

Contents

About the Editor	vii
List of Contributors	xxiii
Acknowledgments	xxvii
Introduction	xxix
1 General Principles	1
<i>Mohamed B. Abou-Donia</i>	
1.1 Introduction	1
1.1.1 Definition of Toxicology	1
1.1.2 Toxicological Studies	1
1.1.3 Accreditation in Toxicology	1
1.1.4 Societies of Toxicology	1
1.2 Toxic Responses to Xenobiotics	2
1.2.1 Molecular Changes	2
1.2.2 Subcellular Changes	2
1.2.3 Cellular Changes	2
1.2.4 Allergic or Sensitization Reactions	2
1.2.5 Idiosyncrasy	2
1.3 Evaluation of Chemical-Induced Diseases	3
1.3.1 Strength	3
1.3.2 Consistency	4
1.3.3 Specificity	4
1.3.4 Temporality	4
1.3.5 Biological Gradient	4
1.3.6 Plausibility	4
1.3.7 Coherence	4
1.3.8 Experiment	5
1.3.9 Analogy	5
1.3.10 Differential Diagnosis	5
1.4 Toxicological Studies	5
1.4.1 Definitions	5
1.4.2 Evaluation of Toxicity	5
1.4.3 Therapeutic Index (IT)	6
1.5 Toxicological Studies	7
1.5.1 Test Compound	7
1.5.2 Impurities	7
1.5.3 Dose	7
1.5.4 Animals	7
1.5.5 Temperature	8
1.5.6 Diet	8
1.5.7 Controls	8
1.5.8 Parameters Recorded in Acute Toxicity Studies	8
1.6 Acute Toxicity	9
1.6.1 Methods for Evaluating Acute Toxicity	9
References	14

2 Alternatives to <i>In-Vivo</i> Studies in Toxicology	15
<i>Shayne C. Gad</i>	
2.1 Introduction	15
2.2 Test Systems: Characteristics, Development, and Selection	18
2.3 <i>In-Vitro</i> Models	19
2.3.1 Tissue Culture	21
2.4 Lethality Testing	22
2.4.1 Lethality Testing in Lower-Species Animals	23
2.4.2 Ocular Irritation	24
2.4.3 Dermal Irritation	27
2.4.4 Irritation of Parenterally Administered Pharmaceuticals	27
2.4.5 Sensitization and Photosensitization	28
2.4.6 Phototoxicity and Photosensitization	29
2.4.7 Developmental Toxicity	30
2.4.8 Target Organ Toxicity Models	30
2.5 In-Silico Methods	34
2.6 The Final Frontier and Barrier: Regulatory Acceptance	36
2.7 Conclusions	36
References	40
Further Reading	46
3 The Application of Omics Technologies to the Study of Mammalian Toxicology	49
<i>Scott S. Auerbach and B. Alex Merrick</i>	
3.1 Introduction	49
3.2 Genomics	50
3.2.1 Technologies Used in Genomics	50
3.2.2 Approaches in Genomics	51
3.2.3 Applications of Genomics	51
3.3 Epigenomics	53
3.3.1 Technologies Used in Epigenomics	54
3.3.2 Approaches in Epigenomics	54
3.3.3 Applications of Epigenomics	55
3.4 Transcriptomics	56
3.4.1 Technologies Used in Transcriptomics	57
3.4.2 Approaches to Transcriptomics	57
3.4.3 Applications of Transcriptomics	57
3.5 Proteomics	59
3.5.1 Technologies Used in Proteomics	59
3.5.2 Approaches to Proteomics	61
3.5.3 Applications of Proteomics	61
3.6 Metabolomics	62
3.6.1 Technologies Used in Metabolomics	62
3.6.2 Approaches to Metabolomics	63
3.6.3 Applications of Metabolomics	63
3.7 Systems Toxicology	65
3.7.1 Applications of Systems Toxicology	65
3.8 Analysis of Omics Data	66
3.9 Conclusion	68
References	68
4 Cell Death Pathways in Toxicological Response	75
<i>Joshua L. Andersen and Jeffrey C. Rathmell</i>	
4.1 Tissue Homeostasis	75
4.2 Death Is the Default	75
4.3 Forms of Cell Death	76
4.4 The Key Constituents of Apoptosis	77
4.4.1 Caspases	77
4.5 Mitochondria and Bcl-2 Family Proteins	77

4.6	The Apoptosome	78
4.7	Extrinsic and Intrinsic Apoptosis	78
4.8	Toxins Kill Cells by Activating Apoptotic Pathways	79
4.9	Toxins Can Also Trigger a Cell's Survival Response	80
4.10	Outcomes of Cell Death on Tissues	81
4.11	Toxicological Regulation of Cell Death: An Overview	82
	References	82
5	Principles of Toxicokinetics and Predictive Toxicokinetics Modeling	85
	<i>Hisham El-Masri, Eva McLanahan, and Sheppard Martin</i>	
5.1	Introduction	85
5.2	Absorption	85
5.2.1	Oral Absorption	85
5.2.2	Inhalational Absorption	87
5.2.3	Dermal Absorption	89
5.3	Distribution	90
5.3.1	Oral Dosing	90
5.3.2	Inhalation Dosing	90
5.3.3	Dermal Dosing	90
5.3.4	Distribution within Tissues	90
5.3.5	Perfusion- and Diffusion-Limitation	91
5.4	Metabolism	91
5.5	Excretion	92
5.5.1	Urinary Excretion	92
5.5.2	Fecal Excretion	92
5.5.3	Exhalation	92
5.5.4	Sweat	93
5.5.5	Lactation	94
5.6	Pharmacokinetic Predictive Modeling	94
5.6.1	One-Compartment Models	94
5.6.2	Multi-Compartment Models	95
5.6.3	Physiologically Based Pharmacokinetic (PBPK) Models	96
5.7	Toxicokinetics: Applications to Human Health Risk Assessment	98
	References	98
6	Metabolic Biotransformation of Xenobiotics	101
	<i>Mohamed B. Abou-Donia</i>	
6.1	Introduction	101
6.1.1	Tissue Localization of Xenobiotic-Metabolizing Enzymes	101
6.1.2	Reactions of Metabolic Biotransformation	101
6.2	Xenobiotic-Metabolizing Reactions: Phase I	102
6.2.1	Cytochrome P450 (Microsomal Mixed-Function Oxidase, MFO)	102
6.2.2	Cytochrome P450-Mediated Reactions	106
6.2.3	Reactions Other Than Microsomal Mixed-Function Oxidase	112
6.3	Xenobiotic-Metabolizing Reactions: Phase II	118
6.3.1	Conjugation with Sugars	119
6.3.2	Sulfation	122
6.3.3	Glutathione Conjugation	125
6.3.4	Other Conjugation Reactions	127
6.3.5	Phase II Metabolism of Endogenous Compounds	128
	References	128
7	Pesticides	131
	<i>Mohamed B. Abou-Donia</i>	
7.1	Introduction	131
7.2	Insecticides	141
7.2.1	Axonal Transmission as an Insecticidal Target	141
7.2.2	The Synapse as an Insecticidal Target	145

7.3	Mitochondrial Injury	155
7.3.1	Organophosphorus Ester-Induced Chronic Neurotoxicity (OPICN)	155
7.4	Herbicides	158
7.4.1	Health Effects of Herbicides	158
7.4.2	Chlorophenoxy Acetic Acid Herbicides	158
7.4.3	Nitrophenolic and Chlorophenolic Herbicides	159
7.4.4	Dipyridyl Herbicides	159
7.4.5	Chlorate Salts	160
7.4.6	Atrazine	161
7.4.7	Organophosphate Herbicides	161
7.5	Fungicides	161
7.5.1	Thiocarbamates and Dithiocarbamates	161
7.5.2	Phthalimides	162
7.5.3	Hexachlorophene	162
7.6	Rodenticides	162
7.6.1	Anticoagulants	162
7.6.2	Sodium Monofluoroacetate (1080)	163
7.6.3	Zinc Phosphide	163
7.6.4	Strychnine	164
7.7	Insect Repellents	164
7.7.1	DEET	164
7.8	Combined Pesticide Exposure	165
7.9	Stress and Pesticide Toxicity	165
7.10	Pesticide Formulations and Inert Ingredients	166
7.10.1	Dusts	166
7.10.2	Wettable Powders (WPs)	166
7.10.3	Emulsifiable Concentrates (ECs)	166
7.10.4	Suspendable Concentrates (CSs) or Flowables	166
7.10.5	Water-Soluble Powders (SPs)	166
7.10.6	Solutions	166
7.10.7	Granules	166
7.10.8	Water-Dispersible Granules (WGs)	166
7.10.9	Ultra-Low-Volume (ULV)	166
7.10.10	Aerosols	167
7.10.11	Controlled Release (CR) Formulations	167
7.10.12	Baits	167
	References	167
8	Metal Toxicology	171
	<i>Ebany J. Martinez-Finley, Sam Caito, Stephanie Fretham, Pan Chen, and Michael Aschner</i>	
8.1	Introduction	171
8.2	Human Health Effects	173
8.2.1	Types of Health Effect	173
8.2.2	Trace Metals	174
8.2.3	Administration: Routes of Exposure	174
8.2.4	Transport and Distribution: The Systemic Toxicity of Metals	174
8.2.5	Biotransformation (Metabolism)	177
8.2.6	Elimination	177
8.3	Properties of Metals	177
8.3.1	Determinants of Reactivity	177
8.3.2	Mechanisms of Action	179
8.4	Methodologies	180
8.4.1	Administration of Metals in Mammalian Systems	180
8.4.2	Detection of Metals	181
8.5	Conclusions	183
	Acknowledgments	183
	References	183

9 Organic Solvents	187
<i>James V. Bruckner</i>	
9.1 Introduction	187
9.2 Occupational Exposures	188
9.3 Environmental Exposures	189
9.4 Toxicokinetics	190
9.4.1 Absorption	190
9.4.2 Transport and Distribution	192
9.4.3 Metabolism	192
9.4.4 Elimination	193
9.5 Aromatic Hydrocarbons	194
9.5.1 Benzene	194
9.5.2 Toluene	195
9.5.3 Styrene	196
9.6 Aliphatic Hydrocarbons	197
9.6.1 The Chemical Class	197
9.6.2 <i>n</i> -Hexane	198
9.7 Halogenated Aliphatic Hydrocarbons	200
9.7.1 Methylene Chloride	200
9.7.2 Chloroform	201
9.7.3 Carbon Tetrachloride	202
9.7.4 Trichloroethylene	204
9.7.5 Tetrachloroethylene	207
References	209
10 Gases	219
<i>Mohamed B. Abou-Donia</i>	
10.1 Introduction	219
10.1.1 Threshold Limit Value (TLV)	219
10.2 Action of Gases	220
10.3 Simple Asphyxiants	220
10.3.1 Carbon Dioxide (CO ₂)	220
10.4 Toxic Asphyxiants	221
10.4.1 Carbon Monoxide (CO)	221
10.4.2 Cyanide	222
10.4.3 Hydrogen Sulfide	224
10.4.4 Other Methemoglobinemia-Producing Chemicals	225
10.5 Gases Affecting the CNS and PNS	226
10.5.1 Carbon Disulfide	226
10.6 Irritants	227
10.6.1 Ammonia	227
10.6.2 Chlorine	228
10.6.3 Air Pollutants	228
10.6.4 Oxides of Sulfur (SO _x)	228
10.6.5 Oxides of Nitrogen	229
10.6.6 Ozone	230
10.6.7 Formaldehyde	230
10.7 Sensitizers	231
10.7.1 Methyl Isocyanate	231
10.7.2 Toluene 2,4-Diisocyanate	231
References	231
11 Nanotoxicology: Environmental, Health and Safety (EHS) Considerations for Assessing Hazards and Risks Following Nanoparticle Exposures	233
<i>David B. Warheit and Kenneth L. Reed</i>	
11.1 Introduction	233
11.2 Importance of Physico-Chemical Characterization Studies on Nanoparticle-Types	234

11.3	Species Differences in Lung Responses to Inhaled Fine and/or Ultrafine TiO ₂ Particles	235
11.4	Strategies for Assessing Pulmonary Hazards to Nanomaterials	236
11.4.1	Pulmonary Bioassay Studies of Fine and Nanoscale TiO ₂ Particle-types	237
11.4.2	Pulmonary Bioassay Studies of Fine and Nanoscale α -Quartz Particle-Types	238
11.5	Evaluating the Risks Associated with Nanomaterial Exposures: The NanoRisk Framework	238
11.6	Safe Handling of Nanomaterials in the Laboratory	242
11.7	Conclusions	242
	References	243
12	Pharmaceutical Toxicity In Humans	245
	<i>Martha M. Abou-Donia</i>	
12.1	Introduction	245
12.1.1	Evolution of the Study and Understanding of Pharmaceutical Toxicity	246
12.1.2	Regulatory Overview of Pharmaceutical Safety	246
12.1.3	Pharmaceutical Decision-Making in Drug Development	247
12.1.4	History of Drug Regulation in the US	247
12.1.5	Definitions of Toxicity	248
12.1.6	Preclinical Testing	249
12.1.7	Clinical Studies and Toxicity	250
12.1.8	Adverse Events	250
12.1.9	Serious Adverse Events	250
12.1.10	Risk : Benefit Analysis	250
12.2	Development of Pharmaceuticals to Ensure their Safe Use	252
12.2.1	Preclinical Testing	253
12.2.2	Clinical Testing	254
12.2.3	Types of Study	255
12.2.4	Types of Test Undertaken	258
12.2.5	Numbers of Patients Tested	258
12.2.6	Data Analyses	258
12.2.7	Potential Toxicity Signs	260
12.2.8	Approval Process, Including Labeling and Post-Approval Use	260
12.2.9	Post-Approval Phase IV Studies	260
12.2.10	Analyses of Data Overall: From Phase I to Phase II to Phase III	261
12.2.11	Drugs with Known Toxicity at Approval	262
12.2.12	Boxed Warnings	262
12.2.13	Risk : Benefit Analysis	262
12.3	Drugs Withdrawn or with Restricted Use or Dosage due to Toxicity Issues	263
12.3.1	Sulfa Drugs	263
12.3.2	Dinitrophenol	263
12.3.3	Acetaminophen (Paracetamol)	264
12.3.4	Thalidomide	264
12.3.5	Alfaxalone	264
12.3.6	Fen-Phen	264
12.3.7	Romozin	264
12.3.8	Vioxx	265
12.3.9	Lotronex TM	265
12.3.10	Statins	265
12.4	Summary	266
	References	266
13	Food Additives	269
	<i>Mohamed B. Abou-Donia and Mohamed Salama</i>	
13.1	Introduction	269
13.1.1	Definition of Food Additives	269
13.2	Regulation of Food Additives	269
13.2.1	Testing for Safety of Food Additives	270
13.2.2	Toxicological Testing	270

13.2.3	The Level of Concerns	270
13.2.4	Generally Recognized as Safe (GRAS)	270
13.2.5	Tolerance, Estimated Daily Intake (EDI) and Acceptable Daily Intake (ADI)	271
13.2.6	The Delaney Clause	271
13.2.7	Sources of Nitrates and Nitrites in Food	271
13.2.8	Negligible Risk	272
13.3	Intentional Food Additives	272
13.3.1	To Maintain and/or Improve Food Quality	273
13.3.2	To Make Food Make more Appealing	273
13.3.3	Processing Aids	278
13.4	Intentional Food Additives	279
13.5	Nonintentional Food Additives	279
13.5.1	Unintentional Food Additives	279
13.5.2	Incidental Additives	279
13.6	Toxicological Action of Food Additives	279
13.6.1	Foods in the US Market That May Be Harmful	281
13.7	Adverse Reactions to Food	282
13.7.1	Definition	282
13.7.2	Food Allergy	282
13.7.3	Food Allergens	283
13.7.4	Food Idiosyncrasies	283
13.7.5	Food Allergic Reactions	283
13.7.6	Pharmacological Food Reactions	284
13.7.7	Metabolic Food Reactions	284
13.8	Nutraceuticals	284
13.8.1	Definition	284
13.8.2	Classification of Nutraceuticals	285
13.8.3	Market Potential	285
13.9	Health Foods	285
13.10	Conclusions	285
	References	286
14	Endocrine Disruptors	289
	<i>Gwendolyn Louis and Tammy Stoker</i>	
14.1	Introduction	289
14.2	Targets of EDC Interference	290
14.2.1	Effects on Intracellular Signaling	290
14.2.2	Effects on Steroidogenesis	292
14.2.3	Effects on Hormone Metabolism	294
14.2.4	EDC Effects on the HPG Axis	294
14.2.5	EDC Effects on Thyroid Function	296
14.2.6	EDC Effects on Pregnancy and Lactation	297
14.2.7	Summary	297
14.3	Endocrine Disruptor Screening Programs	297
14.3.1	<i>In-Vitro</i> Assays for the Detection of EDCs	298
14.3.2	Mammalian <i>In-Vivo</i> Assays for the Detection of EDCs	300
14.3.3	Summary of EDSP	301
14.4	Overall Conclusions	303
	References	303
15	Ionizing Radiation: Toxicologic Action	309
	<i>Heather A. Himburg and John P. Chute</i>	
15.1	Introduction	309
15.1.1	Basics of Radiation Physics	309
15.2	Cellular Effects of Ionizing Radiation	309
15.2.1	DNA Damage and Repair	309
15.2.2	Intrinsic Pathway of Apoptosis	310

15.2.3	Extrinsic Pathway of Apoptosis	311
15.2.4	Senescence and Mitotic Catastrophe	311
15.2.5	Reactive Oxygen Species	312
15.3	Long-Term Effects of Ionizing Radiation	312
15.3.1	Carcinogenesis	313
15.3.2	Developmental Defects	314
15.3.3	Ocular Defects	314
15.4	Normal Tissue Injury from Ionizing Radiation in Adults	314
15.4.1	Hematopoietic System	316
15.4.2	Acute Radiation Sickness and the Hematopoietic Syndrome	318
	References	
16	Immune System Toxicity and Immunotoxicity Hazard Identification	323
	<i>Robert W. Luebke</i>	
16.1	Introduction	323
16.2	Overview of the Immune System	323
16.2.1	Organization	324
16.2.2	Innate Immunity	324
16.2.3	Adaptive (Antigen-Specific) Immunity	326
16.2.4	Host Factors Affecting Immunocompetence and Immunotoxicity	327
16.3	Immunotoxicology: The Immune System as a Target of Environmental Chemicals	328
16.3.1	Immunosuppression and Stimulation	332
16.3.2	Allergic Hypersensitivity	334
16.3.3	Autoimmunity	336
16.4	Immunotoxicity Risk Assessment	336
16.5	New Developments in Immunotoxicity Hazard Identification	337
	References	
17	Carcinogenicity and Genotoxicity	341
	<i>Shayne C. Gad, Charles B. Spainhour, and Samantha E. Gad</i>	
17.1	Introduction	341
17.1.1	History of Xenobiotic Carcinogenesis	342
17.2	Mechanisms and Classes of Carcinogens	342
17.2.1	Genotoxic Carcinogens	345
17.2.2	Epigenetic Carcinogens	347
17.3	Oncogenes	349
17.4	Metals and Carcinogens	349
17.5	The Two-Step Theory of Carcinogenesis	350
17.6	Multiple-Hit Theory of Carcinogenesis	350
17.6.1	Initiation, Promotion, and Progression	352
17.7	Solid-State Tumorigenesis	353
17.8	Traditional Carcinogenicity Bioassays of Xenobiotics	355
17.8.1	Regulatory Requirements and Timing	355
17.8.2	Species and Strain	357
17.8.3	Animal Husbandry	357
17.8.4	Dose Selection	359
17.8.5	Group Size	360
17.8.6	Route of Administration	360
17.8.7	Study Duration	360
17.8.8	Survival	361
17.8.9	Endpoints Measured	363
17.8.10	Statistical Analysis	365
17.8.11	Interpretation of Results	369
17.8.12	Relevance to Humans	370
17.8.13	Conclusions	371
17.9	Carcinogenicity Testing for Medical Devices	373
17.9.1	Dose Selection	

17.10	Interpretation of Results	376
17.10.1	Criteria for a Positive Result	376
17.10.2	Use of Historic Controls	376
17.11	Transgenic Models	376
17.11.1	The Tg-AC Mouse Model	377
17.11.2	The Tg.rasH2 Mouse Model	377
17.11.3	The p53 ^{+/−} Mouse Model	378
17.11.4	The XPA ^{−/−} Mouse Model	378
17.12	Genotoxicity (Predictive <i>In-Vitro</i>)	379
17.12.1	The Link between Mutation and Cancer	379
17.12.2	Cytogenetics	380
17.12.3	<i>In-Vitro</i> Cytogenetic Assays	382
17.12.4	<i>In-Vivo</i> Cytogenetics Assays	383
17.12.5	Sister Chromatid Exchange Assays	383
17.12.6	Predictive Models: QSAR	384
	References	384
18	Neurotoxicity	395
	Mohamed B. Abou-Donia	
18.1	Introduction	395
18.2	The Nervous System	395
18.2.1	Nerve Fibers	395
18.2.2	The Brain	397
18.2.3	Spinal Cord	402
18.2.4	Peripheral Nervous System	402
18.2.5	Nerve Conduction	403
18.2.6	The Synapse and Neurotransmitters	404
18.2.7	Second Messengers	405
18.2.8	Cytoskeletal Proteins	405
18.2.9	Axonal Transport	407
18.2.10	Nervous System Diseases	407
18.3	Classification of Neurotoxic Action	408
18.3.1	Non-Selective Neurotoxic Action	408
18.3.2	Selective Neurotoxic Action	410
	References	419
19	Cardiovascular Toxicology and Its Evaluation	425
	Shayne C. Gad	
19.1	Introduction	425
19.1.1	Cardiotoxins	425
19.2	Pharmacologic Profiling	427
19.2.1	<i>In-Vitro</i> Evaluation of Cardiovascular Toxicity	429
19.3	<i>In-Vivo</i> Parameter Evaluations in Standard Studies	432
19.3.1	Electrocardiograms	433
19.3.2	Blood Pressure and Heart Rate	434
19.3.3	Flow Measurement Techniques	434
19.3.4	Imaging Technologies: Magnetic Resonance Imaging and Echocardiography	436
19.4	Clinical Signs and Observations	437
19.5	Clinical Pathology	438
19.5.1	Electrolytes	438
19.5.2	Osmolality and Acid-Base Balance	438
19.5.3	Enzymes	439
19.5.4	Creatine Phosphokinase	439
19.5.5	Myoglobin	439
19.5.6	Lactate Dehydrogenase	440
19.5.7	Serum Glutamic-Oxaloacetic Transaminase and Serum Glutamic-Pyruvic Transaminase	440

19.5.8	Heart Fatty Acid Binding Protein	440
19.5.9	Troponins	441
19.5.10	Other Proteins	442
19.5.11	Lipids	443
19.6	Pathology	443
19.6.1	Cardiomyopathy	444
19.6.2	Cardiac Hypertrophy	444
19.6.3	Vasculature	445
19.6.4	Hemorrhage	447
19.6.5	Mitochondrial Damage	447
19.7	Medical Devices	448
19.8	Animal Models	448
19.9	Summary	449
	References	449
20	Liver Toxicology	453
	<i>Mitchell R. McGill, C. David Williams, and Hartmut Jaeschke</i>	
20.1	Introduction	453
20.2	Liver Anatomy and Physiology	453
20.2.1	Liver Anatomy	456
20.2.2	Liver Cells and Function	456
20.2.3	Bile Formation and Flow	457
20.3	Mechanisms of Hepatotoxicity	457
20.3.1	Intracellular Mechanisms of Hepatocyte Injury	462
20.3.2	Injury of Non-Parenchymal Cells	463
20.3.3	Extracellular Mechanisms of Hepatocyte Injury	464
20.3.4	Survival Mechanisms	465
20.4	Liver Diseases and the Consequences of Liver Failure	465
20.4.1	Steatosis and Steatohepatitis	465
20.4.2	Cholestasis	465
20.4.3	Circulatory Disturbances	466
20.4.4	Fibrosis and Cirrhosis	466
20.4.5	Hepatic Encephalopathy	466
20.5	Conclusions	467
	References	467
21	Male Reproductive Toxicology: Environmental Exposures versus Reproductive Competence	473
	<i>Gary R. Klinefelter</i>	
21.1	Introduction	473
21.2	Overview of Male Reproductive Biology	474
21.2.1	The Testis	474
21.2.2	The Epididymis	476
21.2.3	Reproductive Development	478
21.3	Why the Human Male is Vulnerable to Toxic Insult	481
21.4	Fertility Assessments	481
21.5	Assessing Toxicity in the Testis	484
21.6	Assessing Toxicity in the Epididymis	486
21.7	Assessing Toxicity during Reproductive Development	488
21.8	Epidemiological and Toxicological Needs	489
	References	491
22	Female Reproductive Toxicology	493
	<i>Jerome M. Goldman and Ralph L. Cooper</i>	
22.1	Introduction	493
22.2	Development of the Reproductive System	494
22.2.1	Sexual Differentiation of the Brain	495
22.2.2	Puberty	496

22.3	The Adult Female Reproductive System	498
22.3.1	The Ovarian Cycle	498
22.3.2	Hypothalamic–Pituitary–Ovarian (HPO) Axis	503
22.3.3	Ovulation	508
22.4	Pregnancy	509
22.4.1	Toxicant Effects on Implantation, Pregnancy Maintenance, and Parturition	510
22.5	Reproductive Risk, Animal Models, and the Use of <i>In-Vitro</i> Assays	511
	Acknowledgments	511
	References	512
23	Pulmonary Toxicology	519
	<i>Aimen K. Farraj, Mehdi S. Hazari, and Daniel L. Costa</i>	
23.1	Pulmonary Disease Epidemiology	519
23.2	Comparative Functional Anatomy of the Lung	520
23.2.1	Ventilation and Perfusion	520
23.2.2	Nasal Passages, Pharynx, Trachea, and Main Bronchi	520
23.2.3	Conducting Airways of the Lung	520
23.2.4	Gas Exchange Region of the Lung	522
23.2.5	Vasculature of the Lung	522
23.2.6	Lymphatics, Innervation, and Connective Tissue	523
23.2.7	Exocrine and Metabolic Functions of the Lung	523
23.3	Principles of Gas and Particle Entry into the Lung, and Clearance	523
23.3.1	Gases and Vapors	523
23.3.2	Particle Deposition	524
23.3.3	Clearance	525
23.4	Susceptibility	525
23.4.1	Pre-Existing Lung Disease and Infection	525
23.4.2	Genetics	526
23.4.3	Age	526
23.5	Key Responses Triggered by Inhaled Agents	527
23.5.1	Spectrum of Responses	527
23.5.2	Oxidant Injury and Ozone	527
23.5.3	Fibrotic Pneumoconiosis and Dust Inhalation	528
23.5.4	Occupational Asthma and Low-Molecular-Weight Chemicals	530
23.5.5	Metal Fume Fever	531
23.5.6	Respiratory Dysfunction and Particulate Matter	531
23.6	Spotlight on Nanomaterials	531
23.7	Lung Injury from Systemic Agents	532
23.7.1	Monocrotaline and Pulmonary Endothelial Injury	532
23.7.2	Paraquat and Alveolar Epithelial Injury	532
23.7.3	Other Systemic Agents	533
23.8	Lung Responses that Trigger Extrapulmonary Effects	533
23.9	Approaches in Pulmonary Toxicology	533
23.9.1	<i>In-Vivo</i> Toxicology	533
23.9.2	Pulmonary Function Assessment	534
23.9.3	<i>In-Vitro</i> and <i>Ex-Vivo</i> Toxicology	534
23.9.4	Modeling	535
23.10	The Future of Pulmonary Toxicology	535
	Acknowledgments	535
	References	536
24	Gastrointestinal Toxicology	539
	<i>Shayne C. Gad</i>	
24.1	Introduction	539
24.2	Structure of the GI Tract	539
24.2.1	Mucosa	541
24.2.2	Submucosa	541

24.2.3	Muscularis	541
24.2.4	Serosa	541
24.2.5	The Mouth	542
24.2.6	Tongue	543
24.2.7	Pharynx	544
24.2.8	Esophagus	544
24.2.9	Stomach	545
24.2.10	Small Intestine	547
24.2.11	Large Intestine	547
24.3	Function of the GI Tract	548
24.3.1	Mechanical and Chemical Digestion in the Mouth	548
24.3.2	Regulation of Gastric Secretion and Motility	550
24.3.3	Regulation of Gastric Emptying	551
24.3.4	Role and Composition of Bile	552
24.3.5	Role of Intestinal Juice and Brush-Border Enzymes	553
24.3.6	Digestion of Carbohydrates	554
24.3.7	Digestion of Proteins	555
24.3.8	Digestion of Lipids	555
24.3.9	Digestion of Nucleic Acids	555
24.3.10	Regulation of Intestinal Secretion and Motility	555
24.3.11	Absorption in the Small Intestine	555
24.3.12	The Large Intestine	558
24.4	Evaluating Effects of Xenobiotic Exposure on GI Tract Function	559
24.5	Nature of Xenobiotic Exposures	559
24.6	Nature of Intestinal Function	560
24.6.1	Chemical-Induced Alterations of Intestinal Function; Study Approaches	560
24.6.2	GI Functions Affected by Xenobiotic Exposure	561
24.7	Intestinal Transit	564
24.7.1	Ulcerogenic activity	564
24.8	Conclusions	565
	References	566
25	Epidemiology	569
	<i>Gregg M. Stave</i>	
25.1	Introduction	569
25.2	Epidemics	569
25.3	Beyond Epidemics	569
25.4	Selection of Study Design	570
25.4.1	Cohort Studies	570
25.4.2	Case-Control Studies	570
25.4.3	Randomized Controlled Trials	570
25.4.4	Probability and Statistics	571
25.5	Bias and Confounding	572
25.6	Counteracting Problems	572
25.7	Correlation is NOT Causation!	572
25.7.1	The Bradford-Hill Criteria	573
25.8	Testing	573
25.9	Screening	575
25.9.1	Cancer Biology	575
25.9.2	Misperception	575
25.9.3	Cancer Screening	576
25.10	Conclusions	576
	References	576
26	Drugs of Abuse	579
	<i>Mohamed B. Abou-Donia</i>	
26.1	Introduction	579
26.1.1	Definitions	579

26.1.2	Drug Addiction	581
26.1.3	Management of Drug Abuse	582
26.2	Drug Tolerance	582
26.3	Withdrawal Symptoms	582
26.4	Controlled Substances Act	583
26.5	CNS Stimulants	583
26.5.1	Amphetamines	583
26.5.2	MDMA ('Ecstasy')	584
26.5.3	'Club Drugs'	584
26.5.4	Cocaine	585
26.5.5	Khat	586
26.5.6	Nicotine	587
26.6	CNS Sedatives and Hypnotics	588
26.6.1	Alcohol	589
26.6.2	Barbiturates	590
26.6.3	Benzodiazepines	591
26.7	Opiates	592
26.7.1	Naturally Occurring Opiates	592
26.7.2	Oxycodone	593
26.8	Neither CNS Depressant nor Stimulant Drugs	594
26.8.1	Cannabis (Marihuana, Hashish)	594
26.9	Hallucinogens (Psychedelics)	596
26.9.1	Lysergic Acid Diethylamide (LSD)	596
26.9.2	Phencyclidine (PCP)	597
26.10	Miscellaneous Drugs	597
26.10.1	Inhalants	597
26.10.2	Steroids (Anabolic)	599
26.10.3	Prescription Medications	600
26.11	Drug Testing	601
26.11.1	Interferences with Urine Drug Testing	601
	References	602
27	Naturally Occurring Toxins	605
	<i>Eman M. El-Masry and Mohamed B. Abou-Donia</i>	
27.1	Introduction	605
27.2	Bacterial Toxins	605
27.2.1	Clostridial Neurotoxins	607
27.2.2	Cholera Toxins	610
27.2.3	Heat-Labile (LT) and Heat-Stable (LS) Enterotoxins from Enterotoxigenic <i>Escherichia coli</i>	611
27.2.4	Shiga and Shiga-Like Toxins	611
27.2.5	Anthrax Toxin	612
27.2.6	<i>Staphylococcus</i> Enterotoxins and Toxic Shock Syndrome Toxin	613
27.2.7	<i>Bacillus cereus</i> Cereulide	613
27.2.8	Diphtheria Toxin	614
27.2.9	Pneumolysin (Ply)	614
27.3	Mycotoxins	615
27.3.1	Aflatoxin	615
27.3.2	Sterigmatocystin	616
27.3.3	Ergot Alkaloids	617
27.3.4	Ochratoxins	618
27.3.5	Citrinin	618
27.3.6	Trichothecenes	618
27.3.7	Fumonisin	619
27.3.8	Patulin	619
27.4	Phytotoxins	620
27.4.1	Mushroom Poisoning	620
27.4.2	Atropine Toxicity	622

27.4.3	Nicotine Poisoning	623
27.4.4	Curare Poisoning	623
27.4.5	β -Oxalyl-L- α,β -Diaminopropionic Acid Toxicity	624
27.4.6	Castor Oil Plant Poisoning	624
27.4.7	Colchicine Poisoning	625
27.4.8	Paclitaxel (Taxol TM)	626
27.4.9	Cycad Toxicity	626
27.4.10	Oxalate and Oxalic Acid Poisoning	627
27.4.11	Cyanogenic Glycosides Poisoning	627
27.4.12	Nutmeg Poisoning	627
27.4.13	Caffeine Toxicity	628
27.4.14	Chocolate Poisoning	629
27.4.15	Digitalis Glycosides Toxicity	630
27.4.16	Glycyrrhizin	631
27.4.17	Goitrin Toxicity	631
27.4.18	Gossypol Poisoning	632
27.4.19	Urushiol Poisoning	633
27.5	Reptile Toxins	633
27.5.1	Snake Venom Toxins	633
27.6	Insects (Bees)	635
27.7	Marine Toxins	635
27.8	Amphibian Toxins	635
27.8.1	Batrachotoxins	635
	References	636
28	Toxicology in the 21st Century	641
	<i>Mohamed B. Abou-Donia</i>	
28.1	Introduction	641
28.2	Toxicology in the 20th Century	641
28.2.1	Major Accidents of Human Exposure to Toxic Agents	641
28.3	Toxicology in the 21st Century	644
28.3.1	Toxicity Testing in the 21st Century	645
28.4	Future Studies in the 21st Century	647
28.5	Concluding Remarks	648
	References	648
	Index	651