Contents

Foreword ix
List of Contributors xv

1. Introduction 1
BRUCE A. FOWLER

2. Quantitative Structure-Activity Relationship (QSAR) Models, Physiologically Based Pharmacokinetic (PBPK) Models, Biologically Based Dose Response (BBDR) and Toxicity Pathways 5
PATRICIA RUIZ, XIAOXIA YANG, ANNIE LUMEN, AND JEFF FISHER

Introduction 5
Application of Structure-Activity Relationship (SAR) and Quantitative Structure-Activity Relationship (QSAR) 6
Physiologically Based Pharmacokinetic (PBPK) Modeling Case Studies 7
VOC Models 8
Metals Models 10
References 16

3. Multiple Chemical Exposures and Risk Assessment 23
JOHN C. LIPSCOMB, NIKKI MAPLES-REYNOLDS, AND MOIZ MUMTAZ

Historical Perspective 23
Regulatory Perspective 24
Mixtures versus Components 26
Additivity Approaches 27
Future Directions 38
References 41

4. Modeling of Sensitive Subpopulations and Interindividual Variability in Pharmacokinetics for Health Risk Assessments 45
KANNAN KRISHNAN, BROOKS McPHAIL, WEIHSUEH CHIU, AND PAUL WHITE

Introduction 45
Physiological Differences and PBPK Modeling of Sensitive Human Subpopulations 47
Animal PBPK Models for Evaluating Sensitive Subpopulations 58
Concluding Remarks 61
Disclaimer 62
References 62

5. Integrated Systems Biology Approaches to Predicting Drug-Induced Liver Toxicity 67
KALYANASUNDARAM SUBRAMANIAN

Introduction 67
General Principles 68
Model Building 68
Energy Homeostasis 69
Glutathione Homeostasis 70
Fatty Acid Metabolism 71
Bile Salt Metabolism and Transport 73
Solving the Equation-Set 74
Model Validation and Predictions 74
Conclusions 79
References 80

6. Computational Translation and Integration of Test Data to Meet Risk Assessment Goals 85
LUIS G. VALERIO JR.

Introduction 85
Computational Analyses and Translational Research 86
Toxicology-Based (Q)SARs 87
Read-Across 97
Data Mining for Computational Translation and Integration of Test Data 98
High-Throughput Screening for Signal Detection in Risk Assessment 100
Integrating Computational Tools with Test Data for Risk Assessment 102
Disclaimer 107
References 108

7. Computational Translation of Nonmammalian Species Data to Mammalian Species to Meet REACH and Next Generation Risk Assessment Needs 113
EDWARD J. PERKINS AND NATÀLIA GARCIA-REYERO

A Changing Regulatory Environment 113
Nonmammalian Species Can Help to Reduce, Refine, and Replace Mammalian Animal Testing 115
Pathway-Based Hazard and Risk Assessment 115
Translating Effects on Nonmammalian Species to Mammalian Species 118
Translating Molecular Initiating Events: Gene/Protein Annotation and Mammalian Ortholog Identification 120
Annotation of Large Gene Sets 122
Pathway-Level Comparison/Translation 123
Pathway-Based Extrapolation to Mammals in Determining Chemical Mode of Action 124
Pathway-Based Dose-Response Relationships 125
Network Inference and Mapping 128
Cross-Species Analysis Using Networks 128
Translating Effects through Computational Modeling at the Systems Level 130
Future Efforts in Use of High-Throughput Screening and "Omics" Technology and Computational Tools in Translation of Nonmammalian Species to Mammalian Species to Meet REACH and Next Generation Risk Assessment Needs 130
References 131

8. Interpretation of Human Biological Monitoring Data Using a Newly Developed Generic Physiological-Based Toxicokinetic Model 137
FRANS JONGENEELEN, WIL TEN BERGE, AND PETER J. BOOGAARD

Introduction 137
The Generic PBTK Model IndusChemFate 139
Examples 141
Discussion 148
Supplementary Information 149
References 149

9. Uses of Publicly Available Data in Risk Assessment 151
ISAAC WARREN AND SORINA EFTIM

Introduction 151
Publicly Available Data Sets with Uses in Risk Assessment 152
Comparison of the NHANES IV and ToxCast™ Data Sets 159
Methods for Compiling Data from Multiple Sources for Risk Assessment 159
Designing Publicly Available Toxicological Data Sets 162
Analogies to the Human Genome Project in Computational Toxicology 163
Chemical Domain and Limitations to Data Analysis of Traditional and Computational Toxicology Data 164
Data Semantics and Limitations to Relating HTS Data to *In Vivo* Effects 165
Conclusions 166
References 166

10. Computational Toxicology Experience and Applications for Risk Assessment in the Pharmaceutical Industry 171
NIGEL GREENE AND MARK GOSINK

Background 171
Two Main Considerations 172
Summary 188
References 188

11. Omics Biomarkers in Risk Assessment 195
HONG FANG, HUIXIAO HONG, ZHICHAO LIU, ROGER PERKINS, REAGAN KELLY, JOHN BERESNEY, WEIDA TONG, AND BRUCE A. FOWLER

Abbreviations and Glossaries 195
Introduction 196
Biomarkers 198
Bioinformatics Approaches: Challenges and Solutions in Omics Biomarker Discovery 201
Decision Forest for Omics Biomarkers 206
Conclusion 210
Disclaimer 210
References 211

12. Translation of Computational Model Results for Risk Decisions 215
WILLIAM MENDEZ AND BRUCE A. FOWLER

Origins and Nature of the Computational Toxicology Applications in Risk Assessment 215
Drivers for the Application of Computational Toxicology to Risk Assessment 220
Translational Research 221
Computational Toxicology Applications in Risk- and Hazard-Based Screening 228
Current Status of Computational Toxicology in Quantitative Risk Assessment 236
Summary 238
References 242

13. Future Directions for Computational Toxicology for Risk Assessment 247
BRUCE A. FOWLER

Needed Essential Elements 247
Specific Elements in Computational Toxicology Needed for the Field to Move Forward 248

Index 251