

The background of the cover is a solid orange color, overlaid with various chemical structures in a lighter orange or yellow hue. These structures include polycyclic aromatic hydrocarbons (like naphthalene and anthracene), complex alkaloids (like morphine), and various heterocyclic compounds (like pyridine, imidazole, and pyrazole). Some structures are partially obscured by the text.

A Textbook of

Modern Toxicology

Third Edition

Edited by
Ernest Hodgson, PhD

A TEXTBOOK OF MODERN TOXICOLOGY

THIRD EDITION

Edited by

Ernest Hodgson

Department of Environmental
and Biochemical Toxicology
North Carolina State University

 WILEY-
INTERSCIENCE

A JOHN WILEY & SONS, INC., PUBLICATION

**A TEXTBOOK OF MODERN
TOXICOLOGY**

THIRD EDITION

A TEXTBOOK OF MODERN TOXICOLOGY

THIRD EDITION

Edited by

Ernest Hodgson

Department of Environmental
and Biochemical Toxicology
North Carolina State University

 WILEY-
INTERSCIENCE

A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2004 by John Wiley & Sons, Inc. All rights reserved.

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400, fax 978-646-8600, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services please contact our Customer Care Department within the U.S. at 877-762-2974, outside the U.S. at 317-572-3993 or fax 317-572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print, however, may not be available in electronic format.

Library of Congress Cataloging-in-Publication Data:

Hodgson, Ernest, 1932–

A textbook of modern toxicology / Ernest Hodgson.—3rd ed.

p. cm.

Includes bibliographical references and index.

ISBN 0-471-26508-X

1. Toxicology. I. Title.

RA1211.H62 2004

615.9—dc22

2003017524

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

CONTENTS

Preface	xix
Contributors	xxi
I Introduction	1
1 Introduction to Toxicology	3
<i>Ernest Hodgson</i>	
1.1 Definition and Scope, Relationship to Other Sciences, and History	3
1.1.1 Definition and Scope	3
1.1.2 Relationship to Other Sciences	8
1.1.3 A Brief History of Toxicology	8
1.2 Dose-Response Relationships	10
1.3 Sources of Toxic Compounds	10
1.3.1 Exposure Classes	11
1.3.2 Use Classes	11
1.4 Movement of Toxicants in the Environment	11
Suggested Reading	12
2 Introduction to Biochemical and Molecular Methods in Toxicology	13
<i>Ernest Hodgson, Gerald A. LeBlanc, Sharon A. Meyer, and Robert C. Smart</i>	
2.1 Introduction	13
2.2 Cell Culture Techniques	13
2.2.1 Suspension Cell Culture	14
2.2.2 Monolayer Cell Culture	14
2.2.3 Indicators of Toxicity in Cultured Cells	14
2.3 Molecular Techniques	16
2.3.1 Molecular Cloning	17
2.3.2 cDNA and Genomic Libraries	17
2.3.3 Northern and Southern Blot Analyses	18
2.3.4 Polymerase Chain Reaction (PCR)	18
2.3.5 Evaluation of Gene Expression, Regulation, and Function	19
2.4 Immunochemical Techniques	19
Suggested Reading	22
3 Toxicant Analysis and Quality Assurance Principles	23
<i>Ross B. Leidy</i>	
3.1 Introduction	23
3.2 General Policies Related to Analytical Laboratories	23

3.2.1	Standard Operating Procedures (SOPs)	24
3.2.2	QA/QC Manuals	24
3.2.3	Procedural Manuals	24
3.2.4	Analytical Methods Files	25
3.2.5	Laboratory Information Management System (LIMS)	25
3.3	Analytical Measurement System	26
3.3.1	Analytical Instrument Calibration	26
3.3.2	Quantitation Approaches and Techniques	26
3.4	Quality Assurance (QA) Procedures	27
3.5	Quality Control (QC) Procedures	27
3.6	Summary	28
	Suggested Reading	28
II	Classes of Toxicants	31
4	Exposure Classes, Toxicants in Air, Water, Soil, Domestic and Occupational Settings	33
	<i>W. Gregory Cope</i>	
4.1	Air Pollutants	33
4.1.1	History	33
4.1.2	Types of Air Pollutants	34
4.1.3	Sources of Air Pollutants	35
4.1.4	Examples of Air Pollutants	36
4.1.5	Environmental Effects	38
4.2	Water and Soil Pollutants	40
4.2.1	Sources of Water and Soil Pollutants	40
4.2.2	Examples of Pollutants	41
4.3	Occupational Toxicants	44
4.3.1	Regulation of Exposure Levels	44
4.3.2	Routes of Exposure	45
4.3.3	Examples of Industrial Toxicants	46
	Suggested Reading	48
5	Classes of Toxicants: Use Classes	49
	<i>W. Gregory Cope, Ross B. Leidy, and Ernest Hodgson</i>	
5.1	Introduction	49
5.2	Metals	49
5.2.1	History	49
5.2.2	Common Toxic Mechanisms and Sites of Action	50
5.2.3	Lead	51
5.2.4	Mercury	52
5.2.5	Cadmium	52
5.2.6	Chromium	53
5.2.7	Arsenic	53
5.2.8	Treatment of Metal Poisoning	54

5.3	Agricultural Chemicals (Pesticides)	54
5.3.1	Introduction	54
5.3.2	Definitions and Terms	55
5.3.3	Organochlorine Insecticides	57
5.3.4	Organophosphorus Insecticides	58
5.3.5	Carbamate Insecticides	60
5.3.6	Botanical Insecticides	60
5.3.7	Pyrethroid Insecticides	61
5.3.8	New Insecticide Classes	61
5.3.9	Herbicides	62
5.3.10	Fungicides	63
5.3.11	Rodenticides	63
5.3.12	Fumigants	64
5.3.13	Conclusions	64
5.4	Food Additives and Contaminants	64
5.5	Toxins	65
5.5.1	History	65
5.5.2	Microbial Toxins	66
5.5.3	Mycotoxins	66
5.5.4	Algal Toxins	67
5.5.5	Plant Toxins	68
5.5.6	Animal Toxins	68
5.6	Solvents	70
5.7	Therapeutic Drugs	70
5.8	Drugs of Abuse	71
5.9	Combustion Products	71
5.10	Cosmetics	71
	Suggested Reading	73
III Toxicant Processing In vivo		75
6	Absorption and Distribution of Toxicants	77
	<i>Ronald E. Baynes and Ernest Hodgson</i>	
6.1	Introduction	77
6.2	Cell Membranes	78
6.3	Mechanisms of Transport	80
6.3.1	Passive Diffusion	80
6.3.2	Carrier-Mediated Membrane Transport	83
6.4	Physicochemical Properties Relevant to Diffusion	85
6.4.1	Ionization	86
6.4.2	Partition Coefficients	87
6.5	Routes of Absorption	88
6.5.1	Extent of Absorption	88
6.5.2	Gastrointestinal Absorption	89
6.5.3	Dermal Absorption	91
6.5.4	Respiratory Penetration	94

6.6	Toxicant Distribution	97
6.6.1	Physicochemical Properties and Protein Binding	97
6.6.2	Volume of Distribution (V_d)	103
6.7	Toxicokinetics	105
	Suggested Reading	109
7	Metabolism of Toxicants	111
	<i>Randy L. Rose and Ernest Hodgson</i>	
7.1	Introduction	111
7.2	Phase I Reactions	112
7.2.1	The Endoplasmic Reticulum, Microsomal Preparation, and Monooxygenations	112
7.2.2	The Cytochrome P450-Dependent Monooxygenase System	113
7.2.3	The Flavin-Containing Monooxygenase (FMO)	128
7.2.4	Nonmicrosomal Oxidations	130
7.2.5	Cooxidation by Cyclooxygenases	132
7.2.6	Reduction Reactions	133
7.2.7	Hydrolysis	135
7.2.8	Epoxide Hydration	135
7.2.9	DDT Dehydrochlorinase	136
7.3	Phase II Reactions	137
7.3.1	Glucuronide Conjugation	138
7.3.2	Glucoside Conjugation	139
7.3.3	Sulfate Conjugation	139
7.3.4	Methyltransferases	141
7.3.5	Glutathione <i>S</i> -Transferases (GSTs) and Mercapturic Acid Formation	143
7.3.6	Cysteine Conjugate β -Lyase	145
7.3.7	Acylation	145
7.3.8	Phosphate Conjugation	148
	Suggested Reading	148
8	Reactive Metabolites	149
	<i>Randy L. Rose and Patricia E. Levi</i>	
8.1	Introduction	149
8.2	Activation Enzymes	150
8.3	Nature and Stability of Reactive Metabolites	151
8.3.1	Ultra-short-lived Metabolites	151
8.3.2	Short-lived Metabolites	152
8.3.3	Longer-lived Metabolites	152
8.4	Fate of Reactive Metabolites	153
8.4.1	Binding to Cellular Macromolecules	153
8.4.2	Lipid Peroxidation	153
8.4.3	Trapping and Removal: Role of Glutathione	153
8.5	Factors Affecting Toxicity of Reactive Metabolites	154
8.5.1	Levels of Activating Enzymes	154

8.5.2	Levels of Conjugating Enzymes	154
8.5.3	Levels of Cofactors or Conjugating Chemicals	154
8.6	Examples of Activating Reactions	154
8.6.1	Parathion	155
8.6.2	Vinyl Chloride	155
8.6.3	Methanol	155
8.6.4	Aflatoxin B ₁	156
8.6.5	Carbon Tetrachloride	156
8.6.6	Acetylaminofluorene	157
8.6.7	Benzo(<i>a</i>)pyrene	158
8.6.8	Acetaminophen	158
8.6.9	Cycasin	159
8.7	Future Developments	160
	Suggested Reading	161
9	Chemical and Physiological Influences on Xenobiotic Metabolism	163
	<i>Randy L. Rose and Ernest Hodgson</i>	
9.1	Introduction	163
9.2	Nutritional Effects	163
9.2.1	Protein	163
9.2.2	Carbohydrates	164
9.2.3	Lipids	164
9.2.4	Micronutrients	164
9.2.5	Starvation and Dehydration	165
9.2.6	Nutritional Requirements in Xenobiotic Metabolism	165
9.3	Physiological Effects	166
9.3.1	Development	166
9.3.2	Gender Differences	168
9.3.3	Hormones	169
9.3.4	Pregnancy	171
9.3.5	Disease	171
9.3.6	Diurnal Rhythms	172
9.4	Comparative and Genetic Effects	172
9.4.1	Variations Among Taxonomic Groups	173
9.4.2	Selectivity	181
9.4.3	Genetic Differences	181
9.5	Chemical Effects	184
9.5.1	Inhibition	185
9.5.2	Induction	190
9.5.3	Biphasic Effects: Inhibition and Induction	199
9.6	Environmental Effects	199
9.7	General Summary and Conclusions	201
	Suggested Reading	201
10	Elimination of Toxicants	203
	<i>Gerald A. LeBlanc</i>	
10.1	Introduction	203

10.2	Transport	205
10.3	Renal Elimination	205
10.4	Hepatic Elimination	207
	10.4.1 Entero-hepatic Circulation	208
	10.4.2 Active Transporters of the Bile Canaliculus	209
10.5	Respiratory Elimination	210
10.6	Conclusion	210
	Suggested Reading	211
IV Toxic Action		213
11 Acute Toxicity		215
	<i>Gerald A. LeBlanc</i>	
11.1	Introduction	215
11.2	Acute Exposure and Effect	215
11.3	Dose-response Relationships	217
11.4	Nonconventional Dose-response Relationships	219
11.5	Mechanisms of Acute Toxicity	220
	11.5.1 Narcosis	220
	11.5.2 Acetylcholinesterase Inhibition	220
	11.5.3 Ion Channel Modulators	222
	11.5.4 Inhibitors of Cellular Respiration	223
	Suggested Reading	224
12 Chemical Carcinogenesis		225
	<i>Robert C. Smart</i>	
12.1	General Aspects of Cancer	225
12.2	Human Cancer	228
	12.2.1 Causes, Incidence, and Mortality Rates of Human Cancer	228
	12.2.2 Known Human Carcinogens	231
	12.2.3 Classification of Human Carcinogens	233
12.3	Classes of Agents Associated with Carcinogenesis	236
	12.3.1 DNA-Damaging Agents	237
	12.3.2 Epigenetic Agents	239
12.4	General Aspects of Chemical Carcinogenesis	240
12.5	Initiation-Promotion Model for Chemical Carcinogenesis	241
12.6	Metabolic Activation of Chemical Carcinogens and DNA Adduct Formation	243
12.7	Oncogenes	245
	12.7.1 Mutational Activation of Proto-oncogenes	245
	12.7.2 <i>Ras</i> Oncogene	246
12.8	Tumor Suppressor Genes	247
	12.8.1 Inactivation of Tumor Suppressor Genes	247
	12.8.2 p53 Tumor Suppressor Gene	247
12.9	General Aspects of Mutagenicity	248

12.10	Usefulness and Limitations of Mutagenicity Assays for the Identification of Carcinogens	249
	Suggested Reading	250
13	Teratogenesis	251
	<i>Stacy Branch</i>	
13.1	Introduction	251
13.2	Principles of Teratology	251
13.3	Mammalian Embryology Overview	252
13.4	Critical Periods	255
13.5	Historical Teratogens	256
	13.5.1 Thalidomide	256
	13.5.2 Accutane (Isotetrinoin)	256
	13.5.3 Diethylstilbestrol (DES)	256
	13.5.4 Alcohol	257
	13.5.5 “Non Chemical” Teratogens	257
13.6	Testing Protocols	257
	13.6.1 FDA Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use	258
	13.6.2 International Conference of Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)—US FDA, 1994	258
	13.6.3 Alternative Test Methods	259
13.7	Conclusions	259
	Suggested Reading	259
V	Organ Toxicity	261
14	Hepatotoxicity	263
	<i>Ernest Hodgson and Patricia E. Levi</i>	
14.1	Introduction	263
	14.1.1 Liver Structure	263
	14.1.2 Liver Function	263
14.2	Susceptibility of the Liver	264
14.3	Types of Liver Injury	264
	14.3.1 Fatty Liver	264
	14.3.2 Necrosis	266
	14.3.3 Apoptosis	266
	14.3.4 Cholestasis	266
	14.3.5 Cirrhosis	266
	14.3.6 Hepatitis	267
	14.3.7 Oxidative Stress	267
	14.3.8 Carcinogenesis	267
14.4	Mechanisms of Hepatotoxicity	268
14.5	Examples of Hepatotoxicants	269
	14.5.1 Carbon Tetrachloride	269
	14.5.2 Ethanol	270

14.5.3	Bromobenzene	270
14.5.4	Acetaminophen	271
14.6	Metabolic Activation of Hepatotoxicants	272
	Suggested Reading	272
15	Nephrotoxicity	273
	<i>Ernest Hodgson and Patricia E. Levi</i>	
15.1	Introduction	273
15.1.1	Structure of the Renal System	273
15.1.2	Function of the Renal System	273
15.2	Susceptibility of the Renal System	274
15.3	Examples of Nephrotoxicants	275
15.3.1	Metals	275
15.3.2	Aminoglycosides	276
15.3.3	Amphotericin B	276
15.3.4	Chloroform	277
15.3.5	Hexachlorobutadiene	277
15.3.6	Tetrafluoroethylene	278
	Suggested Reading	278
16	Toxicology of the Nervous System	279
	<i>Bonita L. Blake</i>	
16.1	Introduction	279
16.2	The Nervous system	279
16.2.1	The Neuron	280
16.2.2	Neurotransmitters and their Receptors	282
16.2.3	Glial Cells	283
16.2.4	The Blood-Brain Barrier	284
16.2.5	The Energy-Dependent Nervous System	285
16.3	Toxicant Effects on the Nervous System	286
16.3.1	Structural Effects of Toxicants on Neurons	287
16.3.2	Effects of Toxicants on Other Cells	289
16.3.3	Toxicant-Mediated Alterations in Synaptic Function	290
16.4	Neurotoxicity Testing	293
16.4.1	In vivo Tests of Human Exposure	293
16.4.2	In vivo Tests of Animal Exposure	295
16.4.3	In vitro Neurochemical and Histopathological End Points	296
16.5	Summary	297
	Suggested Reading	297
17	Endocrine System	299
	<i>Gerald A. LeBlanc</i>	
17.1	Introduction	299
17.2	Endocrine System	299
17.2.1	Nuclear Receptors	302
17.2.2	Membrane-Bound Steroid Hormone Receptors	304

17.3	Endocrine Disruption	306
17.3.1	Hormone Receptor Agonists	306
17.3.2	Hormone Receptor Antagonists	308
17.3.3	Organizational versus Activational Effects of Endocrine Toxicants	309
17.3.4	Inhibitors of Hormone Synthesis	310
17.3.5	Inducers of Hormone Clearance	310
17.3.6	Hormone Displacement from Binding Proteins	311
17.4	Incidents of Endocrine Toxicity	311
17.4.1	Organizational Toxicity	311
17.4.2	Activational Toxicity	312
17.4.3	Hypothyroidism	313
17.5	Conclusion	314
	Suggested Reading	315
18	Respiratory Toxicity	317
	<i>Ernest Hodgson, Patricia E. Levi, and James C. Bonner</i>	
18.1	Introduction	317
18.1.1	Anatomy	317
18.1.2	Cell Types	317
18.1.3	Function	317
18.2	Susceptibility of the Respiratory System	320
18.2.1	Nasal	320
18.2.2	Lung	320
18.3	Types of Toxic Response	320
18.3.1	Irritation	320
18.3.2	Cell Necrosis	321
18.3.3	Fibrosis	321
18.3.4	Emphysema	321
18.3.5	Allergic Responses	321
18.3.6	Cancer	321
18.3.7	Mediators of Toxic Responses	322
18.4	Examples of Lung Toxicants Requiring Activation	322
18.4.1	Introduction	322
18.4.2	Monocrotaline	322
18.4.3	Ipomeanol	323
18.4.4	Paraquat	324
18.5	Defense Mechanisms	324
	Suggested Reading	325
19	Immunotoxicity	327
	<i>MaryJane K. Selgrade</i>	
19.1	Introduction	327
19.2	The Immune System	327

19.3	Immune Suppression	330
19.4	Classification of Immune-Mediated Injury (Hypersensitivity)	335
19.5	Effects of Chemicals on Allergic Disease	336
	19.5.1 Allergic Contact Dermatitis	337
	19.5.2 Respiratory Allergens	338
	19.5.3 Adjuvants	340
19.6	Emerging Issues: Food Allergies, Autoimmunity, and the Developing Immune System	341
	Suggested Reading	342
20	Reproductive System	343
	<i>Stacy Branch</i>	
20.1	Introduction	343
20.2	Male Reproductive Physiology	343
20.3	Mechanisms and Targets of Male Reproductive Toxicants	344
	20.3.1 General Mechanisms	344
	20.3.2 Effects on Germ Cells	345
	20.3.3 Effects on Spermatogenesis and Sperm Quality	345
	20.3.4 Effects on Sexual Behavior	345
	20.3.5 Effects on Endocrine Function	345
20.4	Female Reproductive Physiology	346
20.5	Mechanisms and Targets of Female Reproductive Toxicants	347
	20.5.1 Tranquilizers, Narcotics, and Social Drugs	347
	20.5.2 Endocrine Disruptors (EDs)	348
	20.5.3 Effects on Germ Cells	348
	20.5.4 Effects on the Ovaries and Uterus	348
	20.5.5 Effects on Sexual Behavior	348
	Suggested Reading	349
VI	Applied Toxicology	351
21	Toxicity Testing	353
	<i>Helen Cunny and Ernest Hodgson</i>	
21.1	Introduction	353
21.2	Experimental Administration of Toxicants	355
	21.2.1 Introduction	355
	21.2.2 Routes of Administration	356
21.3	Chemical and Physical Properties	358
21.4	Exposure and Environmental Fate	358
21.5	In vivo Tests	358
	21.5.1 Acute and Subchronic Toxicity Tests	359
	21.5.2 Chronic Tests	370
	21.5.3 Reproductive Toxicity and Teratogenicity	371
	21.5.4 Special Tests	378
21.6	In vitro and Other Short-Term Tests	385
	21.6.1 Introduction	385
	21.6.2 Prokaryote Mutagenicity	385

21.6.3	Eukaryote Mutagenicity	387
21.6.4	DNA Damage and Repair	389
21.6.5	Chromosome Aberrations	390
21.6.6	Mammalian Cell Transformation	392
21.6.7	General Considerations and Testing Sequences	393
21.7	Ecological Effects	393
21.7.1	Laboratory Tests	394
21.7.2	Simulated Field Tests	394
21.7.3	Field Tests	395
21.8	Risk Analysis	395
21.9	The Future of Toxicity Testing	395
	Suggested Reading	396
22	Forensic and Clinical Toxicology	399
	<i>Stacy Branch</i>	
22.1	Introduction	399
22.2	Foundations of Forensic Toxicology	399
22.3	Courtroom Testimony	400
22.4	Investigation of Toxicity-Related Death/Injury	400
22.4.1	Documentation Practices	401
22.4.2	Considerations for Forensic Toxicological Analysis	401
22.4.3	Drug Concentrations and Distribution	402
22.5	Laboratory Analyses	403
22.5.1	Colorimetric Screening Tests	403
22.5.2	Thermal Desorption	403
22.5.3	Thin-Layer Chromatography (TLC)	403
22.5.4	Gas Chromatography (GC)	404
22.5.5	High-Performance Liquid Chromatography (HPLC)	404
22.5.6	Enzymatic Immunoassay	404
22.6	Analytical Schemes for Toxicant Detection	404
22.7	Clinical Toxicology	405
22.7.1	History Taking	406
22.7.2	Basic Operating Rules in the Treatment of Toxicosis	406
22.7.3	Approaches to Selected Toxicoses	407
	Suggested Reading	409
23	Prevention of Toxicity	411
	<i>Ernest Hodgson</i>	
23.1	Introduction	411
23.2	Legislation and Regulation	411
23.2.1	Federal Government	412
23.2.2	State Governments	416
23.2.3	Legislation and Regulation in Other Countries	416
23.3	Prevention in Different Environments	417
23.3.1	Home	417
23.3.2	Workplace	418
23.3.3	Pollution of Air, Water, and Land	419

23.4	Education	420
	Suggested Reading	421
24	Human Health Risk Assessment	423
	<i>Ronald E. Baynes</i>	
24.1	Introduction	423
24.2	Risk Assessment Methods	424
	24.2.1 Hazard Identification	424
	24.2.2 Exposure Assessment	425
	24.2.3 Dose Response and Risk Characterization	426
24.3	Noncancer Risk Assessment	427
	24.3.1 Default Uncertainty and Modifying Factors	428
	24.3.2 Derivation of Developmental Toxicant RfD	429
	24.3.3 Determination of RfD and RfC of Naphthalene with the NOAEL Approach	430
	24.3.4 Benchmark Dose Approach	430
	24.3.5 Determination of BMD and BMDL for ETU	431
	24.3.6 Quantifying Risk for Noncarcinogenic Effects: Hazard Quotient	432
	24.3.7 Chemical Mixtures	432
24.4	Cancer Risk Assessment	433
24.5	PBPK Modeling	436
	Suggested Reading	437
VII	Environmental Toxicology	439
25	Analytical Methods in Toxicology	441
	<i>Ross B. Leidy</i>	
25.1	Introduction	441
25.2	Chemical and Physical Methods	442
	25.2.1 Sampling	442
	25.2.2 Experimental Studies	446
	25.2.3 Forensic Studies	446
	25.2.4 Sample Preparation	447
	25.2.5 Separation and Identification	448
	25.2.6 Spectroscopy	455
	25.2.7 Other Analytical Methods	460
	Suggested Reading	461
26	Basics of Environmental Toxicology	463
	<i>Gerald A. LeBlanc</i>	
26.1	Introduction	463
26.2	Environmental Persistence	464
	26.2.1 Abiotic Degradation	465

26.2.2	Biotic Degradation	465
26.2.3	Nondegradative Elimination Processes	466
26.3	Bioaccumulation	467
26.3.1	Factors That Influence Bioaccumulation	469
26.4	Toxicity	470
26.4.1	Acute Toxicity	470
26.4.2	Mechanisms of Acute Toxicity	471
26.4.3	Chronic Toxicity	472
26.4.4	Species-Specific Chronic Toxicity	473
26.4.5	Abiotic and Biotic Interactions	474
26.5	Conclusion	477
	Suggested Reading	477
27	Transport and Fate of Toxicants in the Environment	479
	<i>Damian Shea</i>	
27.1	Introduction	479
27.2	Sources of Toxicants to the Environment	480
27.3	Transport Processes	483
27.3.1	Advection	483
27.3.2	Diffusion	485
27.4	Equilibrium Partitioning	487
27.4.1	Air–Water Partitioning	487
27.4.2	Octanol–Water Partitioning	488
27.4.3	Lipid–Water Partitioning	488
27.4.4	Particle–Water Partitioning	489
27.5	Transformation Processes	490
27.5.1	Reversible Reactions	490
27.5.2	Irreversible Reactions	493
27.6	Environmental Fate Models	497
	Suggested Reading	498
28	Environmental Risk Assessment	501
	<i>Damian Shea</i>	
28.1	Introduction	501
28.2	Formulating the Problem	503
28.2.1	Selecting Assessment End Points	503
28.2.2	Developing Conceptual Models	506
28.2.3	Selecting Measures	506
28.3	Analyzing Exposure and Effects Information	507
28.3.1	Characterizing Exposure	508
28.3.2	Characterizing Ecological Effects	510
28.4	Characterizing Risk	512
28.4.1	Estimating Risk	512
28.4.2	Describing Risk	512

28.5	Managing Risk	516
	Suggested Reading	517
VIII	Summary	519
29	Future Considerations for Environmental and Human Health	521
	<i>Ernest Hodgson</i>	
29.1	Introduction	521
29.2	Risk Management	522
29.3	Risk Assessment	523
29.4	Hazard and Exposure Assessment	523
29.5	In vivo Toxicity	523
29.6	In vitro Toxicity	524
29.7	Biochemical and Molecular Toxicology	524
29.8	Development of Selective Toxicants	524
	Glossary	525
	Index	543

PREFACE

There are some excellent general reference works in toxicology, including *Casarett and Doull's Toxicology, 6th, edition*, edited by Klaassen; a 13-volume *Comprehensive Toxicology*, edited by Sipes, Gandolfi, and McQueen; as well as many specialized monographs on particular topics. However, the scarcity of textbooks designed for teacher and student to use in the classroom setting that impelled us to produce the first and second editions of this work is still apparent. With the retirement of Dr. Levi, a mainstay of the first two editions, and the continuing expansion of the subject matter, it seemed appropriate to invite others to contribute their expertise to the third edition. All of the authors are, or have been, involved in teaching a course in general toxicology at North Carolina State University and thus have insights into the actual teaching process as well as the subject matter of their areas of specialization.

At North Carolina State University, we continue to teach a course in general toxicology that is open to graduate students and undergraduate upperclassmen. In addition, in collaboration with Toxicology Communications, Inc., of Raleigh, North Carolina, we present an accelerated short course at the same level. Our experience leads us to believe that this text is suitable, in the junior or senior year, for undergraduate students with some background in chemistry, biochemistry, and animal physiology. For graduate students it is intended to lay the foundation for subsequent specialized courses in toxicology, such as those in biochemical and molecular toxicology, environmental toxicology, chemical carcinogenesis, and risk assessment.

We share the view that an introductory text must present all of the necessary fundamental information to fulfill this purpose, but in as uncomplicated a manner as possible. To enhance readability, references have been omitted from the text, although further reading is recommended at the end of each chapter.

Clearly, the amount of material, and the detail with which some of it is presented, is more than is needed for the average general toxicology course. This, however, will permit each instructor to select and emphasize those areas that they feel need particular emphasis. The obvious biochemical bias of some chapters is not accidental, rather it is based on the philosophy that progress in toxicology continues to depend on further understanding of the fundamental basis of toxic action at the cellular and molecular levels. The depth of coverage of each topic represents that chapter author's judgment of the amount of material appropriate to the beginning level as compared to that appropriate to a more advanced course.

Thanks to all of the authors and to the students and faculty of the Department of Environmental and Molecular Toxicology at North Carolina State University and to Carolyn McNeill for much word processing. Particular thanks to Bob Esposito of John Wiley and Sons, not least for his patience with missed deadlines and subsequent excuses.

ERNEST HODGSON
Raleigh, North Carolina

CONTRIBUTORS

Baynes, Ronald E., Cutaneous Pharmacology and Toxicology Center, College of Veterinary Medicine, North Carolina State University, Raleigh, NC

Blake, Bonita L., Department of Pharmacology and Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Bonner, James C., National Institute of Environmental Health Sciences, Research Triangle Park, NC

Branch, Stacy, Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Cope, W. Gregory, Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Cunmy, Helen, Bayer Crop Science, Research Triangle Park, NC

Hodgson, Ernest, Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

LeBlanc, Gerald A., Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Leidy, Ross B., Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Levi, Patricia E., Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Meyer, Sharon A., Department of Toxicology, University of Louisiana, Monroe, LA

Rose, Randy L., Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Selgrade, MaryJane K., United States Environmental Protection Agency, Research Triangle Park, NC

Shea, Damian, Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

Smart, Robert C., Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC

