

The background of the cover is a dark, textured brown with several bright blue, circular, fuzzy structures that resemble biological cells or microorganisms. These structures are scattered across the cover, with one prominent one in the top center and another in the bottom right.

# **Biological Concepts and Techniques in Toxicology**

**An Integrated Approach**

Edited by

**Jim E. Riviere**

# Contents

*Preface . . . . . iii*

*Contributors . . . . . xi*

**1. Introduction and Overview . . . . . 1**  
*Jim E. Riviere*

## **PART I. NEW CONCEPTS AND APPROACHES**

**2. Toxicogenomics: Gene Expression Analysis and  
Computational Tools . . . . . 5**  
*Rupesh P. Amin, Hisham K. Hamadeh, J. Todd Auman, Lee Bennett,  
Cynthia A. Afshari, Pierre R. Bushel, Richard S. Paules, and  
J. Christopher Corton*

Introduction . . . . . 5

Microarray-Based Gene Expression Profiling . . . . . 6

Selection of Differentially Expressed Genes . . . . . 9

Finding Expression Patterns . . . . . 11

Data Management . . . . . 13

Biological Databases Useful for Toxicogenomics . . . . . 14

Examples from an In Vivo Toxicogenomics Study . . . . . 14

Future Prospects for Toxicogenomics . . . . . 19

References . . . . . 21

**3. Proteomics . . . . . 25**  
*Frank A. Witzmann*

Introduction . . . . . 25

Differential Expression Proteomic Technologies . . . . . 27

A 2-D Gel-Based Toxicoproteomic Analysis of  
Jet Fuel Exposure . . . . . 39

Conclusion . . . . . 41

References . . . . . 42

<b>4. The Potential of Metabonomics in Toxicology</b> . . . . .	<b>47</b>
<i>Julian L. Griffin</i>	
Introduction . . . . .	47
Metabonomics and Genomics . . . . .	49
Metabonomics and Disease . . . . .	51
Metabonomics and Transcriptomics . . . . .	51
MS and Metabonomics . . . . .	55
Metabonomics and Systems Biology . . . . .	56
Future Developments . . . . .	56
Conclusions . . . . .	58
References . . . . .	59
<b>5. Quantitative Structure–Toxicity Relationships Using Chemodescriptors and Biodescriptors</b> . . . . .	<b>61</b>
<i>Subhash C. Basak, Denise Mills, and Brian D. Gute</i>	
Introduction . . . . .	61
The Molecular Structure Conundrum . . . . .	62
The HiQSAR Approach . . . . .	63
Statistical Methods . . . . .	69
Applications in Toxicokinetics and Toxicodynamics . . . . .	70
Cell Level Toxicity Estimation . . . . .	71
Molecular Similarity and Predictive Toxicology . . . . .	75
Discussion . . . . .	76
References . . . . .	79
<b>6. Hormesis: A Key Concept in Toxicology</b> . . . . .	<b>83</b>
<i>Edward J. Calabrese</i>	
What Does This Mean Today? . . . . .	90
References . . . . .	90

**PART II. INTEGRATION INTO PRACTICE**

<b>7. Chemical Risk Assessment</b> . . . . .	<b>93</b>
<i>Ronald E. Baynes and Jennifer L. Buur</i>	
Introduction . . . . .	93
Hazard Identification . . . . .	94
WOE . . . . .	96
Dose–Response Assessment . . . . .	98
Quantifying Risk for Noncarcinogenic Effects: Hazard Quotient . . . . .	103
Chemical Mixtures . . . . .	104
Dermal RA . . . . .	107
PBPK Modeling . . . . .	108
Conclusion . . . . .	114
References . . . . .	114

<b>8. Toxicokinetics: Fundamentals and Applications in Drug Development and Safety Assessment</b>	<b>117</b>
<i>Rakesh Dixit</i>	
Introduction	117
Pharmacokinetics and Toxicokinetics	117
Conclusions	156
References	157
<b>9. Validation of In Vitro Methods for Toxicology Studies</b>	<b>161</b>
<i>William S. Stokes</i>	
Introduction	161
The Concept of Test Method Validation	162
Evolution Process for Test Methods	162
Validation and Regulatory Acceptance Criteria	164
The Validation Process	165
ICCVAM Role in Validation and Regulatory Acceptance	170
Summary	173
References	174
<b>10. Chemical Mixtures Risk Assessment and Technological Advances</b>	<b>177</b>
<i>M. M. Mumtaz, B. A. Fowler, C. T. De Rosa, P. Ruiz, M. Whittaker and J. Dennison</i>	
Disease Conditions Caused by Chemical Mixtures	177
Assessment Approaches	184
New Developments	192
Research Advancements in Joint Toxicity of Metals	195
Perspectives and Future Needs	197
References	199

### **PART III. EXAMPLES APPLIED TO PROBLEMS**

<b>11. Risk-Based Approach to Foods Derived from Genetically Engineered Animals</b>	<b>205</b>
<i>Larisa Rudenko, Kevin J. Greenlees, and John C. Matheson III</i>	
Introduction: The Need to Move Beyond	
Traditional Dose-Exaggeration Studies	205
Underlying Risk Basis and Paradigm Setting	208
Toward a Risk-Based Approach	209
Hazard Analysis for GE Animals Traditionally	
Consumed for Food	210
Looking Forward	213
References	214

<b>12. Toxicology of Nanomaterials</b> .....	<b>217</b>
<i>Nancy A. Monteiro-Riviere and Jessica P. Ryman-Rasmussen</i>	
Introduction .....	217
What Are Nanomaterials? .....	217
Nanomaterial Nomenclature .....	218
Characterization .....	219
Nanomaterials and Toxicity .....	219
Exposure and Risk Assessment .....	228
Environmental Impact .....	229
Conclusion .....	230
References .....	230
<b>13. The Biological Basis of Experimental Toxicity of Jet Propulsion Fuel-8</b> .....	<b>235</b>
<i>Simon S. Wong and Mark L. Witten</i>	
Introduction .....	235
Pulmonary Toxicity .....	236
Dermal Toxicity .....	241
Immune Toxicity .....	245
References .....	247
<b>14. Drug Safety Toxicology</b> .....	<b>249</b>
<i>Joseph P. Hanig and Robert E. Osterberg</i>	
Introduction .....	249
Background of Drug Safety Regulation .....	249
U.S. Food and Drug Administration Toxicity Testing Documents .....	250
Modern Approaches to the Development of Methods for Drug Testing and Safety Evaluation .....	251
History of Regulatory Assay Review and/or Acceptance .....	257
The Impact of FDA's "Critical Path" Concept on Future Development of Drug Safety Methodology .....	265
Crucial Issues and Challenges .....	266
Conclusions .....	267
References .....	268
<b>15. Statins and Toxicity</b> .....	<b>273</b>
<i>John Farmer</i>	
Introduction .....	273
Pathogenesis of Atherosclerosis and the Potential of Statin Toxicity .....	274
Statin Toxicity .....	277
References .....	292

<b>16. Inhalation Toxicology</b> .....	<b>297</b>
<i>Roger O. McClellan, Michele A. Medinsky, and M. Burton Snipes</i>	
Introduction . . . . .	297
Planning Inhalation Toxicology Research . . . . .	299
Characteristics of Toxicants and Targets . . . . .	302
Fate of Inhaled Materials . . . . .	309
Exposure Systems, Generation of Atmosphere, and Characterization of Atmosphere . . . . .	321
Study Design . . . . .	327
Respiratory Tract Responses . . . . .	330
Assessing Human Risks of Inhaled Particles . . . . .	334
Quality Control and Quality Assurance . . . . .	355
Additional References . . . . .	355
Summary . . . . .	356
References . . . . .	357
<b>17. Modern Gas Chromatography–Mass Spectrometry in Human Forensic Toxicology</b> .....	<b>365</b>
<i>Beat Aebi and Werner Bernhard</i>	
Introduction . . . . .	365
Types of GC–MS and Experimental Setups . . . . .	366
Gas Chromatography . . . . .	366
Mass Spectrometry with Quadrupole Analyzers . . . . .	367
Sector Field Instruments, Tandem and Hybrid Mass Spectrometers . . . . .	368
TOF-MS . . . . .	369
Screening Analyses with GC–MS . . . . .	370
Alternative Matrices and Samples . . . . .	372
Quality of Analytical Data . . . . .	372
Limitations of GC–MS, Traps and Pitfalls . . . . .	373
Summary and Outlook, Expanding LC–MS, New Technologies . . . . .	377
References . . . . .	378