



Introduction to Toxicology

FOURTH EDITION

**John Timbrell
and Frank A. Barile**



CRC Press
Taylor & Francis Group

Introduction to Toxicology

As with the previous editions, *Introduction to Toxicology*, Fourth Edition, continues to chart the evolution of the field of toxicology, from the use of natural toxins by ancient tribes through the developments established by Paracelsus, and progresses through to the current topics of public interest. For centuries, the study of toxicology has fascinated students. The book begins with basic toxicological principles, including an historical summary, dose-response relationships (NEW chapter), exposure-response relationships (NEW chapter), disposition, and metabolism of xenobiotic toxic substances. Other important new chapters include target organ toxicity, toxicity of carcinogenic agents and new and updated concepts in toxicity testing, and antidotes and treatment of poisonings. In all, nine new or expanded chapters from the third edition are included.

Current concerns about the effects of therapeutic drugs, carcinogens, industrial toxins, pesticides, and herbicides on human health, animal welfare, and the stability and maintenance of the ecosystem continue to highlight toxicology as an important and growing scientific discipline.

Key features:

- Comprehensive coverage of the field of toxicology which illustrates its importance to and impact on society;
- Uses pertinent examples, tables, and diagrams to aid understanding with learning objectives, summaries, questions, and answers for each chapter;
- Clearly and concisely written and presented concepts for easy comprehension by toxicology, biomedical, health science students and chemistry;
- Examines the complex interactions associated with toxicological events;
- Covers the effect of toxins on biological and physiological systems.

This book successfully condenses the diffuse literature in the field into an accessible and readable text, made easier with the insertion of many tables and figures. It introduces fundamental concepts and builds upon these using topical and relevant historical examples. Its improved format includes learning objectives and summaries of each chapter, as well as questions and answers suitable for self-assessment.

This latest edition is an invaluable resource for undergraduate and graduate toxicology students, as well as an introductory text for other health care students and professionals. The book also functions as a comprehensive introductory reference text for environmental scientists, medical biologists and chemists, chemical engineers, and regulatory agencies, with interests in toxicologically related areas.



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CRC Press

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Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

Designed cover image: Cover photo courtesy of John Trimbell

Fourth edition published 2023

by CRC Press

6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742

and by CRC Press

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

CRC Press is an imprint of Taylor & Francis Group, LLC

© 2023 John Timbrell and Frank A. Barile

First edition published by Taylor & Francis 1989

Third edition published by Taylor & Francis 2002

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Library of Congress Cataloging-in-Publication Data

Names: Timbrell, John A., author. | Barile, Frank A, author.

Title: Introduction to toxicology / John Timbrell, Frank A. Barile.

Description: Fourth edition. | Boca Raton, FL : CRC Press, 2023. |

Revised edition of: Introduction to toxicology / John Timbrell. Third edition. 2001. |

Includes bibliographical references and index.

Identifiers: LCCN 2022038922 (print) | LCCN 2022038923 (ebook)

Subjects: LCSH: Toxicology.

Classification: LCC RA1211 .T56 2023 (print) | LCC RA1211 (ebook) |

DDC 615.9—dc23/eng/20220831

LC record available at <https://lcn.loc.gov/2022038922>

LC ebook record available at <https://lcn.loc.gov/2022038923>

ISBN: 978-1-032-03699-1 (hbk)

ISBN: 978-1-032-03692-2 (pbk)

ISBN: 978-1-003-18857-5 (ebk)

DOI: 10.1201/9781003188575

Typeset in Century Old Style
by codeMantra

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Dr. Barile received the Faculty Recognition Award, Am. Association of University Professors (AAUP)-Faculty Association, St. John's University, 2002–2003, 2004–2005, 2013–2014, and 2015–2016, and received the prestigious Public Health Service Medallion from the Director of the NIEHS, Dr. Linda Birnbaum, for contributions to SACATM (2009).

Dr. Barile continues as Science Advisor for the Humane Society of the U.S. to encourage development, incorporation, and substitution of *in vitro* alternative methods for the reduction, refinement, and replacement to animal experimentation and toxicology testing.

Preface to the Fourth Edition

It is my pleasure to collaborate with Dr. John Timbrell on the fourth edition of *Introduction to Toxicology*. Since the publication of the third edition in 2002, the discipline of toxicology has journeyed through a rapidly changing planet that traditionally did not present fast-moving developments. Unlike other evolving technological fields, such as computer engineering and mobile devices, toxicology has not been a prime mover in the applied sciences, and even slower in many parts of the world. Also, in comparison to other biomedical applications, advances in toxicology are also not as rapid as those encountered within genetic, stem cell, or immunologic therapeutics. However, the crosstalk among these areas involving the basic tenets of toxicology has enabled the latter to express a variety of new applications and knowledge within the last generation, advances which reflect the problems and issues encountered by society. The topics reflect increasing societal concerns such as those seen with the environment, endocrine-disrupting chemicals (endocrine disruptors, ED), and chemical and biological threats to public health. In particular, the basic science of toxicology has shifted consistently toward applied realms, including understanding the fundamentals of poisons and their mechanisms, notwithstanding the features, causes, and pathologies. Consequently, this fourth edition retains its previous commitment to, and is primarily concerned with, the basic underlying principles of toxicology at the introductory level.

The fourth edition presents the field of toxicology as a thought-provoking update. To students in the health and biomedical sciences and to established health professionals, the arena of toxicology is inspiring and is important for overall knowledge of biomedical systems. The reviews, criticisms, and suggestions garnered over the last 20 years, since the presentation of the last edition has enabled the production of an updated, applied, and mechanistic text. Each chapter has been revised to include topical information, as well as clearer illustrations and explanatory tables, while several new chapters are inserted. In addition, some

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chapters have been rewritten and updated with biochemical formulas, chemical structures, and toxicological mechanisms.

The fourth edition also highlights new fields of toxic exposure, such as dose-response relationships, target organ toxicity, teratogenic and mutagenic compounds, and risk assessment.

In general, and as with previous versions, the book examines the complex interactions associated with toxicological events because of intentional or inadvertent chemical and drug exposure. Special emphasis is placed on pharmacological and toxicological mechanisms of action, **toxicokinetics**, and detection and identification of chemicals in physiological compartments. Other contemporary issues in toxicology, including various means of possible exposure to therapeutic and non-therapeutic agents, an overview of protocols for therapeutic management of various toxic administrations, and the remedies associated with their pathology, are conveyed. Lastly, chapter summaries, learning objectives, study questions, and references are updated.

It is hoped that this edition inspires a greater respect among toxicology and health professional students as they strive to understand the consequences of exposure to the multitude of chemicals. As our society becomes more scientifically adept at many levels, its thirst for information about chemical exposure increases. Accordingly, students and established scientists in the field will develop a greater awareness and appreciation for the costs of exposure to chemical compounds, of the risk from biological threats, or of the adverse effects of environmental pollutants. As a generation becomes more knowledgeable, its preparedness is stronger and its response to threats is more formidable.

FAB, December 2022

Acknowledgments

My appreciation is extended to Dr. John Timbrell for my participation in revising the fourth edition of *Introduction to Toxicology*. I am most appreciative to the editorial staff at CRC Press, particularly Stephen Zollo, Editor for Toxicology Group, for coordinating this collaboration, Ms. Laura P., Editorial Assistant and Ms. Assunta P., Project Manager. Their patience and focus were of great sustenance in the completion of this project.

I am continuously indebted to my wife Pauline, whose encouragement, inspiration, and reassurance have sustained my efforts by believing in my abilities, in the force of my dedication, and in the value of my contributions.



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Introduction

Chapter Outline

This chapter introduces historical highlights and basic principles of toxicology:

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1.1 Introduction

Toxicology is the study of interactions between chemicals or drugs,¹ and biological systems. Humans, mammals, and environmental entities on the planet are increasingly exposed to chemicals of an enormous variety. These substances range from

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metals and inorganic chemicals to large complex organic molecules, yet all possess the potential to induce toxicity. Accordingly, toxicology is multidisciplinary which encompasses the study of pathological, biochemical, and physiological effects of such substances within interacting species. Thus, the challenge in this field refers to the application of basic chemistry, biochemistry, physiology, and pathology, along with experimental observation, to gain an understanding of how and why substances cause disruption in biological systems, which lead to toxic effects.

Approximately 100,000 chemicals, plastics, gases, metals, and therapeutic drugs are produced yearly in the United States, up to 10,000 of which are newly synthesized. This escalation in chemical production renders our environment and inhabitants vulnerable to their effects (Figure 1.1), compelling the toxicology community to pursue and understand the causes and mechanisms of the untoward effects and to accurately monitor, carefully analyze, and predict risk for science and public health.

In recent years, the problem of human and animal exposure to potentially toxic chemicals in the environment was brought to the attention of the public through the publication of *Silent Spring* (Rachel Carson, 1962). The book describes the devastating effects of **pesticides** on the flora and fauna of the North American environment. The discussion of the issue was continued in *The Apocalypitics: Cancer and the Big Lie* (Edith Efron, Simon & Schuster Pub., 1984), declaring that Carson and other scientists probably exaggerated the dangers of chemicals. However, today few would contest the importance of awareness and



Figure 1.1 Toxicology is concerned with the exposure of living systems in the environment to toxic substances from a variety of sources. (Air pollution by brick factories at Mahalaxmi municipality, Lalitpur, Nepal. Janak Bhatta, https://commons.wikimedia.org/wiki/File:Air_pollution3.jpg, Creative Commons CC0 1.0 Universal Public Domain Dedication.)

knowledge of the potential toxicity posed to humans from synthetic chemicals spilled into the environment. Thus, the field of toxicology in general, and environmental toxicity in particular, has spawned another dimension: the social, moral, and legal aspects of exposure of human and animal populations to chemicals of unknown or uncertain threats, of which hazard and risk assessments and value judgments have emerged. The regulatory toxicologist, whose unique role has recently blossomed in our society, is often asked to make such decisions.

1.2 Historical Aspects

In the public arena, toxicology has been referred to as ‘the study of poisons’, which begs the question ‘what is a poison?’ Poisons span a wide range of sources and chemical forms, from naturally occurring plant alkaloids to synthetic nerve gases. Thus, a poison is a substance that has harmful effects on living systems; in addition, designation of a substance as a poison depends on its application, dose, and concentration. For example, historically, arsenic has been considered a poison for humans; however, it has also been used and is currently approved as a therapeutic drug. The apparent conflicting aspects of such a notorious chemical will be further explained in later sections as our concept of toxicology evolves.

Recently the study of poisons has become a justifiable scientific pursuit. At one time, however, it was mainly a practical art utilized for malevolent intentions. Poisons have also played an important part in human history as subtle and silent military weapons.

Prehistoric humans were aware that liquids extracted from animals and plants contained natural poisons which were used on their weapons. For instance, early hunters dipped arrowheads into liquids containing poisonous concoctions (thus the origin of the term *toxikon*) and propelled on an arrow from a bow. Subsequent study and categorization of poisons probably started by 1500 BCE, evidenced in part by the *Ebers papyrus*, the earliest collection of medical records, containing many references and recipes for poisons. Ancient Egyptians were able to distill prussic acid from peach kernels; arsenic, aconite, and opium were also known in Hindu medicine as recorded in the *Vedas*, around 900 BCE, and the ancient Chinese used **aconite** as an arrow poison. In his writings, Hippocrates (400 BCE) documented the ancient Greek’s professional awareness of poisons and the principles of toxicology; in particular, they demonstrated advanced knowledge of principles regarding the treatment of poisoning by the influence absorption and the development of antidotes. For example, Nicander of Colophon (185–135 BCE), physician to Attalus, King of Pergamon, experimented with poisons using condemned criminals as subjects. His studies produced treatises like *Theriaca and Alexipharmica*, documents on antidotes to poisonous reptiles and substances. The document mentions 22 specific poisons including ceruse (white lead), litharge (lead oxide), aconite (wolfsbane), cantharides (blistering agent), conium (hemlock), hyoscyamus (henbane), and opium (narcotic). He also recommended linseed tea to induce vomiting and suggested that extracting the venom from the bite of a venomous animal be used as treatment. Similarly, Mithridates



Figure 1.2 Painting depicting the death of Socrates in prison about to drink hemlock given by his executioner, Jacques-Louis David. (Metropolitan Museum of Art, New York City, USA. https://commons.wikimedia.org/wiki/File:David_-_The_Death_of_Socrates_-_detail2.jpg. <https://www.metmuseum.org/collection/the-collection-online/search/436105>. Creative Commons CC0 1.0 Universal Public Domain Dedication.)

(132–36 BCE), King of Pontus (Asia Minor, modern-day eastern Black Sea Region of Turkey), used incarcerated criminals to identify antidotes to venom and poisonous substances and regularly protected himself with a mixture of 50 different antidotes (*Mithridatum*²).

The first documented law against poisoning was issued in Rome by Sulla in 82 BCE to protect against careless dispensing. The Greek physician Dioscorides (50 AD) made a particularly significant contribution to toxicology by classifying poisons as animal, plant, or mineral and recognized the value of emetics in the treatment of poisoning. His treatise on *Materia Medica* was a major work on the underlying principles of poisons and their antidotes, establishing this text as common knowledge for fifteen centuries.

The use of poisons in society for murder, suicide, and political assassination is also well documented in the origins of toxicology. For example, in 399 BCE Socrates committed suicide by drinking from the executioner's cup of poisonous hemlock (Figure 1.2). Claudius, Emperor of Rome (41–54 AD), was purportedly poisoned with arsenic by his wife Agrippina (and niece). Nero, Claudius'

successor, employed a professional to poison Claudius' son, Britannicus, who dissolved arsenic in the water used to cool the banquet soup, thus avoiding the suspicions of the Emperor's taster.

The abundant use of poisons and the difficulty in detecting them in food or specimens made it necessary for treatments to be devised, and one of the first documents known on treatments for poisoning was written by Maimonides (1135–1204) in *Treatise on Poisons and Their Antidotes*, that detailed some of the treatments thought to be effective.

In the Middle Ages, the art of poisoning for political ends developed into a cult. In the ancient Italian republics, the Borgias were infamous during the fifteenth and sixteenth centuries. In seventeenth-century Italy, a woman by the name of Toffana prepared cosmetics containing arsenic (Aqua Toffana) which were used to remove unwanted rivals, husbands, and enemies! Similarly, Catherine de Medici prepared poisons and tested them on the poor and sick of France, noting all the clinical signs and symptoms.

One of the most important concepts in toxicology was espoused in the sixteenth century by the scientist Paracelsus. He was born Philippus Theophrastus Aureolus Bombastus von Hohenheim near Zurich in 1493, to a physician who was interested in chemistry and biology and an expert in occupational medicine. Paracelsus was a free thinker who disagreed with the dogma current at the time and was espoused by Galen. Paracelsus thought observation was crucial and understood the importance of chemistry in medicine. He believed that 'like cures like', contrary to Galen who taught that diseases of a particular intensity would be cured by a medicine of opposite intensity. Consequently in Paracelsus's understanding, 'a poison in the body would be cured by a similar poison – but the dosage is very important.' He advocated for the use of inorganic chemicals, such as salts, as treatments. Although these salts were believed to be too poisonous by contemporaries, he emphasized that the dose was very important in establishing cures. Paracelsus summarized this concept in a renowned statement: 'All substances are poisons; there is none that is not a poison. The right dose differentiates a poison from a remedy.'

This perception is especially crucial for the safe use of drugs but also important for proper handling of other chemicals (see below). It underlies the basis of risk assessment of chemicals which is founded on the assessment of threshold doses as well as in establishing safe and non-toxic levels. Even seemingly innocuous substances such as common table salt (sodium chloride) could be poisonous given the optimum circumstances.

Paracelsus also believed that diseases were localized to particular organs and that poisons could damage particular organs (target organs), a concept that has been generally proven to be correct. His contribution to medicine and toxicology is significant although not recognized until after his death in 1541.

Another significant figure in toxicology was Orfila, a Spanish physician (1787–1853) who recognized it as a separate discipline. He contributed to the specialized field of forensic toxicology by devising means of detecting poisonous substances, with the intention of substantiating that the act of poisoning had taken place. Since then toxicology developed in a more systematic scientific style

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The New York Times

NEW YORK, MONDAY, JANUARY 28, 1984

The Bhopal Disaster: How It Happened

By MICHAEL S. RASSNER

NEW DELHI, Jan. 27 — The Bhopal gas leak disaster, which killed more than 2,000 people and injured tens of thousands, was caused by a combination of factors, including a faulty safety system, a lack of maintenance, and a failure to heed warnings from the British firm that owned the plant, according to a report by a government commission.

The report, which is the first of a series of articles on the disaster, says that the British firm, Union Carbide India Ltd., which owned the plant, was negligent in not providing adequate safety systems and in not maintaining them properly. It also says that the Indian government was negligent in not enforcing safety regulations and in not providing adequate medical care for the victims.

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MUM CITY SOIRS OURS

By MICHAEL S. RASSNER

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SILENCE ATTENDS SHUTTLE'S LANDING, ENDING 3-DAY TRIP

By MICHAEL S. RASSNER

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Auschwitz Echoes to Prayer As Mengele's Victims Return

By MICHAEL S. RASSNER

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Family of Victim Levels Charges Of Deceit in Autopsy Conclusion

By PHILIP SHENKIN

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Line of Song Provides a Clue on Ancient Troy

By JOHN CAMPBELL

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MEDICAL INFLATION SLACKENS SLIGHTLY

By MICHAEL S. RASSNER

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Mixture of New Tax Benefits And Harsher Rules for Many

By GARY KLITZ

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ENTERTAINMENT

NEW YORK, Jan. 27 — The first of a series of articles on the Bhopal gas leak disaster, which killed more than 2,000 people and injured tens of thousands, was caused by a combination of factors, including a faulty safety system, a lack of maintenance, and a failure to heed warnings from the British firm that owned the plant, according to a report by a government commission.

Figure 1.3 From The New York Times headline of January 28, 1984: "The Bhopal Disaster: How It Happened". (<https://www.nytimes.com/1985/01/28/world/the-bhopal-disaster-how-it-happened.html>.)

and began to include the study of the mechanism of action of poisons; that is, the molecular basis for how drugs and chemicals interact with the organs, tissues, and cells. Indeed, Claude Bernard (1813–1878) believed that the study of the effects of substances on biological systems could not only shed light on the mechanism of the poison but also enhance the understanding of those systems with which it interacted. For instance, he was the first to identify the site of action of curare, a neuromuscular blocking muscle relaxant, as either the nerve ending or the neuromuscular junction.

More recently, in 1945, Sir Rudolph Peters studied the mechanism of action of arsenical war gases. He was able to devise the effective **antidote**, British Anti-Lewisite (BAL) used for the treatment of military personnel exposed to these gases. Other examples of toxic chemicals have been studied at the mechanistic level and have benefited our understanding of basic biochemistry, including cyanide and fluorocitrate. Cyanide inhibits the mitochondrial electron transport chain, while fluorocitrate inhibits aconitase, a critical enzyme of the Krebs cycle.

In the 20th century, some industrial chemical disasters have occurred which have highlighted the need not only for understanding the toxicity of compounds, drugs, and food additives used in industry but also created the need for the organized study of toxic substances by the industries manufacturing them and for government legislation to control them. This has resulted in the establishment of government regulatory agencies to implement administrative action.

For example, in 1984 one of the worst industrial disasters occurred in Bhopal, India where a factory manufacturing the insecticide, carbaryl, leaked a large amount of an intermediate reaction chemical gas, the extremely noxious compound methyl isocyanate (Figure 1.3). The leak ‘that killed at least 2,000 people resulted from operating errors, design flaws, maintenance failures, training deficiencies and economy measures that endangered safety, according to present and former employees, company technical documents and the Indian Government’s chief scientist’ (New York Times, January 1984).

At the time, since little was known of the toxicity of this compound, treatment of the victims was uncertain and inadequate.

Another major reason for testing chemicals in toxicity studies is to allow the substances to be classified according to hazard categories such as toxic, explosive, or flammable. This enables enactment of regulatory decisions about marketing, distribution, transport, storage, and labeling, among other uses. The categories thus established encompass almost all chemicals that are encountered in the environment. With this in consideration, the question becomes ‘are all chemicals toxic?’ The following common knowledge phrase perhaps provides an answer: ‘there are no safe chemicals, only safe ways of using them.’

1.3 Classification of Toxic Substances

Toxic substances are classified according to their use or exposure: pharmaceutical agents (*drugs*), food additives, pesticides, herbicides, occupational (industrial) chemicals, environmental pollutants, naturally occurring toxins, and commercially available (household) chemical products. These categories are individually discussed in greater detail in later chapters but are briefly introduced here.

1.3.1 *Pharmaceutical and Therapeutic Agents*

As pharmacologically active agents, 'drugs and chemicals are our friends'. Their benefit to society has enabled humans to improve their quality of life as well as their lifespan.³ However, they have generally been designed to be highly potent in biological systems, making them potentially toxic. Thus, drug toxicity may be a consequence of an overdose, a rare untoward (**idiosyncratic**) effect, an adverse reaction (*side effect*), or an accumulation of the compound in the biological system (see Chapter 5 for details).

Drugs vary enormously in chemical structure and possess a wide variety of biological activities. They are the only foreign substances with known biological activity that humans ingest intentionally, including alcohol, the active principles in cigarettes, and mood-enhancing drugs. Drugs used in veterinary practice are also considered and included here since humans consume the products from animals treated with these substances.

1.3.2 *Food Additives*

Food additives are xenobiotic (external) substances usually of low biological activity which are also ingested. Many different additives are combined with food-processing systems to alter the flavor or color, prevent spoilage, or chemically change the nature of the foodstuff. There are also several potentially toxic substances that are regarded as contaminants occurring naturally in food, resulting from cooking, storage, or processing. Most of these substances, both natural and artificial, are present in food in undetectable amounts, but for the majority, little is known of their chronic or cumulative toxicity. In many cases, they are ingested daily for perhaps decades, exposing a tremendous number of people. Public awareness of this has influenced the preparation and manufacture of foodstuffs, such as additive-free nutrients available for consumption.

1.3.3 *Industrial Chemicals*

Industrial chemicals contribute to environmental pollution and are a direct or indirect hazard in the workplace where they are handled, formulated, or manufactured. There is a vast range of chemical types, and many different industries involve the handling or manufacture of hazardous chemicals. In general, industrial exposure includes exposure to chemical solvents used as a basis for chemical reactions. Although government regulations are set to limits of exposure and safety practices in the workplace, actual exposure levels still prove to be hazardous chronically and acute exposure due to accidents occurs. The time between the development of diseases such as cancer, which is often diagnosed later in life, often makes it difficult to determine if a chemical is the cause, until and unless

sufficient numbers of persons in the workforce have presented with the disease in order to establish an association with the toxic compound.

1.3.4 Environmental Pollutants

There are several chemical sources of environmental pollution including industrial processes, such as the manufacture of chemicals, the spreading of commercial chemical products, such as pesticides and herbicides, and the release of chemical waste into the environment. Environmental pollutants are released into the atmosphere, waterways, oceans, or discarded on land.⁴

Commercial pesticides, including insecticides and rodenticides, as well as herbicides, are purposely sprayed onto agricultural land and on household lawns with the potential for human exposure either via the crop itself or through contamination of drinking water or air. A major problem with the release of pesticides is their **persistence** in the environment with a corresponding increase in concentration during passage through the **food chain**.

1.3.5 Naturally Occurring Toxins

Many plants and animals produce toxic substances for both defensive and offensive purposes. Naturally occurring toxins of animal, plant, and microbiological origins comprise a wide variety of chemical types, result in a variety of toxic effects, and are a significant cause of human poisonings. The concept currently expounded by some individuals that 'natural (organic) is safer' is not entirely accurate since some of the most toxic substances on the planet are of natural origin. Natural toxins feature in poisoning via contamination of food, by accidental exposure to poisonous plants or animals, and by insect or animal vectors (stinging or biting).

1.3.6 Household Poisons

Household poisons include some of the substances in the previous categories such as pesticides, drugs, and solvents. Exposure to these types of compounds is usually acute rather than chronic. Many household substances used for cleaning, disinfecting, and elimination of indoor pests are irritants and corrosive. Consequently, they cause severe skin and eye lesions upon exposure. If swallowed in significant quantities or if highly concentrated solutions are ingested, household materials such as bleach and baking soda cause severe tissue damage to the nose, throat, esophagus, and stomach. Some drugs and pesticides are widely available and consequently are often found in the home and are also hazardous. For example, the herbicide paraquat and the analgesic drug acetaminophen are toxic and have both contributed significantly to human poisoning deaths.

1.4 Classification of Exposure

In some cases, the pathway to exposure is determined by the nature of the toxic substance. For example, gases and vapors from volatile solvents lead to inhalation exposure, whereas non-volatile liquids are associated with skin contact. Many industrial chemicals are often linked to chronic effects due to long-term occupational exposure, whereas household substances are usually involved in acute poisoning following a single episode of accidental exposure.

Types of exposure are briefly discussed at this introductory stage, but the topic is further explored in later chapters.

1.4.1 *Intentional Ingestion*

Therapeutic drugs, food additives, and nutritional supplements are consumed daily by many, often for long periods of time. Exposure to these compounds, especially repeated or chronic exposure, is eventually associated with some adverse responses such as **allergic reactions** or **tolerance**. Alcohol, smoking, and drug consumption are ubiquitous social habits, often on a chronic basis, ultimately responsible for chronic toxic effects.

It is important to note that illicit, illegal acts of violence, such as suicide and homicide, are not uncommon and involve acute or chronic poisons. Both illicit and prescribed drugs are often employed, although household products are easily available and readily administered in opportunistic circumstances.

1.4.2 *Occupational Exposure*

Occupational exposure is encountered in an industrial setting or in private commercial businesses, such as in manufacturing settings or with commercial contractors. Toxicity is predominantly chronic and continuous; the route toward exposure is either via inhalation or dermal. Consequently, pulmonary **irritation** and dermatitis are common occupational illnesses. Acute exposure occurs in the event of an accident such as a fire, explosion, spillage, leakage, or as a result of poor working practices. For example, cleaning reactor vessels that store contained solvents leads to acute toxicity resulting from excessive contact with the chemical or its vapors.

1.4.3 *Environmental Exposure*

Gaseous or liquid effluents from manufacturing briefly or continuously contaminate the immediate environment as well as more distant atmospheric or aquatic targets. This form of exposure is usually chronic, but isolated accidents at factories have occurred where acute exposure of humans outside the factory has resulted in severe toxicity.⁵ Chronic exposure to gases, such as sulfur dioxide, nitrogen oxides, and carbon monoxide, occurs in industrial areas and regions of

heavy traffic and results in acute irritation; chronic toxic effects, however, are largely unknown.

Environmental exposure is also important in relation to pesticides capable of contaminating air, water, and food. Large-scale spraying potentially exposes communities to chemicals or their residues both within their food and via the air.

1.4.4 Unintentional, Accidental Poisoning

Unintentional, accidental poisoning is usually acute rather than chronic. Drugs, pesticides, household products, and natural products are involved in this type of exposure; children and the elderly are the most common victims. Erroneous unintentional ingestion of a poisonous herbal or vegetable product, cleaning fluid, or pharmaceutical agent is responsible for toxicity seen in this category as does accidental ingestion of an excessive dose of a drug. Inhalation of fumes from heaters, ovens, gas burners, and fires is also an important cause of accidental poisoning.

1.4.5 Selective Toxicity

An important concept in toxicology, selective toxicity, encompasses the differences in susceptibility to toxic effects between different species of animal or plant, or between different cells in the body, such as the susceptibility of tumor cells versus normal cells.

In many cases, selective toxicity is a useful attribute which is incorporated in the design of antibacterial drugs, pesticides, or chemotherapeutic agents (anti-cancer drugs); that is, it is the basis of having selective toxic action at those targets while sparing normal cells. It is also of relevance to the prediction of risk in humans based on studies in other species.

The explanations for selective toxicity vary but are divided into those due to differences in absorption, distribution, metabolism, and excretion of a chemical (toxicokinetics) or those due to biochemical differences affecting the presence of a receptor or target molecule (**toxicodynamics**). For example, insects are more susceptible to the toxicity of DDT than mammalian organisms for two reasons: (1) DDT penetrates insect cuticles more readily than mammalian skin, and (2) insects have greater surface area to volume ratio and therefore absorb relatively more of the insecticide. Insects are also more susceptible to some organophosphorus insecticides because the compounds are metabolized by oxidative desulphuration which produces a product that inhibits acetylcholinesterase; in mammals, however, this enzymatic hydrolysis produces a metabolite that is more readily excreted and does not inhibit acetylcholinesterase.

The rodenticide norbormide is active against rodents because they possess a receptor in smooth muscle, whereas humans, cats, and dogs do not. Other rodenticides take advantage of the feature that rodents do not have a vomit reflex, unlike many other mammals. Therefore, with oral ingestion of a poisonous chemical, the rat is unable to rid itself of the substance by vomiting.

In therapeutics, the antibiotic penicillin is active against a variety of bacteria because the drug interferes with synthesis of the cell wall as the bacteria multiply. Since mammalian cells do not have cell walls, they are not affected by the action of the antibiotic.

1.5 Summary and Learning Objectives

This chapter presents the *origins* of toxicology in antiquity, sometimes in relation to intentional poisoning. Some notable figures were mentioned especially Maimonides, Paracelsus, Orfila, and Bernard, individuals who all helped develop toxicology from an art to a science. The breadth and scope of toxicology are illustrated by the variety of types of toxic substances to which humans and animals are exposed, ranging from drugs, food additives, industrial chemicals, environmental pollutants, household poisons, to naturally occurring toxins.

The types of exposure, such as occupational, accidental, or intentional, are outlined, while toxicity is selective, affecting different cell types uniquely (tumor vs. normal) or species (mammalian vs. microorganism). This concept is used for the design of anticancer drugs, antibiotics, and pesticides.

One of the most important concepts that underlie toxicology is the dose-response relationship. First formulated by Paracelsus (in his famous phrase ‘All substances are poisons, there is none that is not; the right dose distinguishes a poison from a remedy’) establishes the relationship between the dose of a toxicant and the effect it produces or the toxic response.

Notes

1. For convenience, the term “chemicals” include organic, inorganic, synthetic, naturally-occurring agents and compounds, and therapeutic and non-therapeutic drugs.
2. *Mithradatic effect* refers to immunity against the action of a poison produced by small and gradually increasing doses of the same. The King supposedly was unsuccessful in committing suicide by poison because of his ingestion of repeated small doses taken to become invulnerable to assassination by poison.
3. In less than a century, in the western world, the advent of modern pharmaceuticals has universally has contributed to the increase in human lifespan to an average of over 80 years.
4. Smoke from factories and car exhaust fumes contain several known toxic constituents and constitute a major source of air pollution.
5. See Bhopal.

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