Melvin E. Andersen

WILEY

Quantitative Modeling in Toxicology

Editors

KANNAN KRISHNAN

Département de santé environnementale et santé au travail, Ecole de santé publique & Faculté de médecine, Université de Montréal, Montréal, Canada

MELVIN E. ANDERSEN

Program in Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

WILEY

A John Wiley and Sons, Ltd., Publication

This edition first published 2010

Registered office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

Library of Congress Cataloging-in-Publication Data

Quantitative modeling in toxicology / editors, Kannan Krishnan, Melvin
E. Andersen.
p. ; cm.
Includes bibliographical references and index.
Summary: "In Quantitative Modeling in Toxicology leading experts outline the current state of knowledge on the modeling of dose, tissue interactions and tissue responses. Each chapter describes the mathematical foundation, parameter estimation, challenges and perspectives for development, along with the presentation of a modeling template. Additionally, tools and approaches for conducting uncertainty, sensitivity and variability analyses in these models are described"–Provided by publisher.
ISBN 978-0-470-99809-0 (cloth)
1. Toxicology–Mathematical models. I. Krishnan, Kannan, 1961- II. Andersen, Melvin E.
[DNLM: 1. Toxicology–methods. 2. Environmental Exposure–adverse effects. 3. Hazardous Substances–toxicity.
4. Models, Biological. 5. Toxicity Tests–methods. QV 602 Q13 2010]
RA1199.4.M37Q36 2010
615.9001′5118–dc22

2009045991

A catalogue record for this book is available from the British Library.

ISBN 978-0-470-99809-0

Typeset in 10/12pt Times by Aptara Inc., New Delhi, India.
Printed and bound in Great Britain by CPI Antony Rowe, Chippenham, Wiltshire.

The figure on the front cover, showing the "cusp catastrophe surface" for a biological feedback loop, illustrates the dynamic behavior for different selections of binding affinities. Steady-state values for the interacting proteins are plotted against respective binding affinities. The arrow indicates those sets of affinities where an abrupt, discrete transition would be observed, as expected for processes such as cellular differentiation. The region of the surface "under the fold" represents the parameter

Quantitative Modeling in Toxicology

Preface

The goal of most toxicology studies is to help reach some conclusion about likely risks posed to humans or to other species from chemical exposures. Test results, both from *in vivo* and *in vitro* studies, require various forms of extrapolation to make risk predictions for specific exposures and in specific populations. Over the past 50 to 60 years, a variety of modeling tools have emerged that help in describing toxicological processes quantitatively and in making these extrapolations. These quantitative models have substantially improved our understanding of human exposure, pharmacokinetics, mode of action and toxic responses associated with chemicals. In recent years, toxicology, as true for other biological disciplines, has also been enriched by the new tools from genomic biology and by the increasing emphasis on computational systems biology for describing cell and tissue function.

The opportunity now exists for toxicology to transition from a qualitative science cataloging responses in various animal species to a discipline capable of quantitatively describing key mechanistic processes that determine dose-response behaviors for animal and human responses. Quantitative modeling in toxicology includes approaches that simulate (i) exposure and disposition of chemicals in the body, (ii) biochemical interaction between toxic moiety and target tissues, (iii) molecular and cellular alterations emanating from the initial interactions; and (iv) adverse responses at the organ or organism level. Properly developed, these quantitative mechanistic models can provide unambiguous, testable statements of working hypotheses regarding chemical uptake, biochemical interactions, and the initiation and progression of toxicity in the exposed organism.

Integration of quantitative tools within experimental design, data collection and analysis as well as risk assessment applications is more important than ever. Specifically, these tools are important (i) for conducting scientifically sound extrapolations of dosimetry and responses for risk assessment purposes, (ii) for refining/reducing animal use in toxicology studies by facilitating the development of new, novel and efficient experiments, and (iii) for creating a framework with which to integrate the various observations (exposure, dose, mechanism, response) at a quantitative level. Despite the growth in interest in these quantitative models in toxicology, there are few resources to serve as a guide in learning more about these tools. The two of us, along with other colleagues, have taught modeling courses at our respective institutions through lectures and computer demonstrations. In these courses, we have also felt the need for a concise overview of quantitative modeling in toxicology and began discussions leading to this book.

Quantitative Modeling in Toxicology now brings together contributions from key scientists on the modeling of exposure, tissue dose, tissue interaction and toxicological responses. Chapters 2-5 describe the quantitative models of pharmacokinetics of individual chemicals

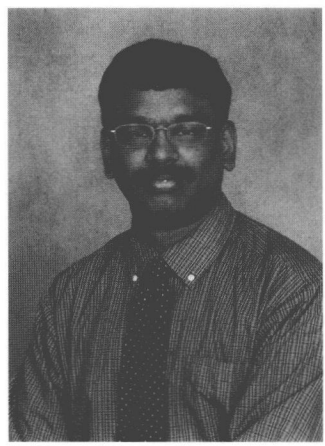
and mixtures. Chapters 6 through11 describe models for toxicant-target tissue interaction. Chapters 12 through 15 describe models for cellular, organ, and organism responses. The simulation models of toxic effects based on the toxicant-target interaction models and mode of action information are highlighted with specific examples. Finally, Chapters 16 through 21 present the approaches, tools and challenges regarding the application and evaluation of quantitative models for exposure and risk assessments. Based on the breadth of the material in these chapters, this book should serve as an initial reference for toxicologists and risk assessors who are interested in developing quantitative models for a better understanding of dose-response relationships.

The process of simulation modeling requires writing computer code to represent the biological systems and the consequences of exposure. The models are written in a computer language and then solved by numerical integration. The examples throughout the book use a variety of commercial software, including ACSL©, BERKELEY MADONNA©, MATLAB©, EXCEL© and MEGen©. We do not endorse any particular software and did not require our contributors to use any particular software. In general, the source code developed in one language can be easily recoded into alternative language. Code for running various models in the book have been included in specific chapters and made available for download from the publisher. The text files for these models are intended to assist the interested reader in developing models for their own use or for use for instruction. We would appreciate comments from our readers about the value of these models for learning more about quantitative modeling in toxicology.

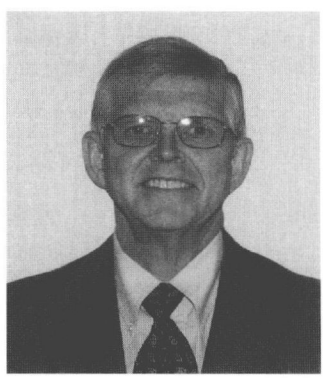
Needless to say, the completion of this work was in large part due to our group of talented authors. Thanks to all! We also thank Richard Davies of Wiley for his enthusiasm and cooperation throughout this project as well as Michelle Gagné and Mathieu Valcke of Université de Montréal for editorial assistance.

KK and MEA

About the Editors . . .



Kannan Krishnan, PhD, DABT, FATS is Professor of Occupational and Environmental Health at Université de Montreal and Director of the Inter-University Toxicology Research Center (CIRTOX), Montreal, Canada. An expert in the areas of PBPK modeling, chemical mixture toxicology and health risk assessment methods, Dr. Krishnan has held visiting scientist/faculty appointments at the Karolinska Institutet, Sweden (2004), Toxicology Excellence for Risk Assessment (TERA, Cincinnati, OH) (2007) and Environmental & Occupational Health Sciences Institute of UMDNJ-Rutgers University, NJ (2007). He received the *Veylian Henderson Award* of the Society of Toxicology of Canada (2000) and the SOT Board of Publications Award for the *best paper in Toxicological Sciences* (2003) for a land-mark publication on the PBPK modeling of metabolic interactions and health risk assessment of chemical mixtures. He was a significant contributor to the U.S. EPA report "Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment" (2006) and IPCS/WHO guidance document "Characterization and application of PBPK models in support of risk assessment" (2010).



Melvin Ernest Andersen, PhD, DABT, CIH, FATS is Director, Program in Chemical Safety Sciences at The Hamner Institutes for Health Research, Research Triangle Park, NC, U.S.A. He is reknown for his career contributions in developing quantitative models of the dosimetry and effects of drugs and toxic chemicals as well as applying these models in safety assessments and quantitative health risk assessments, Through short-courses in quantitative modeling in toxicology, Dr Andersen has trained several hundred toxicologists and risk assessors in quantitative modeling. An author or a co-author of 325 papers and 60 book chapters, he has received several awards for professional contributions; including the Herbert Stokinger Award (American Conference of Industrial Hygienists, 1988), the

Kenneth Morgareidge Award (International Life Sciences Institute, 1989), the George Scott Award (Toxicology Forum, 1993), and the Frank R. Blood (1982), Achievement (1984), and Arnold J. Lehman (2004) Awards from the Society of Toxicology. Recognized as a 'highly cited' scientist by the Institute for Scientific Information (June 2002), Dr. Andersen co-edited a 2005 book, "Physiologically Based Pharmacokinetics: Science and Applications".

About the Book . . .

Quantitative modeling in toxicology is a must-read for those interested in computer simulation of the biological fate and effects of chemicals. It brings together a diverse group of experts in this area to provide the reader with the current state of knowledge regarding the modeling of dose, tissue interactions and tissue responses. Additionally, tools and approaches for model evaluation and application are described. Access to an electronic MODEL LIBRARY containing the source code for several dosimetry, toxicant interaction and toxicity models is included with the book in order to allow the interested reader to reconstruct the examples in the various chapters. This book will be of particular interest to graduate students, practicing toxicologists and risk assessors who are fascinated by the application of quantitative modeling approaches to simulate perturbations of biological systems upon exposure to xenobiotics.

List of Contributors

Melvin E. Andersen Program in Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Sudin Bhattacharya Division of Computational Biology, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Jonathan Boyd C Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV, USA

Harvey J. Clewell III Center for Human Health Assessment, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Rory B. Conolly Integrated Systems Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, USA

Mark T.D. Cronin School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, England

Michael L. Dourson Toxicology Excellence for Risk Assessment, Cincinnati, OH, USA

Hisham A. El-Masri Integrated Systems Toxicology Division, National Health and Environmental Effects Research Laboratory, US EPA, Research Triangle Park, NC, USA

Jeffrey W. Fisher College of Public Health, University of Georgia, Athens, GA, USA

Panos G. Georgopoulos Computational Chemodynamics Laboratory, Environmental and Occupational Health Sciences Institute (EOHSI), Piscataway, NJ, USA

Lynne T. Haber Toxicology Excellence for Risk Assessment, Cincinnati, OH, USA

Sami Haddad Département des sciences biologiques, Centre TOXEN, Université du Québec à Montréal, Montréal, Québec, Canada

Dale Hattis Marsh Institute Center for Technology, Environment and Development, Clark University, Worcester, MA, USA

Paul M. Hinderliter Center for Biological Monitoring and Modeling, Pacific Northwest National Laboratory, Richland, WA, USA

Sastry S. Isukapalli Computational Chemodynamics Laboratory, Environmental and Occupational Health Sciences Institute (EOHSI), Piscataway, NJ, USA

Douglas O. Johns National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

Melissa J. Kohrman-Vincent Toxicology Excellence for Risk Assessment, Cincinnati, OH, USA

Yana K. Koleva School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, England

Kannan Krishnan Groupe de recherche interdisciplinaire en santé et Département de santé environnementale et santé au travail, Université de Montréal, Montréal, Canada

Kai H. Liao Drug Safety and Metabolism, Wyeth Research, Pearl River, NY, USA

John Lipscomb National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

George Loizou Computational Toxicology Section, Health and Safety Laboratory, Buxton, United Kingdom

Michael A Lyons Quantitative and Computational Toxicology Group, Colorado State University, Fort Collins, CO, USA

Judith C. Madden School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, England

Eva D. McLanahan College of Public Health, University of Georgia, Athens, GA, USA

Patricia M. Nance Toxicology Excellence for Risk Assessment, Cincinnati, OH, USA

Andy Nong The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA. Current address: Health Canada, Ottawa, Ontario, Canada

Elizabeth Oesterling Owens Postdoctoral Fellow, Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

Torka S. Poet Center for Biological Monitoring and Modeling, Pacific Northwest National Laboratory, Richland, WA, USA

Babasaheb Sonawane National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Martin Spendiff Computational Toxicology Section, Health and Safety Laboratory, Buxton, United Kingdom

Yu-Mei Tan Center for Human Health Assessment, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Robert Tardif Groupe de recherche interdisciplinaire en santé, Département de santé environnementale et santé au travail, Université de Montréal, Montréal Canada

Michael D. Taylor Environmental Science, Afton Chemical Corp., Richmond, VA, USA

Chad M. Thompson National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA; Present address: ToxStrategies, Houston, TX, USA

Charles Timchalk Center for Biological Monitoring and Modeling, Pacific Northwest National Laboratory, Richland, WA, USA

Courtney G. Woods Division of Computational Biology, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Raymond S. H. Yang Quantitative and Computational Toxicology Group, Colorado State University, Fort Collins, CO, USA

Miyoung Yoon Division of Computational Biology, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Qiang Zhang Division of Computational Biology, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA

Q. Jay Zhao U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH, USA

Contents

Section 1
Introduction