UNDERSTANDING TOXICOLOGY

A BIOLOGICAL APPROACH

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Production Credits
VP, Executive Publisher: David D. Cella
Publisher: Michael Brown
Associate Editor: Nicholas Alakel
Associate Editor: Danielle Bessette
Associate Production Editor: Rebekah Linga
Senior Marketing Manager: Sophie Fleck Teague
Manufacturing and Inventory Control Supervisor: Amy Bacus
Composition: CAE Solutions Corp.
Cover Design: Kristin E. Parker
Rights & Media Specialist: Merideth Tumasz
Media Development Editor: Shannon Sheehan
Cover Image: © kgtoh/age fotostock
Printing and Binding: Edwards Brothers Malloy
Cover Printing: Edwards Brothers Malloy

Library of Congress Cataloging-in-Publication Data
Mercurio, Steven D., author.
Understanding toxicology : a biological approach / Steven D. Mercurio.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-7637-7116-4 (paper)
I. Title.
[DNLM: 1. Drug-Related Side Effects and Adverse Reactions. 2. Biological Factors--toxicity. 3. Environmental Exposure. 4. Hazardous Substances--toxicity. 5. Toxicology. QV 600]
RA1226
615.9'02--dc23

2015011989

6048

Printed in the United States of America
20 19 18 17 16 10 9 8 7 6 5 4 3 2 1

Dedication

This book is dedicated to the many students I have taught over a nearly 30-year period at Minnesota State University and to their struggles with understanding the complexity of the biological response to chemicals, biological agents, and physical stressors, including radiation. Their ability to engage in toxicology research and contribute to scientific investigation has always been a source of inspiration. I wanted to provide a tool that they could understood more logically than other sources of information. Toxicology is at the heart of the biological sciences, as toxins have been used to investigate various mechanisms of biologic action, they are taken as medications, and they are used for various other purposes. In a world and climate that has been altered by industrialization and chemical use, the study of toxicology helps us to understand the benefits and risks of humanity's ongoing experiment in the use of chemicals to enhance the economy and extend lifespan.

Contents

	Preface	xiii
	Chapter Overview and Pedagogical Features	xv
	Acknowledgments	xvii
	About the Author	xix
PART I	**Introduction**	**1**
1	**Biological Research in Toxicology**	**3**
	Toxicology Research Area Specialties	4
	Selected Research Experiments to Consider During Your Study of Toxicology	5
	Biology as the Arbiter of Toxicology	9
	Questions	11
	References	11
2	**Development of the Field of Toxicology**	**13**
	Development of the Science of Toxicology	14
	Questions	17
	References	17
3	**Toxicology Terms and How They Relate to Organisms**	**19**
	The Cell	20
	Tissues, Organs, and Complex Organisms	21
	Ecosystems	31
	Questions	34
	References	34
4	**Hazard, Exposure, and Risk Modeling**	**37**
	Framework	38
	Cells	39

	Complex Organisms—Tissues and Organs: Therapeutic or Human Risk	42
	Ecosystems	49
	Questions	56
	References	56
PART II	**Toxic Reactions of Cells**	**59**
5	**Absorption and Transport of Toxicants Through Membranes: Toxic Damage to Membranes**	**61**
	Cellular Barriers	62
	Mechanisms of Cellular Transport	63
	Mechanisms of Membrane Damage	68
	Questions	74
	References	74
6	**Receptor-Mediated Toxicities on the Outside of Cells**	**79**
	Receptors and Signal Transduction Mechanisms	81
	Targeting Ion-Channel Receptors	82
	Targeting Transmembrane Enzyme Receptors and Downstream Enzymes	84
	Targeting G Protein–Linked Receptors and Downstream Signal Transduction	86
	Questions	89
	References	89
7	**Detoxication and Activation by Cells: Metabolism of the Original Toxicant**	**91**
	Biotransformation	94
	Anaerobic Bacteria	95
	Hybrid Reactions of Facultative Anaerobes: Metabolism of Aromatic Compounds	96
	Aerobic Organisms' Phase 1 Metabolism	96
	Aerobic Organisms' Phase 2 Metabolism: Conjugation	123
	Questions	129
	References	129
8	**Damage to Cytosolic and Endoplasmic Reticulum Activities**	**135**
	Reactive Chemical Species	138
	Cellular Damage and Adaptation Mechanisms	147
	Antidotes	156
	Questions	158
	References	159
9	**Damage to Mitochondrial and Chloroplast Activities**	**165**
	Mitochondria	167
	Chloroplasts and Plant Mitochondria	175
	Questions	179
	References	180

10	**Damage to Nuclear Structures/DNA: Mutagenesis and Carcinogenesis**	**183**
	Nuclear Membrane	189
	Mutagenesis	190
	Carcinogenesis	203
	Questions	223
	References	223
11	**Selective Genetic Sensitivity of Cells to Toxicants**	**227**
	Selective Toxicity	231
	Absorption and Elimination Differences	231
	Metabolism/CYP Polymorphisms	232
	Receptor Interaction Alterations	235
	Questions	239
	References	239
12	**Nutritional Toxicity and Sensitivity**	**243**
	Nutritional Toxicology	250
	Undernutrition	251
	Overnutrition/Pharmacologic or Toxic Concentrations of Nutrients	256
	Naturally Occurring Toxicants in Food	267
	Genetics and Nutrition/Nutritional Genomics	269
	Questions	270
	References	271
PART III	**Toxic Reactions of Tissues/Organs**	**279**
13	**Routes of Administration and Which Organs Are Most Likely Impacted Based on Route and Toxicokinetic Models**	**281**
	Transcutaneous Absorption	284
	Ocular Absorption	288
	Oral Absorption	289
	Inhalation	295
	Parenteral Routes	297
	Questions	301
	References	301
14	**Forensic Toxicity Testing**	**305**
	Most Likely Suspects	309
	Signs/Symptoms of Exposure	310
	Sampling Techniques	313
	Analysis Methodology	315
	Flow Chart of a Typical Postmortem Examination	321
	Therapeutic Drug (Medication) Monitoring in Living Human Patients	323
	Questions	326
	References	326

15	**The Skin and Eye: Most Likely Exposure Routes and Toxicities Due to Contact Exposure and Dose Toxicities**	**329**
	Forensic Analysis of Skin Damage	335
	Percutaneous Absorption	349
	Dermal Toxicity Tests	351
	Forensic Analysis of Eye Damage	354
	Eye Toxicity Tests	366
	Questions	368
	References	369
16	**Gastrointestinal System Toxicity and Oral Exposure (GI Tract, Pancreas, Liver)**	**375**
	Forensic Analysis of GI Damage	383
	Forensic Analysis of Pancreatic Damage	399
	Forensic Analysis of Liver Damage	401
	GI Toxicity Tests	412
	Pancreas Toxicity Tests	414
	Liver Toxicity Tests	414
	Questions	415
	References	416
17	**The Lung and Gill Exposures Representing Toxic Concentrations—Model for Environmental Toxicology**	**423**
	Forensic Analysis of Lung Damage	429
	Forensic Analysis of Gill Damage	439
	Lung Toxicity Tests	442
	Gill Toxicity Tests	443
	Microcosm for Environmental Toxicology	444
	Questions	445
	References	445
18	**The Cardiovascular System as Conduit for a Dose Becoming a Dosage: Exposure and Toxicities**	**449**
	Forensic Analysis of Blood as a Diagnostic Tool	455
	Forensic Analysis of Vascular Toxicants	465
	Forensic Analysis of Cardiac Toxicants	468
	Questions	477
	References	477
19	**Bone Marrow and Immune Organ Toxicity via Lymphatic and Blood Transport**	**485**
	Recognition of Foreign Antigens	489
	Hypersensitivity Reactions (Allergy and Autoimmunity)	505
	Autoimmunity Versus Immune Suppression	514
	Toxicity Tests	515
	Questions	519
	References	519

20	**The Nervous System and Exposure to Lipophilic Toxicants or Transported Neurotoxic Agents**	**523**
	Central Nervous System Toxicity	529
	Nerve Toxicity Tests	549
	Questions	553
	References	554
21	**Toxicity to Neuroendocrine Organs and Endocrine Disruption**	**557**
	Primary Endocrine Organs	565
	Secondary Endocrine Organs	585
	Endocrine Organ Disruption Tests	586
	Questions	590
	References	590
22	**Toxicity to Reproductive Organs and Developmental Toxicity**	**597**
	Mutagenic Damage	605
	Epigenetic Developmental Disruption	605
	Early Male Developmental Toxicity	607
	Early Female Developmental Toxicity	612
	Fertilization	614
	Embryo Toxicity/Fetal Toxicity	614
	Late Male Developmental Toxicity	619
	Late Female Developmental Toxicity	620
	Reproductive/Developmental Tests	621
	Questions	629
	References	629
23	**Excretion of Hydrophilic Toxicants and Metabolites and Kidney Toxicity**	**633**
	Prerenal Azotemia	638
	Vascular Damage	639
	Glomerular Damage	639
	Proximal Convoluted Tubular (PCT) Injury	640
	Interstitium	643
	Loop of Henle	643
	Distal Convoluted Tubule	643
	Collecting Duct	644
	Acid–Base Balance and Electrolyte Balance	645
	Species Specificity	645
	Kidney Toxicity Tests	645
	Questions	648
	References	648

PART IV	**Toxic Reactions of Ecosystems**	**651**
24	**Dispersion Modeling in Air, Water, and Soil: Likely Route of Exposure and Most Sensitive Organism Based on Dispersion and Concentration**	**653**
	Ecotoxicology and Environmental Toxicology	656
	Dispersion	660
	Route of Exposure	668
	Questions	672
	References	672
25	**Agricultural Chemicals (Pesticides and Fertilizers): Exposure and Impacts**	**675**
	Fertilizers/Nutrients	684
	Pesticides	688
	Questions	748
	References	749
26	**Industrial Chemicals That Biodegrade: Organic Chemical Exposures and Impacts**	**761**
	Solvents	765
	PAHs (Arenes—Multiple Rings)	784
	Polychlorinated Biphenyls (PCBs)	784
	Dibenzodioxins and Dibenzofurans	784
	Questions	785
	References	785
27	**Industrial Chemicals That Change Lipophilicity But Do Not Biodegrade: Metal Impacts**	**789**
	Toxic Metals	793
	Essential Metals	803
	Biological Interest: Nickel	812
	Medical	812
	Questions	816
	References	816
28	**Industrial Chemicals That Cause Atmospheric Changes and Direct Versus Indirect Toxicity: Gases, Vapors, Aerosols, and Radiation**	**821**
	Gases and Vapors—Direct Effects	824
	Aerosols—Direct Effects	829
	Gases and Vapors—Indirect Effects	830
	Particles—Indirect Effects	831
	Radiation	832
	Questions	842
	References	843

29	**Toxicity of Pharmaceuticals and Personal Care Products (PPCPs) into Water**	**845**
	Environmental Effects of PPCPs	849
	Possible Human Effects of PPCPs	852
	Treatment of Effluents to Prevent Exposure to PPCPs	853
	Questions	853
	References	854
PART V	**Biological Toxicants**	**855**
30	**Venoms and Injection Toxicity Versus Poisonous Animals or Cells and Ingestion or Contact Toxicity**	**857**
	Chordata: Amniota: Reptilia: Squamata Venoms	865
	Eumetazoa: Bilateria: Ecdysozoa: Arthropod Venoms	871
	Chordata: Craniata Venoms	873
	Lophotrochozoa: Mollusca Venoms	874
	Eumetazoa: Cnidaria Venoms	874
	Echinodermata: Holothuroidea Venom	876
	Chordata: Mammalia: Eutheria: Soricomorpha: Soricidae Venoms	876
	Venom Economy	876
	Chordata: Tetrapoda: Amphibia Poisons	877
	Fish Poisons	881
	Chordata: Avialae: Aves Poisons	883
	Discussion of Poisons' Evolution and Proper Attribution/ Biological Classification	883
	Eukarya: Chromalveolata: Alveolata: Dinoflagellata Poisons	884
	Eukaryota: Chromalveolata: Heterokontophyta: Bacillariophyceae Poisons	886
	Eukaryota: Opisthokonta: Fungi Poisons	886
	Bacteria Poisons	887
	Questions	890
	References	891
31	**Poisonous Plants or Plant Cells and Ingestion or Contact Toxicity**	**895**
	Seed Poisons	903
	Root Poisons	906
	Fruit Poisons	906
	Plant Leaves and Flowers	907
	Questions	915
	References	915
	Index	**919**

Preface

This first edition of *Understanding Toxicology: A Biological Approach* is meant to serve both undergraduate and graduate students in the biological sciences who are interested in a subject that examines all levels of biological inquiry—from cellular/molecular, to complex organism, to ecosystem. This primary text will allow those students to first approach the subject from a research perspective and then from a public policy perspective, as published research reports are utilized in agencies to drive regulation.

The logical progression of the first section (Part I: Introduction) examines toxicology at all three levels of analysis—cellular, complex organism, and ecosystem. Then, students will examine common toxic mechanisms that affect cells (Part II: Toxic Reactions of Cells) from the outside to the inside, as toxicants impact various membranes, organelles, and signaling pathways. In this section, mitochondria and chloroplasts are covered, as biological impacts on plants and animals differ. Similarly, organ systems (Part III: Toxic Reactions of Tissues/Organs) start with the skin, eye, GI tract, and lung as the routes of likely entry of toxicants into a complex organism. The final organ system is the kidney, marking excretion. Each organ system is viewed from the point of entry of the toxicant to the likely exit, unless the organ is damaged beyond repair. Forensics is stressed in an introductory chapter to this section and then throughout each organ system so students can understand what the key features are of the damage that each toxicant causes to a given organ (how a pathologist might discover how complex organisms became sick or died). Environmental toxicity begins (Part IV: Toxic Reactions of Ecosystems) with a section on dispersion so that students can understand how toxicants become a concentration that is experienced by organisms in the environment. The ecosystems are based on modern land use: rural/agriculture and urban/industrial. The toxicants are then grouped into classes so students can understand how some disperse into soil, water, or air and then have their impacts. Those toxicants that biodegrade are listed together, and persistent organic chemicals have their own category within that chapter. Those that do not biodegrade (metals) are covered in their own chapter. Radiation is discussed in the chapter on toxicants that are found in the atmosphere, as these impacts are most likely based on nuclear weapons use or accidents at nuclear power plants. The inclusion of a chapter on pharmaceuticals and personal care products reflects the impact of human use of medications, musks, and antiseptic soaps and the impact of these products via sewage release into surface waters. The last section (Part V: Biological Toxicants) deals with venoms, poisonous animals, and poisonous plants. However, these sections also wrestle with the true biological origins of these toxicants, which does not always categorize them neatly into animal or plant toxins. The evolution of these biological toxicants, their roles for use by the organisms, and the metabolic cost of production and use of these toxicants are considered.

Chapter Overview and Pedagogical Features

Each chapter starts with Conceptualizing Toxicology, which gives an outline of the chapter so that the instructor and the students have a ready outline. There is also an Instructor Manual and slides in PowerPoint format with figures available for the instructor that can be made available to the students. Chapters give proper citations and websites for students to get additional information. Figures and tables in the chapter provide visual aids and summaries that aid in learning the information.

Chapter 1 sets the stage with research institutions and associations that are fully engaged in toxicology research and provide the experiments to consider throughout the course, if desired. It makes a good introductory lecture/interaction session.

Chapter 2 provides the history of the field and is provided to be thorough and indicate how dose and dosage concepts were developed along with morbidity and mortality that are toxicology concepts.

Chapter 3 focuses on toxicology terms at all three biological levels. Terms are bolded to indicate their importance. This makes a good introduction for either an introductory toxicology course or a refresher for an environmental toxicology course.

Chapter 4 is a three-level approach to risk assessment.

Chapter 5 involves absorption and damage done to cell walls or cell membranes.

Chapter 6 is an introduction to signal transductions starting with receptor-mediated toxicities on the outside of cells and downstream signaling that results in toxicity.

Chapter 7 is the biotransformation chapter. Its placement here is due to the presence of metabolic enzymes in the endoplasmic reticulum and the cytosol. Some instructors may like to cover this earlier in their courses. However, the stress up to this point is the original compound.

Chapter 8 examines cytosolic and endoplasmic reticulum damage in light of activation of some compounds by metabolism. Reactive chemical species are examined in detail as are antidotal therapies.

Chapter 9 examines how energy functions are affected by toxicants. Mitochondria and chloroplasts are examined and instructors can examine either, depending on whether herbicides will be a major focus of their course or not.

Chapter 10 examines mutagenesis, clastogenesis, and carcinogenesis. Again, some instructors like this to come earlier and it can be used that way. However, its placement here reflects the interior nature of the eukaryote nucleus. Epigenetic mechanisms are also examined, as they are important in gene expression.

Chapter 11 starts the selective toxicity/hypersensitivity discussion, as brought about by polymorphisms of genes involved in absorption, biotransformation, etc.

Chapter 12 is a chapter on nutritional toxicology and indicates how nutritional state is important in hypersensitivity.

Chapter 13 goes more thoroughly into toxicokinetics, as distribution to organs is important here. This can be a starting point if an instructor wishes to examine mainly mammalian or medical toxicity.

Chapter 14 indicates how forensic toxicity is assessed to give a sample of forensic science to students who understand that autopsies and toxicology tests are used to determine poisoning by pharmaceutical, drugs of abuse, toxic chemicals, radiation, etc.

Chapter 15 starts with the outside of the body where exposure results from spilling or misuse of chemicals.

Chapter 16 indicates toxicity to the GI tract starting with the mouth and continuing to the anus, and the digestive organs of the pancreas and liver. Accidental or intentional ingestion is how many poisonings occur.

Chapter 17 indicates the last route of exposure from the outside, inhaling particles, gases, vapors, etc. Environmental toxicity is stressed at the end of the chapter, as this route is a microcosm of how chemicals may be dispersed in an environment similar to the portion of the respiratory tract affected by different-sized agents in various chemical states.

Chapter 18 examines the cardiovascular system and how it is affected during circulation of a toxicant.

Chapter 19 is the immunotoxicology chapter and represents both blood and lymph circulation, which affecting lymph nodes, spleen, and bone marrow.

Chapter 20 is the neurotoxicology chapter and examines the peripheral and central nervous system action of toxicants including breaching the blood–brain barrier.

Chapter 21 is the endocrine organ toxicity chapter and involves discussion of endocrine disruption.

Chapter 22 gives all the reproductive indices and examines reproductive organ toxicity mechanisms.

Chapter 23 is the renal toxicity chapter and involves excretion of the metabolized toxicant. This ends organ toxicity.

Chapter 24 examines models of dispersion to show how environmental toxicology models concentrations at various distances from point sources or non-point sources.

Chapter 25 is the longest chapter, as it involves agricultural toxicants such as nutrients and pesticides (herbicides, insecticides/miticides, rodenticides, fungicides, and fumigants).

Chapter 26 involves all organic chemicals—from solvents to large, persistent highly halogenated aromatic compounds such as PCBs or TCDD.

Chapter 27 examines metal toxicity.

Chapter 28 describes compounds that are mainly atmospheric emissions, along with their direct toxicity and environmental alterations that yield indirect toxicity (e.g., CFCs' effects on the ozone layer and UV toxicity). Gases, vapors, aerosols, and radiation highlight the chapter's focus.

Chapter 29 is a chapter derived from the EPA's concerns with pharmaceutical and personal care products that have found their way into the sewage and drinking water of many communities. This ends the environmental section.

Chapter 30 classifies the biological origins and evolution of animal venoms and poisons. As all kingdoms cannot be given separate chapters, poisonings associated with consuming animals are in the animal chapter even though the origins may be from bacteria or even diatoms (plants).

Chapter 31 examines plant poisons and finishes the book.

An appendix is given that includes answers to the questions poised in each chapter for students to test their understanding.

Acknowledgments

I would like to acknowledge my colleagues at Minnesota State University who helped me comprehend the evolution of toxicants from phages to bacteria (Dr. Dorothy Wrigley) and other more complex organisms (Dr. Robert Sorensen). We all stand on the shoulders of preceding published work in our fields, and we must acknowledge the people who published scientific accounts of their work (and the easy access to this literature by the invention of the Internet). I would like to thank the people at Jones & Bartlett Learning who have guided this project forward, including Mike Brown, Chloe Falivene, Nick Alakel, Rebekah Linga, and Mary Flatley. Finally, I would like to thank my family for putting up with my writing and discussion of the writing effort over the last 7 years.

About the Author

Steven D. Mercurio is Professor of Biology at Minnesota State University, Mankato. He instituted the toxicology emphasis in the Department of Biological Sciences in 1986 and has served as the program coordinator. Dr. Mercurio has taught Introduction to Toxicology, Environmental Toxicology, Principles of Pharmacology, Industrial Hygiene, Toxicology Seminar, Methods of Applied Toxicology and Applied Toxicology Project. He has worked with many undergraduates and graduate students in a variety of research areas in toxicology. In addition to being an AAAS-EPA Fellow in 1995, his memberships include the Society for Environmental Toxicology and Chemistry, Society of Toxicology, New York Academy of Sciences, American Association for the Advancement of Science, and American Society for Nutritional Sciences. His BA, MA, and PhD were from the University of Pennsylvania and he held postdoctoral positions at University of Minnesota and Cornell University prior to his current position.