CHAPTER 1

Introduction and Historical Background

1.1 Introduction

The word 'toxicology' is derived from the Greek word 'toxicon' which means 'poison' and logos means to study. Thus toxicology literally means the study of poisons. It can thus be defined as '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 study of special effects of toxicants developmental toxicity, teratogenicity, carcinogenicity, mutagenesis, immunotoxicity, neurotoxicity, endocrine disruption, etc.

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" e.g. 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 történelmi történelmi venoms. Since ancient times, people have learnt how to protect themselves from the harmful 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, archaeological literature and history books. The Ebers Papyrus (1550 BC) is perhaps the earliest medical record which contains a number of disease conditions and prescriptions employs in Egyptian medicine at that time. Many of these contain recognized poisons, e.g. aconite, an arrow poison of the ancient time; and opium both as a poison and antidote.

Hippocrates (460-375 BC) is regarded as the “Father of Rational Medicine”. The Hippocrates School formed by a group of physicians providing an ethical basis for the practice of therapeutics who has the knowledge of lead, mercury, copper, antimony, etc. as poisons and had some knowledge of their properties. They advocated hot oil as an antidote in poisoning and induced vomiting to prevent absorption of the poisons. Hemlock, which contains the alkaloid coniine, was the poison used. Socrates (470-390 BC) was sentenced to death by hemlock. Theophrastus (371-287 BC), the most dedicated pupil of Aristotle, provided 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 and mineral). His classification of natural substances as being toxic or therapeutic is valid still 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 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 describing the treatment of poisonings from insects, snakes and dogs. In 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 set, and contracts 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 very period, poisonings 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, Towards 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 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 himself as Paracelsus, from his belief that his work was beyond the work of Celsus, a first century Roman physician was perhaps the first to promote a focus on the toxicon, the 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 that are now accepted as fundamental concepts for the field of toxicology. In contrast to earlier emphasis on mixtures, he focused on the 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 something 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 carried out by numerous dedicated workers. It is the outcome of the rational thinking, experimentation, relationship between dose and therapeutics as compared with toxic, and 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), German pharmacist who isolated the specific narcotic substance from opium and named as morphine after Morpheus, the Roman God of sleep. Subsequently (M J B) Mattie Josesph Benaventura Orfila (1787-1853), a Spanish physician who is considered as “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 has taken place. His treatise Traite des Poisons published in 1814 laid the foundations of 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 on clinical toxicology was “A Practical Treatise on Poisons” written by O Costill, and published in 1848.

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 transmitted his interest to his famous student Claude Bernard (1813-1878) who continued to study of arrow poisons and employed these toxicants to learn more about the mechanism of body functions.

Louis Lewin (1854-1929) was a German scientist who took up 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 e.g. development of dimercaprol (BAL) as an antidote for arsenic and discovery of insecticidal properties of DDT by Paul Hermann Muller in 1939. He was awarded Nobel Prize in 1948 “for his discovery of the high efficiency of DDT as a contact poison against several arthropods”.

Gerhard Schrader (1903-1990) 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, thus, 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”.

1.2.4 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 made the beginning in understanding in depth the nature and mechanism of the effects of poisons and inventions of their specific antidotes. Along with other sciences, toxicology contributes in development of safer chemicals to be used as drugs, food additives, pesticides, industrial chemicals, and several other chemicals required for use in day to day life.

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

1.2.5 After World War II

The mid-1950s witnessed the strengthening of the U.S. 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, updated by the U.S. 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 U.S. 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, as 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 over 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, as well as 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 have been 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, ca. 1890: active anthelmintics from fern, action of croton oil catharsis, poisonous mushrooms
C. Voegtlin, 1923: mechanism of action of As and other metals on the SH groups
K.K.CHEN 1934: demonstrated antagonistic effect of sodium nitrite and sodium thiosulphate in cyanide poisoning
P.M¨uller, 1944–1946: 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"

1.3 Status of Toxicology in India

1.3.1 Professional Organization and Academic Recognition

Toxicology is one among the branches classified into Ayurveda, a comprehensive healthcare system of medicine that has been traditionally practiced in India for more than

5000 years. In India toxicology received the formal recognition as scientific discipline in mid 1900‘s after inclusion as a part of course curriculum in pharmacology and forensic sciences for undergraduate and postgraduate medical students. However, real toxicology research was introduced as a separate identity with the establishment of first Plant Toxicology Research Laboratory at the Indian Veterinary Research Institute, Izatnagar (UP) in the year 1959. In 1960’s the Indian Institute of Toxicology Research (IITR) (formerly: Industrial Toxicology Research Centre), Lucknow, a constituent laboratory of Council of Scientific & Industrial Research, Government of India, New Delhi., concentrated research on industrial toxicology and the National Institute of Occupational Health, a constituent laboratory of Indian Council of Medical Research, New Delhi on occupational health related problems. The broad charter of these Institutes was "Safety to Environment & Health and Service to Industry". To meet the challenges in the field of industrial and environmental toxicology, country has reoriented its programs and focused the efforts not only to identify and monitor the toxicants, but also to predict and prevent risks associated with chemicals and products. Subsequently, with the establishment of Agricultural Universities, toxicology was introduced as a separate discipline in various departments of Pharmacology of Veterinary Colleges/Institutes and forensic toxicology became part and parcel of forensic medicine in Medical Institutes all over in India.

On the other hand, India identified the need of time and took the initiative to facilitate the exchange of ideas, information and knowledge among scientists, practitioners and policy makers working in different research and development areas of environment and occupational health or related areas of toxicology. To meet and achieve this goal and to bring the toxicologists at one platform, Prof P.K.Gupta organized the Society of Toxicology of India (STOX) in 1979. The core activity of STOX is focused to disseminate the scientific data to the masses on adverse effects of pesticides, drugs and chemicals in both target as well as non-target species exposed in environment or in occupational setups. STOX has formed specialty sections and regional chapters to accommodate the scientists involved in toxicology.

STOX is a founder member of the International Union of Toxicology (IUTOX) since 1980. Since its inception, STOX, the society has organized conferences and annual meetings at regular basis apart from the 2nd Congress of Toxicology in Developing Countries in 1991-92. The society now has its own website: *www.http://stoxindia.org*

1.3.2 Published Toxicology Literature

In order to publish the research findings, Prof P.K.Gupta, the author of this book introduced a scientific research Journal ‘Indian Journal of Toxicology’ in 1994 which later on was renamed as ‘Toxicology International’ and served as the founder Editor-in-Chief of the Journal. This research publication covers the entire range of experimental and clinical toxicology of drugs, chemicals and other environmental factors and is published by Medknow Publications Pvt Limited, Mumbai. The journal publishes research, review and general articles besides opinions, comments, news-highlights and letters to the editor. The journal is online and indexed by PubMed. In addition, the journal is being indexed by Biosis Preview, CAB Abstracts, Caspur, Chemical Abstracts, DOAJ, EBSCO

Publishing's Electronic Databases, Genamics Journal Seek, Google Scholar, Index Copernicus, Open J Gate, Primo Central, ProQuest, PubMed, Pubmed Central, SCOLOAR, SCOPUS, SIIC databases, Summon by Serial Solutions, Ulrich's International Periodical Directory, and Zoological Record. Those interested for more details may visit the website: *www.http://toxicologyinternational.com*

Although there is no limit to the information available from other countries, the published literature from Indian authors is very limited. In India individual authors took initiative to prepare teaching material for courses to be taught for those graduating and specializing in the area of toxicology. In the past the author (Dr Gupta) has made attempt to summarize the concepts of toxicology and the most popular book was published in India is a three volume set on "Modern Toxicology". The book was published in 1985 in three volumes. The volume one deals with "Basis of Organ and Reproduction Toxicity", the second "Adverse Effects of Xenobiotics" and the third "Immune System and Clinical Toxicology". Subsequently a book on "Veterinary Toxicology" authored by him appeared in 1988. In view of the demand of the three-set volume on "Modern Toxicology" the 2nd reprint of the book has appeared in 2010.

Many authors contributed other books such as Textbook of Veterinary Toxicology (authored by Dr H.S.Sandhu) published in 2000 and 2nd edition in 2009; Veterinary Toxicology (edited by Dr S.K.Garg) published in 2000; Comprehensive Medical Toxicology (authored by Dr V.V.Pillay) published in 2003 and 2nd edition in 2008.

India has upgraded the skills and expertise, and introduced good laboratory practices in various laboratories in a major way. It is noteworthy that on March 2011, India has been accorded full adherent status for Mutual Acceptance of Data (MAD) by the Organization for Economic Co-operation and Development (OECD) council. As per this provision, all non-clinical studies conducted in a Good Laboratory Practices (GLP) facility approved by the National Compliance Monitoring Authorities of India will be accepted by the OECD member countries and other adhering countries. Currently, India has about two dozen GLP certified toxicology contract research organizations (CRO's) /companies, which are providing toxicological services to the National and International clients involved in Pharmaceutical and Agricultural Product Development. Now there are about two dozen NABL accredited laboratories that speaks of the high standards of toxicology research in India.

Being a GLP member country and otherwise also, there is a need for Board certified toxicologists in the country. With our vast experience, India identified the need of time and took the initiative of convincing the American Board of Toxicology (ABT) to offer Diplomate (ABT examination to award DABT) to deserving candidates in India. Our unstinted efforts convinced the ABT and for the first time outside USA, India conducted the DABT examination in Bangalore in October 2008. The ABT has been very impressed by the enthusiasm and the competence level of the toxicologists in India and has decided to conduct these exams every year in India. As of now, we have about 60 candidates from India, who have successfully passed the DABT examination and we expect this number to increase exponentially in due course of time.

Of more recent origin are toxicologist's effort to introduce full fledged degree courses in Universities and other higher institutes of learning. Now more than three dozen veterinary colleges, several universities such as Jamia Hamdard, New Delhi; CCS University, Meerut; Dyalbagh University, Agra; Post-graduate Institute of Basic Medical Education, Chennai, etc. are the premiere organizations of toxicology research and places for developing skilled toxicologists in the country. Universities and Research organizations have produced a good number of post-graduates and PhD's in toxicology, which constitutes and contributes the bulk of toxicologists in the country. The same colleges also offer postgraduate training in pathology, which ultimately end up in toxico-pathology assessment in most pharma/biotech companies and contract research organizations (CRO's). Moreover facilities in the emerging areas of toxicology for early identification, prediction and prevention of nano-material toxicity, *in silico* toxicology, bioinformatics, and genome and proteome studies have been created and updated in the major research centres in the country. However, we need a good source of infrastructure of animal facilities having global standards. Nevertheless, many of the existing toxicology laboratories do conduct good quality regulatory toxicology work which complies with US EPA, OECD, and FDA guidelines. It is realistic to believe that with increased investment in the infrastructure of animal facilities and the number of increasing DABTs with the return of experienced toxicologists from US /Europe to India, Indian CRO's will become reliable partners for companies from US /Europe who would like to leverage on the India advantage.