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Aquatic Toxicology in Freshwater

The Multiple Biomarker Approach

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Chapter 1
History of Aquatic Toxicology

Arzu Uçar

Abstract The history of toxicology provides a fascinating insight not only into the development of the science of toxicology, but also into its changing approach to disease prevention for the protection of public health. It would not be an exaggeration to say that the knowledge about the toxic/healing properties of minerals, plants, and animals that have shaped civilization for thousands of years, toxic substances and their uses is as old as human history. Throughout the ages, the science of toxicology has provided information that has shaped and guided society, laying the foundations for modern toxicology. The science of toxicology has been built sometimes on the findings obtained as a result of basic experiments, sometimes by chance discoveries. This process, which is similar to other branches of science, has required more emphasis as it affects the health of living things in dimensions leading up to death. This chapter examines the development of the discipline of toxicology and its impact on humanity, highlighting key milestones and discoveries related to toxicology. In addition to shedding light on the beginnings of toxicology, it provides a brief overview of the story of aquatic toxicology up to the present day, taking into account the availability of xenobiotics to aquatic life and the characteristics of the aquatic environment that determine the fate of foreign chemicals within the organism.

Keywords Aquatic toxicology · History · Poison · Freshwater toxicology · Dose

List of Abbreviations

BC	Before christ
FDA	Food and drug administration
IPCS	International program on chemical safety
WHO	World health organization

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PCB	Polychlorinated biphenyls
DDT	Dichloro diphenyl trichloroethane
US EPA	US Environmental Protection Agency
EEC	European economic community
DDT	Diklorodifeniltrikloroetan
APHA	American public health association
ASTM	American society for testing and materials
MAFF	Ministry of agriculture fisheries and food
PARCOM	Paris commission
SETAC	Society of environmental toxicology and chemistry
WRC	Water research centre

1.1 Introduction

Toxicology is defined as the qualitative/quantitative study of the positive/negative effects of physical, chemical and biological agents observed as structural and functional changes in living organisms. While effects can be observed either positively or negatively, this discipline focuses more on negative effects. In the light of the data obtained from research in this field, the protection of all living things, especially humans, from harmful effects is the main purpose and duty of this branch of science. In this branch of study, the determination of the safety of chemical substances developed in the highly improved chemical industry and new ones added every day is also accepted within the job description (Wexler and Hayes 2019). It is a dynamic, developing and predictive science that never loses its relevance despite its long history.

Toxicology has a multidisciplinary backbone with dozens of disciplines such as biology, chemistry, physics, anatomy, physiology, pathology, psychology, zoology, pharmacology, genetics, biochemistry, statistics and mathematics. The purpose of the researcher determines which one(s) of these disciplines will act in common with the properties of the chemical or living organism used and the test methods utilized. When we want to simplify the definition, toxicology can be defined as the study of the interaction of living organisms with substances, toxins, xenobiotics or stressors (Nepovimova and Kuca 2019). A more descriptive definition of toxicology is the study of the nature and mechanisms underlying the direct or indirect toxic effects of substances such as biological, chemical, physical, genetic or physiological agents on living organisms and other biological systems. More specifically, toxicology is concerned with the chemical and physical properties of poisons, their physiological or behavioral effects on living organisms, qualitative/quantitative methods for their analysis in biological and non-biological materials, and the development of procedures for the treatment of poisoning (Wexler and Hayes 2019). Toxicology also deals with the quantitative or qualitative assessment of adverse effects related to the concentration, dosage, duration and frequency of repetition to which organisms are exposed (Lee 2017).

1.1.1 Story of Aquatic Toxicology

The history of toxicology is likely to be as old as human history: The first man had to learn to "distinguish between what is good for food and what is not", to learn about the healing or harmful effects of plants and other materials as he explored his environment and searched for food. He observed that the bites of certain insects/reptiles caused illness or death and found the necessity to avoid them in the first place. The doctrine of not consuming the plant that harmed him or the efforts to destroy the creatures that have negative effects on health can be considered as the foundations of this science. This leads to the idea that knowledge of animal poisons and plant extracts probably predates recorded history (Wexler 2014).

1.1.2 Middle Ages

When the recorded history of toxicology is investigated, it is seen that 'hemlock', a plant-based poison, was used as an official state poison in ancient Greeks. In addition, it is found in written sources that Socrates (470–399 BC) was sentenced to death with "hemlock". In 132–163 BC, experiments on prisoners in the Pontic state of Pontus led to the discovery of an antidote to a wide range of toxic substances and experimentally demonstrated that humans became immune to it.

In the continuation of the written records of the science of toxicology, it has been observed that the first law for poisons was drafted in Ancient Rome, called "Lex Cornelia" (82 BC) (Sánchez 2014). It is seen that lead poisoning was observed by the lead-lined cistern and pipes contaminating drinking water by the architect Vitrivius Pollio (80–70 BC), and the potential health hazards of mining were reported for the first time in history.

Ibn Sina's "Kitab al Kanun Fit Tibb" (known as Avicenna in the West), an important step in the history of toxicology, mentions important antidotes against different poisonings (3). The Ebers Papyrus (1500 BC), one of the oldest known records, contains information on many known poisons, including plants such as hemlock, aconite, opium and metals such as lead, copper and antimony. The Book of Job (ca. 1400 BC) mentions poisoned arrows (Job 6:4), while Hippocrates (400 BC) introduced many poisons, adding a number of principles of poison and clinical toxicology related to therapy and bioavailability in overdose. In addition, he reported the occurrence of poisoning in workers working in lead mines and laid the foundation of industrial toxicology by revealing the relationship between lead poisoning and occupational diseases.

Poisons identical to today's arsenic were made, such as Cantarella, allegedly used during the reign of Pope Alexander VI and made by the Borgias, a medieval family, and these poisonings are reported to have been very important in the social and political life of Italy. Catherine de Medici was another important figure who practiced poisoning methods in Italy (Preziosi et al. 2003).

Mattieu Joseph Bonaventura Orfila (1787–1853), recognized as the founder of modern toxicology, was the first to explain the relationship between the chemical and biological properties of poisons. In his work "Traite de toxicologic", there is information revealing that poisons are collected in many organs after being absorbed from the digestive system. Orfila, who developed many methods for the identification of toxic substances, also emphasized the relationship between chemistry and forensic medicine, two different disciplines, in his work "Legons de medecine Legale". This research was the first time that "analytical toxicology" and "forensic toxicology" were clearly defined. Orfila's research and books have been taught in the field of forensic medicine all over the world and his "A Treatise on Poisons" has been published many times in Europe and America (Vural 2005).

Theophrastus (370–286 BC), a student of Aristotle, made numerous references to poisonous plants in De Historia Plantarum. Dioscorides, a Greek physician at the court of the Roman emperor Nero, made the first attempt to classify poisons into plant, animal and mineral poisons in his De Materia Medica, which refers to about 600 plants.

Although the history of poisons dates back to the earliest times, the science of toxicology has important traces of Paracelsus (1493–1541) and Orfila (1757–1853). The sixteenth-century physician Paracelsus (1493–1541), who was clearly aware of the dose–response relationship, wrote: "All substances are poison, the difference between medicine and poison is the dose. He has a determination that states, "The right dose separates the poison from the drug". With this determination, he revealed that the "therapeutic" and "toxic" properties of the chemical substance should be separated. Paracelsus claimed that specific chemicals are actually responsible for the toxicity of a plant or animal poison, that there is no non-toxic substance in the world where the therapeutic and toxic properties of substances cannot be distinguished down to a single parameter, namely the dose (Nepovimova and Kuca 2019). This assumption is still one of the pillars of modern toxicology. It also revealed that the body's response to these chemicals depends on the dose taken, that low doses of a substance can be harmless or even beneficial, while larger doses can be toxic, which points to the dose–response relationship (hormesis) known in toxicology (Öztürk et al. 2022).

The foundations of the development of toxicology as a distinct branch of science were laid in the eighteenth and nineteenth centuries. The detection of poisons started with the investigation of the toxic effects of drugs and chemicals in animals. The mystical approach to poisons was replaced by a scientific and realistic approach and was first systematized by Matthieu Orfila (1787–1853) in the nineteenth century. Accordingly, the functions of the toxicologist have traditionally been to identify poisons, search for antidotes and other ways of treating toxic injuries (Britannica 2018). In the late eighteenth century, Matthieu Joseph Bonaventure Orfila, a Spanish physician working at the University of Paris, first produced a systematic correlation between the chemical and biological properties of the poisons of the time. Using autopsy materials for poisons and associated tissue damage, he demonstrated the effects of toxic substances and compounds on specific organs. He stated that research of this scale is too important to be left to people who do not have sufficient knowledge and experience, and emphasized that toxicology should be a separate science (Langman and Kapur 2006).

Research on the analysis of arsenic, the most widely used poison of the 1700s, formed the basis of analytical toxicology. During this period, research into the mechanisms of toxic action was concentrated in France and Germany. Froncois Magendie (1783–1855) investigated the mechanisms of action of emetine, strychnine and cyanide, and his student Claud Bernard (1813–1878) conducted important research to understand the mechanisms of action of carbon monoxide and curare.

Louis Lewin (1850–1929) was the first scientist to emphasize the difference between the pharmacological and toxicological mechanisms of drugs.

By the 1800s, Louis Lewin (1850–1929) was the first scientist to emphasize the difference between the pharmacological and toxicological mechanisms of drugs. After these years, toxicology was acknowledged as a science and toxic effects mechanisms such as acute and chronic toxicity, neurotoxicity, selective toxicity, internal effects of radioactivity were started to be studied by Carl Voegtlin et al. (1923) and Rudolf Peters et al. (1945). Biological effect (dose–response) relationship has also started to be evaluated by examining drugs and chemical substances in blood and urine. With the introduction of instrumental analysis into toxicology, analysis of substances and compounds in tissues and other biological materials began in the 1940s. In this period, developments in the field of toxicology enabled toxicology to work together with other disciplines and continued to develop until today.

More than 2000 years ago, Aristotle studied the effect of salinity by placing freshwater animals in seawater. This experimental practice was later considered as a toxicity study. With this study, the effect of a substance on an organism aroused the curiosity of many physiologists. However, mankind first used chemicals and then studied their effects. Although the harmful effects of these substances on many organisms are known, toxicity studies in the disciplinary sense were not recorded much until the 1940s and 1950s. Before World War II, some researchers studied the toxic effects of metals, especially in fish. After the war, many toxicity laboratories were established in England, the United States and Canada.

Investigations of toxic effects at the molecular level and the explanation of the mechanisms of chemical carcinogenesis are seen in the 1940s. Miller identified mixed function oxidases in the endoplasmic reticulum and started research on cytochrome p450 oxidase enzymes. In 1947, Williams published "Mechanisms of Detoxication" in which he described the many mechanisms involved in the detoxification of toxins. In the United States, the Food and Drug Administration (FDA) legalized a toxicology and safety assessment program in 1955 to ensure the safety of food, drugs and cosmetics. The 1960 "thalidomide disaster" brought to the forefront the importance of toxicological research in pharmaceuticals.

In parallel, WHO initiated the publication of an International Program on Chemical Safety (IPCS) and a series of Environmental Health Criteria, and organochlorine insecticides were recognized in the 1960s as contaminants of water systems worldwide in the chromatograms of environmental analyses (Vasseur et al. 2021). With this regulation, the classification of pollutants has been formalized and a serious record has been kept on the issues to be complied with.

These negativities have shown that the studies to be carried out by this branch of science will be prepared worldwide. These events, which are defined as negative, have been positive for the toxicology discipline and have revealed areas of study. The effects of mercury, cadmium and PCB poisoning on humans in Japan, the observation of toxic effects due to DDT (dichloro diphenyl trichloroethane) in birds and fish in the Great Lakes region of North America (Peakall 1994), ecotoxicology, which developed with the pollution of the environment by industrial and agricultural pollutants (Ramade 1992), revealed the first evidence in the 1960s (Narbonne 2021). This area of work has contributed to raising awareness of the environmental trajectories and impacts of pollutants and the negative side effects of the chemicals used.

The environmental science book “Silent Spring” written by Rachel Carson in 1962 focused on the effects of pesticides, ecological problems, pollution of surface and ground water, inadequate water treatment facilities, persistence and transfer of chlorinated hydrocarbons, the use of natural products for biological control, human safety and the harm of pesticide resistance on target organisms. Focusing on water pollution, this book’s explanations of pesticide impacts on a broad scale have brought what was known to environmentalists to the forefront of the political, commercial, scientific and public sectors of society and, despite controversy, have had a long-lasting impact (Rattner 2009).

The first decade of the 1970s spurred a strong international mobilization for pollution prevention, regulation and research. The US EPA (US Environmental Protection Agency) was established in 1970, Environment Canada in 1971, leading to the banning of most organochlorine insecticides by the EPA in 1972. By Decision of December 21, 1978, the European Economic Community (EEC) issued EEC Directive 79/117/CEE banning (as of 01/01/1981) phytosanitary products containing aldrin, dieldrin, chlordane, DDT, endrin, heptachlor, hexachlorobenzene, alkyl and aryl. At the same time, EEC Directive 79/831/CEE amending the 6th Directive 67/548/CEE on the classification and labeling of chemicals addressed the regulation requiring a notification dossier for new chemical substances since September 18, 1981.

After the 1970s, environmental pollutants came to the forefront of toxicology and a war on toxic substances was initiated by an environmental law in the United States. In the late 1970s and early 1980s, toxicity studies increased tremendously, and the American Public Health Association (APHA), the American Society for Testing and Materials (ASTM), the U.S. Environmental Protection Agency (U.S. EPA), the U.S. The U.S. Army Corps of Engineers of Materials the UK Ministry of Agriculture Fisheries and Food (MAFF), the Paris Commission (PARCOM), the Society of Environmental Toxicology and Chemistry (SETAC) and the Water Research Centre (WRC) have developed a range of standard methods.

1.1.3 *The Story of Toxicology's Subdivision*

Chemical ecology and ecotoxicology is the field of research that emerged between the 1950s and 1970s following increased awareness of information or chemicals that affect biotic interactions or the ecological and ecosystem consequences of anthropogenic pollutants.

How hazardous chemical, biological and physical agents occurring in soil, air and water environments can affect individual living organisms is the central question of Environmental Toxicology, a multidisciplinary scientific field. Similarly, the effects of such agents on individuals, populations, communities and ecosystems form the basis of the multidisciplinary field of Ecotoxicology, which integrates ecology and toxicology and is a sub-discipline of Environmental Toxicology. Therefore, questions about the meaning of the word "clean" are a major challenge for Environmental Toxicology and Ecotoxicology. Toxicological predictions of both research fields are of great importance for national economies and ecological sustainability (Agathokleous and Calabrese 2020).

Metals, pesticides and personal care products are among the most emphasized pollutants that can interfere with the chemical ecology of organisms. Given the widespread environmental pollution of the Anthropocene epoch, it seems important to consider disturbances such as "information pollution" in environmental risk assessment. A wide range of anthropogenic or natural pollutants are involved in biotic interactions as they mediate this degradation. Chemical ecology can provide new response factors that can help determine the non-lethal effects of pollutants. Furthermore, discovering natural, non-toxic alternatives to currently used biocides can help with risk management. The link between both disciplines should be strengthened, as both are already multidisciplinary fields and developing common themes between chemical ecology and ecotoxicology can provide a deeper understanding of ecological processes. It could also help to achieve the objective of the 2020 European chemicals strategy for sustainability towards a non-toxic environment (Gross 2022).

1.1.4 *Modern Toxicology*

Modern toxicology is characterized by sophisticated scientific research and assessment of toxic exposures. As the chemical industry develops new chemicals, this branch of science will continue to develop in a wide range of fields. Modern toxicology has led to the discovery of DNA and various biochemicals that maintain cellular functions, and has sought to expand knowledge of toxic effects on organs and cells. From this point of view, it is recognized that almost all toxic effects are caused by changes in specific cellular molecules and biochemicals. Toxic agents are classified in various ways and there is no single classification that applies to the entire spectrum of toxic substances. Therefore, purpose-built classification systems and their combinations may provide the best system (Gupta and Gupta 2020).