Fundamentals of Toxicology

Fundamentals of Toxicology

Essential Concepts and Applications

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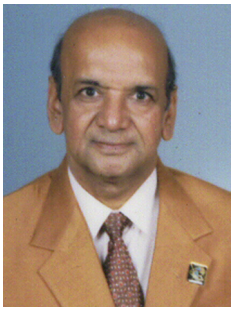

Prof Dr Gupta is an internationally known toxicologist with 48 years of experience in the fields of teaching, research, and research management. He has guided many postgraduate students in their thesis work in toxicology and has been honored with several national and international awards, including best teacher, best researcher, Alarsin award, lifetime achievement awards, and IUTOX-Astra Zeneca Award (USA). To his credit, he has written several books, book chapters (Elsevier, Academic Press, John Wiley, Merck Manual, etc.), and scientific research publications (550) that have been published in national and international peer-reviewed journals of repute. His contributions to the publication *Indian Veterinary Pharmacopeia* are highly praiseworthy. He is the Founder Editor-in-Chief of the peer-reviewed scientific journal *Toxicology International*; Book Review Editor for Marcel Dekker, USA; Expert Member Consultant and Advisor to WHO, Geneva; Consultant to the United Nations FAO, Rome, and to IAEA, Vienna; Founder of the Academy of Sciences for Animal Welfare; Founder and Past President of the Society of Toxicology of India; Adjunct Professor at SRMS; Founder Director and member of the nominating committee of the International Union of Toxicology; Founder President of the Society of Toxicology of India; and has held several prominent positions in scientific organizations in India and abroad.

In addition, Dr. Gupta has also been biographer for several WHO's WHO all over the world, including Marquis WHO's WHO (USA), IBC (UK), and other leading publications around the world. At present, Dr. Gupta is the Director of Toxicology at Consultant Group, Patron and Founder President of the Society of Toxicology of India, and President of the Academy of Sciences for Animal Welfare.

Foreword

Toxicology is the study of chemicals in biological systems. This science was born to deal with the safe use of chemicals, which cause more pain and danger than the illnesses being treated. In recent years, toxicology has evolved into a modern science. Further, new governmental legislations designed to safeguard against a variety of chemical substances have brought a large demand for trained toxicologists all over the world. Advances in the field of toxicology during the past several decades are widely scattered because of their multidisciplinary character. Very few of today's toxicologists and environmentalists are primarily trained in toxicology or environmental science. As such, scientists from other closely related disciplines, such as nutrition, biochemistry, pharmacology, chemistry, or bioengineering, are entrusted with the task of tackling toxicology problems. In addition, to meet the demand of safety evaluations of a large variety of compounds, a good number of multinational organizations have established their laboratories worldwide to perform contract research in toxicology. In the past, toxicology has been a branch of the pharmacology discipline. However, keeping in mind the demand for trained toxicologists, many universities have started offering courses or degrees in the field of toxicology.

Toxicology is a wide and vast subject that needs to be explored by overburdened students in the short time available to them. There are a number of reference books available on the market, but many of them provide only archaic information that is of little to no relevance at the present time. The subject matter of toxicology is rapidly changing and new laws and principles are being enforced. The concept of Good Laboratory Practice has been introduced. As such, there is a need to look at toxicology from a current perspective. I have known the author of this eminently readable book, Professor P.K. Gupta, for more than four decades. His three-volume set about modern toxicology is an excellent reference that is very concise and caters to the needs of students in developing countries. His other publications include his book entitled *Essential Concepts in Toxicology* and a peer-reviewed toxicology journal entitled *Toxicology International*, which is under his stewardship. The journal is a PubMed-indexed scientific research publication. From time to time, he also contributes chapters to various international books of repute published in Western countries. His contribution and commitment to science in general and toxicology in particular are praiseworthy.

For a long time, we were all waiting to have a book that examined toxicology from a fresh angle, and I had no doubt that it was Dr. Gupta who could do it. I am happy to know that he has shown his rich experience as a teacher in writing this book, which is primarily important to those who want first-hand knowledge of toxicology. His present book, *Fundamentals of Toxicology: Essential Concepts and Applications*, is very crisp and concise but covers all vital aspects of toxicology, such as nanomaterial toxicology, chemoinformatics

including Good Laboratory Practice, and regulatory toxicology. This book contains very useful information and is intended to provide a better understanding of the subject for formal courses in graduate toxicology programs or self-study by those individuals who wish to be accredited by various organizations concerned with toxicology. We hope that this book will facilitate the training of toxicologists who are required to have multidisciplinary knowledge in areas like environmental health and clinical and forensic toxicology (detection of intentional or unintentional toxic substances). This book will be useful in private commercial laboratories, in material science toxicology (biomedical and engineering disciplines), in education (courses in pharmacy, medicine, dentistry, agricultural, and veterinary practice), and, finally, for collecting, storing, and retrieving toxicology information. As such, I feel that this book will be an asset for all pharmacy, pharmacology, and medical students and for other concerned groups of readers with an interest in toxicology.

The formatting and printing of this book are of high order. Photographs, line drawings, flow charts, and tables in the book are relevant and extremely useful. The language of the book is simple and easily understandable. Dr. Gupta deserves our compliments for preparing this very readable text, which I hope will become popular among a wide range of readers with an interest in toxicology. I wish this book all success.

R.C. Gupta
Murray State University, Hopkinsville, KY, United States

Preface

Toxicology is a very complex and fascinating subject that deals with a wide variety of poisons and toxicants from a variety of sources such as chemicals, plants, fungi, and animals. Presently, synthetic compounds constitute the largest class of chemicals that are most frequently encountered in poisoning cases and are responsible for environmental contamination and occupational health hazards. My earlier three-volume set on modern toxicology, published in 1985, was designed with the objective of offering a comprehensive reference source to research toxicologists. The encouraging response given to this publication has led to the reprint of the three-volume set in 2010. In addition, there was great demand for a book that can meet the requirements of students from various universities and research institutions offering courses in toxicology. I am experienced in creating and presenting courses in toxicology at various Universities in India and abroad. My experience as a teacher of toxicology over the past five decades has shown me that there is a dearth of readily accessible text material that can provide basic toxicological information to students who wish to specialize in toxicology. Several requests for a well-illustrated book with precise and specific information with relevance to India that can serve the need of beginners in the area of toxicology were received. This encouraged me to write a book entitled *Essential Concepts in Toxicology*, which was published in 2014. While preparing that book, several universities and institutes offering courses in toxicology were consulted so that it may better serve their requirements.

The present book, *Fundamentals of Toxicology: Essential Concepts and Application*, has been designed to meet the requirements of the international market. Keeping this in mind, a short and lucid text that is easily understandable and supported with simple figures and self-explanatory tables has been prepared.

The book is subdivided into five units consisting of 34 chapters. Unit I includes six chapters that provide extensive coverage of general information, including basic concepts, definitions, historical perspectives, and scope of toxicology. These chapters may be useful for understanding the fundamental principles, including natural laws and approaches to toxicology.

Unit II comprises three chapters (chapters 7–9) dealing with absorption, distribution, excretion, biotransformation, and basic principles of toxicokinetics of xenobiotics.

Unit III is specifically focused on regulatory requirements in the United States and REACH regulation of European countries, the role of animal testing, the use of alternate approaches, Good Laboratory Practices, and current trends in toxicology such as chemoinformatics and nanomaterial toxicology. This unit has seven chapters (chapters 10–16) with many novel sections on recent topics such as toxicology testing, in vivo and in vitro test procedures used during assessment of the toxic potential of chemicals, including developmental and reproduction toxicity,

genotoxicity studies, preclinical testing procedures for pharmaceuticals, safety evaluation of biotechnology-derived products, and regulatory toxicology of biomaterials and medical devices used in medical practice.

The main focus of Unit IV (chapters 17−30) is on toxic agents derived from different sources, such as pesticides, drugs, plant and animal toxins, neurotoxins, irritant poisons, cardiotoxicants, asphyxiants, food poisonings, and therapeutic drugs of abuse. The latest information on problems related to adverse effects of radioactive materials on the health is presented.

Unit V is devoted to analytical, forensic, and diagnostic toxicology, which includes basic principles of specific and nonspecific therapeutic measures of common poisonings.

Each chapter is well supported with concise tables, illustrations, diagrams, and important images of plants whenever necessary.

This book is intended to provide a better understanding for those involved in formal courses in graduate programs in toxicology and for those individuals who wish to partake in self-study to be accredited by various toxicology organizations. I hope that this book will facilitate the training of toxicologists who are required to have multidisciplinary knowledge in areas like environmental health and clinical and forensic toxicology (detection of intentional or unintentional toxic substances). In addition, this book will be useful in private commercial laboratories, for material science toxicology (biomedical and engineering disciplines), for educators (courses in pharmacy, medicine, dentistry, agricultural, and veterinary practice), and, finally, for collecting, storing, and retrieving toxicology information.

I hope that this book will find a favorable response from all pharmacy and medical students and other concerned groups of readers, that it will find a suitable place in toxicology literature, and that it will benefit all scientists with an interest in toxicology.

The author welcomes suggestions, constructive criticism, thoughts, and comments from readers for improving this book. Kindly e-mail them to drpkg_brly@yahoo.co.in or to drpkg1943@gmail.com.

P.K. Gupta

CHAPTER

Introduction and historical background

1

CHAPTER OUTLINE

1.1 INTRODUCTION

The word "toxicology" is derived from the Greek word "toxicon," which means "poison," and logos, which means to study. Thus, toxicology literally means the study of poisons. It can thus be defined as the "study of poisons that include their physical and chemical properties, detection and identification, biological effects, treatment, and prevention of disease conditions produced by them." It also includes the study of special effects of toxicant developmental toxicity, teratogenicity, carcinogenicity, mutagenesis, immunotoxicity, neurotoxicity, and endocrine disruption.

1.2 HISTORICAL BACKGROUND

1.2.1 ANTIQUITY

The knowledge of poisons is as old as human civilization. Early poisons were almost exclusively plant and animal toxins and some minerals. They were used mainly for hunting. Some were used as "ordeal poisons," such as physostigmine from *Physostigma venenosum* (Calabar bean) and amygdalin from peach pits. Arrow and dart poisons were very popular for hunting animals (and sometimes fellow humans!). Common arrow poisons included strophanthin, aconitine, and extracts from hellebores (a cardiotoxic plant) and történelmi venoms. Since ancient times, people have learned how to protect themselves from the harmful

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effects of plants and animals. They also knew how to use poisons to destroy their enemies. The earliest records are available in the form of ancient books on mythology and legendry, archeological literature, and history books. The Ebers Papyrus (1550 BC) is perhaps the earliest medical record that contains a number of disease conditions and prescriptions; it was previously used in Egyptian medicine. Many of these contain recognized poisons such as aconite, an arrow poison of ancient times, and opium (both as a poison and antidote).

Hippocrates (460−375 BC) is regarded as the "Father of Rational Medicine." The Hippocrates School was formed by a group of physicians to provide an ethical basis for the practice of therapeutics by those who have knowledge of lead, mercury, copper, antimony, and others as poisons and who have some knowledge of their properties. They advocated hot oil as an antidote to poisoning and induced vomiting to prevent absorption of the poisons. Hemlock, which contains the alkaloid coniine, was one of the poisons used during that time. Socrates (470−390 BC) was sentenced to death by hemlock. Theophrastus (371−287 BC), the most dedicated pupil of Aristotle, provided an early treatise on plant poisons. Experimental toxicology perhaps began with Nicander (204−135 BC). Homicidal poisoning has also had a hoary past. One of the earliest laws against the murderous use of poisons was the *Lex Cornelia* passed in Rome in 81 BC.

During AD 40−80, Pedanius Dioscorides, a Greek army physician, classified poisons according to their origin (animal, vegetable, or mineral). His classification of natural substances as being toxic or therapeutic is still valid today. Dioscorides is famous for writing a five-volume book, *De Materia Medica*, that is a precursor to all modern pharmacopeias and is one of the most influential herbal books in history.

1.2.2 MIDDLE AGES

After the fall of the Roman empire, there was a lull in the development of toxicology until 1198, when a famous Swiss Philosopher, Maimonides (Moses ben Maimon) (1135−1204), published his classic work *Treatise on Poisons and Their Antidotes* in 1198, which describes the treatment of poisonings from insects, snakes, and dogs. During the early Renaissance, the Italians, with characteristic pragmatism, brought the art of poisoning to its zenith. The poisoner became an integral part of the political scene. The records of the city councils of Florence, particularly those of the infamous Council of Ten of Venice, contain ample testimony about the political use of poisons. Victims were named, prices were set, and contracts were recorded; when the deed was accomplished, payment was made. An infamous figure of the time was a lady named Toffana, who peddled specially prepared arsenic-containing cosmetics (*Agua Toffana*).

Unfortunately, during this period, poisoning as a method of homicide became increasingly popular in several parts of Europe, particularly Italy and France, where schools actually existed for teaching the art of poisoning. Among the notorious poisoners, Madame Guilia Toffana killed more than 600 people with white arsenic solution called aqua Toffana that was freely sold as a cosmetic in Italy. Toward the end of the 16th century, the wave was spread

from Italy to France, where poisons were commonly used by all classes of society to get rid of enemies or persons considered undesirable. Criminal poisoning continued in many parts of the world during the 18th and 19th centuries.

1.2.3 AGE OF ENLIGHTENMENT

A significant figure in the history of science and medicine in the late Middle Ages was the renaissance man Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus (1493−1541), who referred to himself as Paracelsus because of his belief that his work was beyond the work of Celsus, a first-century Roman physician who was perhaps the first to promote a focus on toxicon, a toxic agent, as a chemical entity. He recognized the dose−response concept and, in one of his writings, stated: "All substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy." Paracelsus advanced many views that were revolutionary for his time and that are now accepted as fundamental concepts for the field of toxicology. In contrast to previous emphasis on mixtures, he focused on toxicon as a specific primary chemical entity that was toxic. Paracelsus advanced four fundamental concepts:

1. Experimentation is required for examining responses to chemicals.
2. A distinction should be made between the therapeutic and toxic properties of chemicals.
3. The therapeutic and toxic properties are closely related and distinguished by dose.
4. It is possible to ascertain a degree of specificity for chemicals and their therapeutic or toxic effects.

Modern toxicology is a relatively young science based on scientific work performed by numerous dedicated workers. It is the outcome of rational thinking, experimentation, the relationship between dose and therapeutics (as compared with toxic), and the responses to chemicals. Advances made in all allied disciplines contributed to the better understanding of effects of a number of toxicants in humans and animals. Modern toxicology began with Friedrich Serturner (1783−1841), a German pharmacist who isolated the specific narcotic substance from opium and named it morphine after Morpheus, the Roman God of sleep. Subsequently, Mattie Josesph Benaventura Orfila (MJB; 1787−1853), a Spanish physician who is considered the "Father of Toxicology," established toxicology as a discipline distinct from others and defined toxicology as the study of poisons. He advocated the practice of autopsy followed by chemical analysis of viscera to prove that poisoning had taken place. His treatise *Traite des Poisons* published in 1814 laid the foundation for forensic toxicology. In 1829, one of his students, Robert Christison (1797−1882), published a simplified English version titled *A Treatise on Poisons*. The first published work (published in 1848) on clinical toxicology was *A Practical Treatise on Poisons*, written by O. Costill.

Francois Magendie (1783−1855), a pioneer French physiologist and toxicologist, studied the mechanism of action of emetine, morphine, quinine, strychnine,

and other alkaloids, for which he is also called the "Father of Experimental Pharmacology" Magendie passed on his interest to his famous student Claude Bernard (1813–78), who continued to study arrow poisons and used these toxicants to learn more about the mechanism of body functions.

Louis Lewin (1854–1929) was a German scientist who accepted the task of classifying drugs and plants in accordance with their psychological effects. He also published many articles and books dealing with toxicology of methyl alcohol, ethyl alcohol, chloroform, opium, and some other chemicals. His important publications are *Toxicologist's View of World History* and *A Textbook of Toxicology*. Development occurred rapidly in the 20th century with the development of dimercaprol (BAL) as an antidote for arsenic and the discovery of insecticidal properties of DDT by Paul Hermann Muller in 1939. He was awarded a Nobel Prize in 1948 "for his discovery of the high efficiency of DDT as a contact poison against several arthropods."

Gerhard Schrader (1903–90) was a German chemist who accidentally developed the toxic nerve agents serin, tabun, soman, and cyclosarin while attempting to develop new insecticides. Schrader and his team therefore introduced a new class of synthetic insecticides, the organophosphorus insecticides (OP), and defined the structural requirements for insecticidal activity of anticholinesterase (anti-ChE) compounds. He is called the "Father of Nerve Agents."

1.3 MODERN TOXICOLOGY

Toxicology has evolved rapidly during the 1900s. The exponential growth of the discipline can be traced to the World War II era, with its marked increase in the production of drugs, pesticides, synthetic fibers, and industrial chemicals. It also marked the beginning of understanding in-depth the nature and mechanism of the effects of poisons and the invention of their specific antidotes. Along with other sciences, toxicology contributes to the development of safer chemicals to be used as drugs, food additives, pesticides, industrial chemicals, and several other chemicals required for use in everyday life.

Because of the need for an affluent society to protect itself from injurious effects resulting from the introduction of new chemicals, physical agents, and various industrial and consumer products, there has been an expansion of the various facets of toxicology. Therefore, application of the discipline of toxicology to safety evaluation and risk assessment is of utmost importance in today's modern world.

1.3.1 AFTER WORLD WAR II

The mid 1950s witnessed the strengthening of the US Food and Drug Administration's commitment to toxicology under the guidance of Arnold Lehman. Lehman, Fitzhugh, and their co-workers formalized the experimental program for the appraisal of food, drug, and cosmetic safety in 1955, and it was

updated by the US FDA in 1982. The Delaney clause (1958) of these amendments stated broadly that any chemical found to be carcinogenic in laboratory animals or humans could not be added to the US food supply. Regardless of one's view of Delaney, it has served as an excellent starting point for understanding the complexity of the biological phenomenon of carcinogenicity and the development of risk assessment models.

The end of the 1960s witnessed the discovery of TCDD as a contaminant in the herbicide Agent Orange (the original discovery of TCDD toxicity, the "Chick Edema Factor," was reported in 1957). The expansion of legislation, journals, and new societies involved with toxicology was exponential during the 1970s and 1980s and shows no signs of slowing down. Currently, in the United States, there are dozens of professional, governmental, and other scientific organizations with thousands of members and more than 120 journals dedicated to toxicology and related disciplines. As an example of this diversification, one now finds toxicology graduate programs in medical schools, schools of public health, and schools of pharmacy, as well as programs in environmental science and engineering and undergraduate programs in toxicology at several institutions. Surprisingly, courses in toxicology are now being offered in several liberal arts undergraduate schools as part of their biology and chemistry curricula. Some important developments in the field of toxicology are summarized in Table 1.1.

Table 1.1 Some Important Developments in the Field of Toxicology

F. Magendie, 1809: study of "arrowpoisons," mechanism of action of emetine and strychnine
Marsh, 1836: development of method for arsenic analysis
Reinsh, 1841: combined method for separation and analysis of As and Hg
Fresenius, 1845 and von Babo, 1847: development of screening method for general poisons
Stas-Otto, 1851: detection and identification of phosphorus
C. Bernard, 1850: carbon monoxide combination with hemoglobin, study of mechanism of action of strychnine, site of action of curare
Friedrich Gaedcke, 1855: first isolated cocaine from leaves of Erthroxylon coca
Oswald Schmiedeberg, 1869: isolated muscarine from Amanita muscaria
R. Bohm, approximately 1890: active anthelmintics from fern, action of croton oil catharsis, poisonous mushrooms
C. Voegtlin, 1923: mechanism of action of As and other metals in the SH groups
K.K. Chen, 1934: demonstrated antagonistic effect of sodium nitrite and sodium thiosulphate in cyanide poisoning
P. Müller, 1944–46: introduction and study of DDT (dichlorodiphenyltrichloroethane) and related insecticide compounds
R.A. Peters, L.A. Stocken, and R.H.S. Thompson, 1945: development of British anti-Lewisite (BAL) as a relatively specific antidote for arsenic
Judah Hirsch Quastel, 1946: developed 2,4-D, the first widely used systemic herbicide
G. Schrader, 1952: introduction and study of organophosphorus compounds
Rachel Carson, 1962: started crusade against the use of DDT and published the great book, *Silent Spring*

CHAPTER

Definitions and scope of toxicology

2

CHAPTER OUTLINE

2.1 DEFINITIONS

Toxicology: To a lay person, toxicology is the study of adverse effects of chemicals on various biological systems, including humans. However, in modern times, toxicology is considered a scientific discipline and, like medicine, an art that is practiced. Thus, it is the study of poisons, including their physical and chemical properties, detection and identification, biological effects, treatment, and prevention of disease conditions produced by them.

Xenobiotic: Xenobiotic (xeno is a Greek word that means strange or alien) are the substances that are foreign to the body and are biologically active. These cannot be broken down to generate energy or assimilated into a biosynthetic pathway. It is a very wide class of structurally adverse agents, including both natural and synthetic chemicals such as drugs, industrial chemicals, pesticides, alkaloids, secondary plant metabolites and toxins of molds, plants, and animals, and environmental pollutants.

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2.2 SUB-DISCIPLINES OF TOXICOLOGY

Forensic Toxicology: Forensic toxicology deals with medical and legal aspects of the harmful effects of the chemicals.

Clinical Toxicology: Clinical toxicology refers to health problems caused by or associated with abnormal exposure to chemical substance. In other words, it deals with the cause, diagnosis, treatment, and clinical management of health problems/diseases that are caused by or are associated with toxic substance(s).

Nutritional Toxicology: The study of toxicological aspects of food/feed stuffs and nutritional products/habits.

Reproductive Toxicology: The study of the occurrence of adverse effects on the male and female reproductive system due to exposure to chemicals or physical agents.

Development Toxicology: The study of harmful effects of chemicals and drugs on the development of an organism; manifestations of development toxicity include structural malformations, growth restriction, functional impairment, and/or death of an organism.

Veterinary Toxicology: This deals with the cause, diagnosis, and management of established poisonings in domestic and wild animals.

Teratology: The study of malformations induced by toxic agents during development between conception and birth.

Environmental Toxicology: This deals with the effects of pollutants on the environment (food, water, air, or soil) and their prevention. Its specialties could include ecotoxicology, aquatic toxicology, and others.

Analytical Toxicology: The application of analytical chemistry tools in the qualitative and quantitative estimation of the agents involved in the process of toxicity.

Aquatic Toxicology: This deals with the study of adverse effects of chemicals discharged into marine and fresh water on aquatic organisms and the aquatic ecosystem. It is largely a study of water pollution and its ecological effects.

Ecotoxicology: A more specialized area of environmental pollution in populations and communities of living organisms. Ecotoxicology, in general, considers effects of pollutants on organisms other than humans.

Food Toxicology: This deals with natural contaminants, food and feed additives, and toxic and chemo-protective effects of compounds in food.

Formal Toxicology: This deals with the formal toxicological studies that are prerequisites for the release of new drugs/chemicals (eg, calculation of LD_{50} and minimum toxic dose).

Genetic Toxicology: This deals with the study of the interaction of toxicants with the process of hereditary.

Industrial Toxicology: This deals with the clinical study of industry workers and the environment around them.

Occupational Toxicology: This deals with assessing the potential of adverse effects from chemicals in occupational environment and the recommendations of appropriate protective and precautionary measures.

Regulatory Toxicology: This deals with administrative functions concerned with the development and interpretation of mandatory toxicology testing programs and controlling the use, distribution, and availability of chemicals used commercially and therapeutically. For example, the Food and Drug Administration (FDA) regulates drugs, cosmetics, and food additives.

Regulation: Regulation is the control, by statute, of the manufacture, transportation, sale, or disposal of chemicals deemed to be toxic after testing procedures or according to criteria put forth in applicable laws.

Toxicodynamics: The study of biochemical and physiological effects of toxicants and their mechanism of action.

Toxicokinetics: The study of absorption, distribution, metabolism, and excretion of toxicants in the body.

Toxicovigilance: This deals with the process of identification, investigation, and evaluation of various toxic effects in the community with the aim of taking measures to reduce or control exposures involving the substances that produce these effects.

Toxinology: This deals with assessing the toxicity of substances of plant and animal origins and those produced by pathogenic bacteria/organisms.

Toxicoepidemiology: The study of quantitative analysis of toxicity incidences in organisms, factors affecting toxicity, and species involved, and the use of such knowledge for planning prevention and control strategies.

2.3 TOXICANT AND TYPES OF TOXICANTS

Poison: Poison is derived from the Latin *potus*, a drink that could harm or kill. It is any substance that when taken inwardly in a very small dose or applied in any kind of manner to a living body depraves the health or entirely destroys life. Although the word "toxicant" has essentially the same medical meaning, there are psychological and legal implications involved in the use of the word "poison" that makes manufacturers reluctant to apply it to chemicals, particularly those intended for widespread use in large quantities, unless they are required to do so by law. The term "toxicant" is more acceptable to both manufacturers and legislators.

Toxicant: Toxicant is synonym of poison; it is produced by living organisms in small quantities and is generally classified as biotoxin. These may be phytotoxins (produced by plants), mycotoxins (produced by fungi), zootoxins (produced by lower animals), and bacteriotoxins (produced by bacteria).

Endotoxins: These are found within bacterial cells.

Exotoxins: These are elaborated from bacterial cells.

Venom: A toxicant synthesized in a specialized gland and ejected by the process of biting or stinging. Venom is also a zootoxin, but it is transmitted by the process of biting or stinging.

Systemic Toxicant: A toxicant that affects the entire body or many organs rather than a specific site. For example, potassium cyanide is a systemic toxicant that affects virtually every cell and organ in the body by interfering with the cell's ability to utilize oxygen.

Organ Toxicant: A toxicant that affects only specific organs or tissues (may be called tissue toxicant) while not producing damage to the body as a whole. For example, benzene is a specific organ toxicant in that it is primarily toxic to the blood-forming tissues.

Pollutant: Any undesirable solid, liquid, or gaseous matter resulting from the discharge or admixture of noxious materials that contaminates the environment and contributes to pollution.

2.4 TOXICITY AND TOXIC EFFECTS

Toxic and toxicity are relative terms commonly used to compare one chemical with another.

Toxicity: The state of being poisonous or the capacity to cause injury in living organisms.

Toxicosis: The condition or disease state that results from exposure to a toxicant. The term "toxicosis" is often used interchangeably with the term "poisoning" or "intoxication."

Toxic Effects: Undesirable effects produced by a toxicant/drug that are detrimental to either survival or normal functioning of the individual.

Side Effects: Undesirable effects that result from the normal pharmacological actions of drugs. These results may not be detrimental or harmful to the individual.

Selective Toxicity: Toxicity produced by a chemical in one kind of living matter without harming another form of life, even though the two exist in intimate contact.

Safety: Means/implies practical certainty that injury will not result from use of a substance under specified conditions of quantity and manner of use.

Risk-to-Benefit Ratio: This implies that even a toxic agent may warrant use if its benefits for a significant number of people are much greater than the dangers,.

Risk: Expected frequency of occurrence of a harmful effect such as injury or loss arising from exposure to a chemical or physical agent under specified conditions.

Risk Assessment: A quantitative assessment of the probability of deleterious effects under given exposure conditions.

Hazard: The qualitative description of the adverse effect arising from a particular chemical or physical agent with no regard for dose or exposure. The term "hazard" is related to the risk, but it mainly expresses likelihood or probability of danger, irrespective of dose or exposure. Also a property or set of properties of the chemical substance that may cause an adverse health or ecological effect if there is exposure at a sufficient level.

Tolerance: A state or condition in which the size of the dose required for producing a toxic effect increases with repeated exposure. Also, a state of decreased responsiveness to the toxic effect of a chemical resulting from prior exposure to that compound or structurally related compound.

Acceptable Risk: The probability of suffering from disease or injury during exposure to a substance; it is considered to be small but acceptable to the individual.

Acceptable Exposure: Unintentional contact with a chemical or physical agent that results in harmful effects.

Margin of Exposure (MOE): The ratio of the no observed adverse effect level (NOAEL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration.

Threshold Limit Values (TLV): The airborne concentration of a substance that represents conditions under which it is believed that nearly all workers may be repeatedly exposed without adverse effects. These values are expressed as time weight concentration for a 7- to 8-h work day for 40 weeks.

2.4.1 TOXICITY IN RELATION TO FREQUENCY AND DURATION OF EXPOSURE

Acute Toxicity: Toxic effects produced by a single dose or multiple doses during a 24-h period.

Subacute Toxicity: The study of repeated exposure to a toxicant and its effects for 30 days.

Subchronic Toxicity: The study of repeated exposure to a toxicant and its effects for 1 to 3 months.

Chronic Toxicity: The study of repeated exposure to a toxicant and its effects for more than 3 months.

2.4.2 TOXICITY IN RELATION TO TIME OF DEVELOPMENT AND DURATION OF INDUCED EFFECTS

Transient or Reversible or Temporary Toxicity: The toxicity or harmful effect that remains for a short duration of time (eg, narcosis-produced organic solvents).

Persistent or Permanent or Irreversible Toxicity: The toxicity or harmful effect that persists throughout the life span of the individual and is of a permanent nature (eg, scarring of skin produced by corrosives).

Immediate Toxicity: The toxicity that develops soon after a single exposure to a toxicant (eg, cyanide poisoning).

Delayed Toxicity: The toxicity or harmful effect that has a delayed onset of action (eg, peripheral neuropathy produced by some organophosphorus insecticides).

Cumulative Toxicity: Progressive toxicity or harmful effect produced by the summation of incremental injury resulting from successive exposures (eg, liver fibrosis produced by ethanol).

2.5 DOSE AND RELATED TERMS

Dose: The total or absolute quantity or amount of a substance applied or administered at one time to an individual to achieve the desired pharmacological or toxicological response.

Lethal Dose (LD): The lowest dose that causes death in any animal during the period of observation. Various percentages can be attached to the LD value to indicate doses required to kill 1% (LD_1), 50% (LD_{50}), or 99% (LD_{99}) of the test animals in the population.

Lethal Dose 50 (LD_{50}): Also known as median lethal dose (MLD). It is the dose of the toxicant that causes death of 50% of animals under defined conditions such as species, route of exposure, and duration of exposure. It is a commonly used measure of toxicity.

Lethal Concentration (LC): The lowest concentration of the compound in feed (or water in the case of fish) that causes death during the period of observation. It is expressed as milligrams of compound per kilogram of feed (or water).

Lethal Concentration-50 (LC_{50}): The concentration of the compound in feed (or water in the case of fish) that is lethal to 50% of the exposed population. It mainly expresses acute lethal toxicity.

No Observed Effect Level (NOEL): The highest dose level/concentration of a substance that, under defined conditions of exposure, causes no effect (alteration) on morphology, functional capacity, growth, development, or life span of the test animals.

No Observed Adverse Effect Level (NOAEL): The highest dose level/concentration of a substance that, under defined conditions of exposure, causes no observable/detectable effect (alteration) on morphology, functional capacity, growth, development, or life span of the test animals. NOAEL is a variant of NOEL that specifies that only the effect in question is adverse.

Lowest Observed Adverse Effect Level (LOAEL): The highest exposure level/dose level/concentration of a substance under defined conditions of exposure to an observable/detectable effect (alteration) on morphology, functional capacity, growth, development, or life span of the test animals observed.

Reference Dose/Reference Concentration (RfD/RfC): For noncancerous effects, oral intake (RfD) or inhalation reference concentration (RfC) of airborne materials is calculated using the NOAEL or LOAEL as a starting point. These values are developed from the experimentally determined NOAEL or LOAEL.

Maximum Allowable or Admissible/Acceptable Concentration (MAC): The regulatory value defining the upper limit of concentration of certain atmospheric contaminants allowed in the ambient air of the work place.

Maximum Residue Limit/Maximum Residue Level (MRL): The maximum amount of a pesticide or grog (mainly veterinary pharmaceutical) residue that is legally permitted or recognized as acceptable in or on food commodities and animal feeds. Although both terms have the same meaning, in practice the term "maximum residue limit" is used for the pesticide residue and the term "maximum residue level" is applicable for the drug residue.

Maximum Tolerated Dose (MTD): The highest dose/amount of a substance that causes toxic effects but no mortality in the test organism. In a chronic toxicity study, the MLD can cause limited toxic effects in the test organism, but it should not decrease the body weight more than 10% compared with the control group or produce overt toxicity (death of cells or organ dysfunction). The value is often denoted by LD_0.

Maximum Tolerated Concentration (MTC): The highest concentration of a substance in an environment medium that causes toxic symptoms but no mortality in the test organism.

Absolute Lethal Dose (LD_{100}): The lowest dose of substance that, under defined conditions, is lethal to 100% of exposed animals. The value is dependent on the number of organisms used in its assessment.

Absolute Lethal Concentration (LC_{100}): The lowest concentration of substance in an environment medium that, under defined conditions, is lethal to 100% of exposed organisms or species.

Acceptable Daily Intake (ADI): The estimated amount of substance in food or drinking water that can be ingested daily over a lifetime by humans without appreciable health risk. ADI is normally used for food additives (the term "tolerable daily intake" is used for contamination).

2.6 OTHER COMMON TERMS

Alternative Test: Alternative techniques that can provide the same level of information as current animal tests but use fewer animals, cause less suffering, or avoid the use of animals completely. Such methods, as they become available, must be considered whenever possible for hazard characterization and consequent classification and labeling for intrinsic hazards and chemical safety assessment.

Cheminformatics (also Known as Chemoinformatics, Chemioinformatics, and Chemical Informatics): Cheminformatics is the use of computer and informational techniques applied to a range of problems in the field of chemistry. These in silico techniques are used in, for example, pharmaceutical companies in the process of drug discovery.

Endpoint Study Record: International Uniform Chemical Information Database (IUCLID) format of the technical dossier used to report study summaries and robust study summaries of the information derived for the specific endpoint according to the REACH Regulation.

Endpoint: An observable or measurable inherent property/data point of a chemical substance. It can refer to a physical–chemical property like vapor pressure, or to degradability, or to a biological effect that a given substance has on human health or the environment (eg, carcinogenicity, irritation, aquatic toxicity).

In Vitro Test: Literally stands for "in glass" or "in tube"; refers to the test taking place outside of the body of an organism, usually involving isolated organs, tissues, cells, or biochemical systems.

In Vivo Test: A test conducted within a living organism.

In Silico: A phrase coined as an analogy to the familiar phrases in vivo and in vitro. It is an expression used to denote "performed on computer or via computer simulation" and means scientific experiments or research conducted or produced by means of computer modeling or computer simulation.

IUCLID Flag: An option used in the IUCLID software to indicate submitted data type (eg, experimental data) or their use for regulatory purposes (eg, confidentiality).

Prediction Model: A theoretical formula, algorithm, or program used to convert the experimental results obtained by using a test method into a prediction of the toxic property/effect of the chemical substance.

QSARs and SARs (Q(SAR)): Theoretical models that can be used to predict in a quantitative or qualitative manner the physicochemical, biological (eg, (eco)toxicological), and environmental fate properties of compounds from the knowledge of their chemical structure. A SAR is a qualitative relationship that relates a (sub-) structure to the presence or absence of a property or activity of interest. A QSAR is a mathematical model relating one or more quantitative parameters, which are derived from the chemical structure, to a quantitative measure of a property or activity.

Test (or Assay): An experimental system set-up to obtain information about the intrinsic properties or adverse effects of a chemical substance.

Validated Test: A test in which the performance characteristics, advantages, and limitations have been adequately determined for a specific purpose.

Validation: The process by which the reliability and relevance of a test method are evaluated for the purpose of supporting a specific use.

Vertebrate Animal: Animals that belong to the subphylum *Vertebrata*, which are chordates with backbones and spinal columns.

2.7 SOURCES OF POISONING

The exposure of humans and other organisms to toxicants may result from many activities such as intentional ingestion, occupational exposure, environmental exposure, and accidental and intentional (suicidal or homicidal) poisoning. The toxicity of a particular compound may vary with the portal of entry into the body, whether through the alimentary canal, the lungs, or the skin.

2.7.1 ACCIDENTAL POISONING

Accidental poisoning may occur when humans or animals ingest a toxicant accidentally or it is added unintentionally to food or through feed, fodder, or drinking water. Such toxicants come from either natural sources or human-made sources. Natural sources include ingestion of toxic plants, biting or stinging by poisonous reptiles, ingestion of food contaminated with toxins, water contaminated with minerals, and others. Human-made sources include therapeutic agents, household products, agrochemicals, and others.

2.7.2 MALICIOUS POISONING

Malicious poisoning is the unlawful or criminal killing of a human or animal by administering certain toxic/poisonous agents. An incidence of such poisoning is more prevalent in humans and less so in animals.

2.7.3 OCCUPATIONAL EXPOSURE

Occupation exposure to workers is very common because humans live in a chemical environment. Estimates indicate that approximately 68,000 to 101,000 chemicals are in common use. Industrialization and creation of large urban centers have led to the contamination of air, water, and soil. Industrial workers are exposed to these chemicals during the synthesis, manufacture, or packaging of these substances or through their use in the occupational setting. The major emphasis of occupational toxicology is to identify the agent of concern, define the conditions leading to their safe use, and prevent absorption of harmful amounts. Guidelines have been issued to establish safe ambient air concentrations for many chemicals found in the workplace. For toxicological implications of chronic exposure to various chemicals, the reader may refer to other chapters about toxic agents in this book.

2.8 DURATION AND FREQUENCY OF EXPOSURE

The exposure of experimental animals to chemicals can be divided into four categories: acute, sub-acute, sub-chronic, and chronic.

Acute exposure is defined as exposure to a chemical for less than 24 h. Examples of exposure routes are: intraperitoneal (IP), intravenous (IV), and subcutaneous (SC) injection; per os (oral intubation); and dermal application. The exposure usually refers to a single administration; repeated exposures may be given within a 24-h period for some slightly toxic or practically nontoxic chemicals. Acute exposure by inhalation refers to continuous exposure for less than 24 h, most frequently for 4 h.

Repeated exposure is divided into three categories: sub-acute, sub-chronic, and chronic.

1. *Sub-acute exposure* refers to repeated exposure to a chemical for 1 month or less.
2. *Sub-chronic exposure* refers to repeated exposure to a chemical for 1 to 3 months.
3. *Chronic exposure* refers to repeated exposure to a chemical for more than 3 months (usually this refers to studies with at least 1 year of repeated dosing).

These three categories of repeated exposure can be by any route, but most often they occur by the oral route, with the chemical added directly to the diet. In human exposure situations, the frequency and duration of exposure are usually not as clearly defined as in controlled animal studies. However, almost the same terms are used to describe general exposure situations. Thus, workplace or environmental exposures may be described as *acute* (occurring from a single incident or episode), *sub-chronic* (occurring repeatedly over several weeks or months), or *chronic* (occurring repeatedly for many months or years).

CHAPTER

Classification of poisons/ toxicants

3

CHAPTER OUTLINE

3.1 INTRODUCTION

Toxic agents are classified in number of ways depending on the interests and needs of the classifier. There is no single classification applicable for the entire spectrum of toxic agents; therefore, combinations of classification systems based on several factors may provide the best rating system. Classifications of poisons may take into account both the chemical and biological properties of the agent; however, exposure characteristics are also useful in toxicology. Classification based on sources of toxicants (plant toxins, animal toxicants, mineral toxicants, synthetic toxicants), physical state of toxicants (gaseous toxicants, liquid toxicants, solid toxicants, dust toxicants), target organ/system (neurotoxicants, hepatotoxicants, nephrotoxicants, pulmotoxicants, hematotoxicants, dermatotoxicants), chemical nature/structure of toxicants (metals, nonmetals, acids, and alkalies), organic toxicants (carbon compounds other than oxides of carbon, the carbonates, and metallic carbides and cyanides), analytical behavior of toxicants (volatile toxicants, extractive toxicants, metals, and metalloids), type of toxicity (acute, subacute, chronic, etc.), toxic effects (carcinogens, mutagens, teratogens, clastogens), usage (insecticides, fungicides, herbicides, rodenticides, food additives, etc.), mechanism of action, and environmental and public health considerations.

3.2 CLASSIFICATION OF POISONS

According to the main symptoms produced, poisons are basically classified into four groups, namely, corrosive poisons, irritant poisons, systemic poisons, and other poisons. The details are summarized in Tables 3.1–3.4.

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To help physicians and to provide them with some idea regarding the hazardous nature of various poisons in humans, a "toxicity rating" system has been created for common poisons. The higher the toxicity rating for a particular substance (over a range of 1−6), the greater its potency. The toxicity rating based on toxic potential of substances (super toxic, extremely toxic, very toxic, moderately toxic, slightly toxic, and practically nontoxic) is summarized in Table 3.5.

Table 3.1 Corrosive Poisons (Caustics)

Strong Acids		Strong Alkalies	
Inorganic or Mineral Acids	**Organic Acids**	**Hydrates of**	**Carbonates of**
Sulphuric acid Nitric acid	Carbolic acid Oxalic acid Hydrochloric acid	Sodium Sodium	Potassium Potassium

Table 3.2 Irritant Poisons

Inorganic	Organic	Mechanical
Nonmetallic: phosphorus, halogens *Metallic*: arsenic, mercury, lead, copper, etc.	*Vegetable*: Abrus, castor, croton, calatropia, ergot, etc. *Animal*: snake or insect bites and stings	Diamond dust, glass powder, hair, nails, pins, etc.

Table 3.3 Systemic Poisons

Central Nervous System (Neurotoxins)	Cardiovascular	Lungs (Asphyxiants)
Central Soniferous • Opium • Pethidine *Inebriants* • Alcohols, anesthetics • Sedative hypnotics • Insecticides (hydrocarbons) • Benzodiazepines, etc. *Deliriants* • Datura • Cannabis • Cocaine, etc. *Spinal* Strychnine, gelsemium, etc. *Peripheral* Curare, conium, etc.	Oleanders, aconite, nicotine	Carbon monoxide, carbon dioxide, irrespirable gas, cyanogens gas, Amol cyanides

Table 3.4 Miscellaneous Poisons

Domestic poisons	Insecticides (aluminum phosphide, rat poison), kerosene, diesel, petrol, cleaning agents, soaps, detergents, disinfectants, cosmetics, etc.
Therapeutic substance	Salicylates, paracetamol, antidepressants, sedatives, antipsychotics, insulin, etc.
Food poisons	Bacterial, viral, mushrooms, chemicals, etc.
Drugs of dependence	Alcohol, tobacco, hypnotics, hallucinogens, stimulants, organic solvents, etc.

Table 3.5 Toxicity Rating

	Probable Lethal Dose (Human)	
Toxicity Rating or Class	**General Dose, mg/kg**	**For a 70-kg Man**
6 (super toxic)	<5 mg/kg	A few drops
5 (extremely toxic)	5–50 mg/kg	A pinch to 1 teaspoon
4 (very toxic)	51–500 mg/kg	1 teaspoon to 2 tablespoons
3 (moderately toxic)	501 mg/kg to 5 g/kg	1 ounce to 1 pint (1 pound)
2 (slightly toxic)	5.1 g/kg to 15 g/kg	1 pint to 1 quart (2 pounds)
1 (practically nontoxic)	>15 g/kg	More than 2 pounds

3.3 ACTIONS OF POISONS

Poisons usually act in three ways: locally, remotely, and both locally and remotely.

- *Locally Acting*: The chemicals act only at the site of application, such as skin/mucosa (eg, corrosive poisons).
- *Remotely Acting*: These act only after being absorbed into the circulatory system (eg, narcotic poisons, cardiac poisons, etc.).
- *Both Locally and Remotely Acting*: These act by local and remote actions (eg, carbolic acid, etc.).