

Fish Toxicology

Introduction

- ✓ Toxicology is the 'science of poisons'.
- ✓ Poisons are defined as naturally occurring or man-made chemicals, which, following their entry via any route and in relatively small quantities into the body, produce biochemical abnormalities and/or physical lesions. Poisons are also known as toxicants or toxic agents.
- ✓ Like medicine, toxicology is both a science and an art.
- ✓ The science of toxicology is the phase involving observational and data-gathering, while the art of toxicology consists of utilization of data to arrive at the outcome to exposure in human and animal populations.
- ✓ A more descriptive definition of toxicology can be 'the study of the adverse effects of chemicals or physical agents on living organisms and the ecosystems, including the prevention and amelioration of such adverse effects.
- ✓ Toxicology is concerned with all aspects of poisons and poisoning.
- ✓ It includes the identification, chemical properties and biological effects of poisons as well as the treatment of disease conditions they cause.
- ✓ The science of toxicology helps people make informed decisions and balance **Risks vs. Benefits.**
- ✓ Toxin is the word reserved to poisons produced by a biological source like venoms and plant toxins.

- ✓ Toxins from plants are called phytotoxins. Toxins from bacteria are called bacterial toxins. Endotoxins are those toxins found within the bacteria and exotoxins are those toxins elaborated from bacterial cells. Toxins from fungi are called mycotoxins. Toxins from lower animals are called as zootoxins. Toxins that are transmitted by a bite or sting are called venoms.
- ✓ Toxinology deals with the study of toxic effects of toxins.
- ✓ Toxicity is the term used to describe the amount of a poison that, under a specific set of conditions causes toxic effects or results in detrimental biologic changes. It is the inherent capacity of a substance to produce toxic effects or detrimental changes on the organism. Toxicity is the adverse end product of a series of events that is inhibited by exposure to chemical, physical or biological agents. Toxicity can manifest itself in a wide array of forms, from mild biochemical functions to serious organ damage and death.
- ✓ Toxicosis is the term used to describe the condition resulting from exposure to poisons. This term is frequently used interchangeably with poisoning and intoxication.
- ✓ Three phases under which toxicology is studied are:
 - Exposure phase,
 - Toxicokinetic phase and
 - Toxicodynamic phase

Branches of Toxicology

- ❖ **Aquatic Toxicology** deals with the study of adverse effects of chemicals or physical agents on aquatic living organisms and the aquatic ecosystems, including the prevention and amelioration of such adverse effects.
- ❖ **Fish Toxicology** is the branch of aquatic toxicology that exclusively deals with the poisons causing toxicity in fish, shell fish and other aquatic organisms.
- ❖ **Immunotoxicology** - This branch deals with toxins that impair the functioning of the immune system - for example, the ability of a toxicant to impair resistance to infection.
- ❖ **Forensic toxicology** - It is the study of unlawful use of toxic agents and their detection for judicial purposes. Forensic toxicology is concerned with the medicolegal aspects of the adverse effects of chemicals on humans and animals. Although primarily devoted to the identification of the cause and circumstances of death and the legal issues arising there from, forensic toxicologists also deal with sublethal poisoning cases.
- ❖ **Molecular Toxicology** - Molecular toxicology focuses on why and how chemicals cause harm to life. The basis of cellular and molecular processes leading to toxic effects is studied under molecular toxicology.
- ❖ **Clinical Toxicology** – It is the study of the effects of poisons/toxicants on human beings, animals and other living organisms, their diagnosis and treatment and methods for their detection etc.
- ❖ **Nutritional Toxicology** – It is the study of toxicological aspects of food/feed stuffs and nutritional habits.
- ❖ **Environmental Toxicology** – It is the study of the effects of toxicants, whether used/applied purposely (e.g. pesticides, herbicides) or as industrial effluents or pollutants/contaminants, on the health of organisms and environment.
- ❖ **Analytical Toxicology** – It is the application of analytical chemistry tools in the quantitative and qualitative estimation of the agents involved in the process of toxicity.
- ❖ **Occupational Toxicology** – It is the study of occupational hazards associated with individuals working in a particular industry/occupation and their correlation with the possible toxicants and also the possible remedial measures.
- ❖ **Ecotoxicology** – It is the study of fate and effects of toxic substances on ecosystem.

- ❖ **Regulatory Toxicology** – It is the conduct of toxicological studies as per the content and characteristics prescribed by regulatory agencies.
- ❖ **Developmental Toxicology** – It is the study of adverse effects on the developing organisms occurring any time during the life span of the organism due to exposure to chemical or physical agents before conception (either parent), during prenatal development or postnatal until the time of puberty.
- ❖ **Toxicoepidemiology** – This refers to the study of quantitative analysis of the toxicity incidences in organisms, factors affecting toxicity, species involved and the use of such knowledge in planning of prevention and control strategies.
- ❖ **Toxinology**, a specialized area of study, looks at microbial, plant and animal venoms, poisons, and toxins.

Toxicant, toxin, and poison are often used interchangeably in the literature but there are subtle differences as shown below:

Toxicants	Toxins	Poisons
Substances producing adverse biological effects of any kind.	Peptides or proteins produced by living organisms.	Toxins produced by organisms
May be chemical or physical in nature.	Venoms are toxins injected by a bite or sting.	---
Effects may be acute or chronic	---	---

Some Important Terminologies

- ✚ **Lethal Dose (LD)**: This is the dose resulting in the death of an organism.
- ✚ **Effective Dose (ED)**: This is the desired response which is observed at the dose tested. Also, it can be a therapeutic dose.
- ✚ **Toxic Dose**: Dose at which toxicity is observed.
- ✚ **Acute Toxicity**: Toxicity elicited immediately after exposure (generally refers to a single dose).
- ✚ **Chronic Toxicity**: Toxicity caused by long-term exposure to a toxic substance (generally by multiple doses).
- ✚ **No Adverse Effect Level (NOAEL)**: Highest dose level where no adverse effect is observed.
- ✚ **Lowest Observed Adverse Effect Level (LOAEL)**: Lowest dose level that produces a statistically significant effect.

Major Disasters

- ❖ **Ergotism in France and Spain in 992 AD/CE:** Ergot poisoning or ergotism was known as 'holy fire'. The term 'fire' was used because of the burning sensations in the extremities that was experienced by the individuals showing gangrenous ergotism and the term 'holy' was used as it was feared to be punishment from God. Later ergotism was referred to as St. Antony's fire. More than 40,000 people died of ergotism.
- ❖ **Nuclear Bomb Explosions in Japan in 1945:** During the final stages of World War II in 1945, the United States conducted two atomic bombings against the cities of Hiroshima and Nagasaki in Japan, the first on August 6, 1945 and the second on August 9, 1945. Within the first two to four months of the bombings, the acute effects killed 90,000 – 166,000 people in Hiroshima and 60,000 – 80,000 in Nagasaki. Of the people who died on the day of the explosion, 60% died from flash or flame burns, 30% from falling debris and 10% from other causes. During the following months, large numbers died from the effect of burns, radiation sickness and other injuries.
- ✚ **Nuclear accident in Pennsylvania or the Three Mile Island accident** was a core meltdown in a Unit of the Three Mile Island Nuclear Generating Station in Pennsylvania in United States in 1979. It was the most significant accident in the history of the USA commercial nuclear power generating industry, resulting in the release of approximately 2.5 million curies (Ci) of radioactive gases, and approximately 15 curies (Ci) of ^{131}I (The units to measure the intensity of radioactivity are the curie (Ci) and becquerel (Bq). This value refers to the amount of ionizing radiation released when an element (such as uranium) spontaneously emits energy as a result of the radioactive decay of an unstable atom. 1 Ci is equal to 3.7×10^{10} disintegrations per second)
- ❖ **Bhopal gas tragedy:** The Bhopal disaster also known as Bhopal Gas Tragedy was one of the world's worst industrial catastrophes. It occurred on the night of December 2–3, 1984 at the Union Carbide India Pesticide Plant in Bhopal, Madhya Pradesh, India. A leak of methyl-isocyanate gas and other chemicals from the plant resulted in the exposure of hundreds of thousands of people. Estimates vary on the death toll. The official immediate

death toll was 2,259 and the Government of Madhya Pradesh has confirmed a total of 3,787 deaths related to the gas release.

- ❖ **Chernobyl nuclear accident:** The Chernobyl disaster was a nuclear accident that occurred on 26 April 1986 at the Chernobyl Nuclear Power Plant in Ukraine. An explosion and fire released large quantities of radioactive contamination into the atmosphere, which spread over much of Western USSR and Europe. It is considered the worst nuclear power plant accident in history. From 1986 to 2000, 350,400 people were evacuated
- ❖ **Japan nuclear reactor crisis:** Nuclear crisis in Japan occurred recently due to floods and damage to nuclear reactors. The Fukushima disaster is the largest of the nuclear accidents and is the largest nuclear accident since the 1986 Chernobyl disaster, but it is more complex as multiple reactors and spent fuel pools are involved.
- ❖ **Sulfur mustard gas Poisoning:** This is an alkylating agent, first used in the first world war. Since then it has also been used in other conflicts, most recently in the Iran-Iraq war. The numbers affected are unknown. It damages skin and mucus membranes and damage to the eyes and respiratory tract can be profound and long lasting. However, it has also caused problems apart from military use. Following the second world war, some 100 000 tons of mustard gas bombs were deposited in the Baltic Sea. Periodically fishermen have suffered from mustard gas poisoning as the bombs have resurfaced in their nets. By 1985, 197 fishermen had been affected, 26 had required hospital admission and two had died.
- ❖ **Arsenic Poisoning:** Probably the largest environmental disaster to date involved 35–77 million people living in Bangladesh and West Bengal. In Bangladesh surface water supplies have been contaminated with microorganisms causing significant morbidity and mortality. During the 1970s in an attempt to circumvent this problem, the United Nations Children's Emergency Fund (UNICEF) worked with the Department of Public Health Engineering to insert tube wells to give a safe source of drinking water to the population. In 1983 the first cases of arsenic induced skin lesions were identified. Since then thousands of such cases have been identified in the exposed population. The incidence of internal

cancers, particularly those affecting the bladder, genitourinary tract, and lungs, is expected to rise sharply. These tumors have a long latency.

- ❖ **Fluoride poisoning:** Fluoride poisoning occurs within Northern Africa, the Rift Valley system, and in an area extending from Turkey to China. Poisoning usually results from high concentrations of fluoride occurring naturally in the drinking water. Concentrations of fluoride greater than 10 mg/l in drinking water are considered harmful. This has led to skeletal fluorosis and associated skeletal abnormalities. The problem is often compounded by concomitant malnutrition.
- ❖ **Methyl mercury Poisoning:** The initial cohort was four patients in **Minamata** Bay, Japan in 1956 with an unusual neurological disease, initially thought to be an infectious disorder. Further investigation revealed a link to mercury ingestion. Inorganic mercury was used by a local chemical plant as a catalyst in the production of acetaldehyde (though no responsibility was admitted until 1968). Mercury was discharged in the factory's effluent collecting at the bottom of Minamata bay where it was concentrated and bio-transformed to organic mercury by *Venus japonica* and other local shellfish. By a process of biomagnification, the methylmercury accumulated in increasing amounts in predatory fish, to poison local fisherman whose diet consisted almost entirely of what they had caught in the bay. Symptoms typically consisted of ataxia, constriction of visual fields, and impairment of speech, hearing, and gait. Exposure to the problem was widespread, involving up to 50 000 people, with over 2000 of them having certified Minamata disease. In addition, there were 28 congenital cases with a syndrome resembling cerebral palsy and an associated IQ below 75, as well as an unknown number of spontaneous abortions.
- ❖ **Cadmium Poisoning: Itai-Itai (Ouch-Ouch)** disease consists of chronic bone pain (osteomalacia) and renal disease (renal tubules show pronounced atrophy and degeneration) and was first reported in Toyama, Japan in the 1960s.¹⁶ In 1968 the Japanese Ministry of Health attributed it to cadmium poisoning, after it was concluded that the Jinzu River was polluted from mines and zinc refineries. The local population used the water to

irrigate their rice fields, contaminating the rice with cadmium. Numerous cases of chronic cadmium poisoning have been reported.

- ❖ **Mercury Poisoning:** Gold mining and refining using elemental mercury is a major industry in the Brazilian Amazon basin. It is estimated that 100 tons of mercury are released annually. Significant levels of both elemental mercury (from the heating of gold–mercury amalgams) and organic mercury (in river effluents following biotransformation) have been found. This has led to a significant increase in mercury concentrations in both miners and the local fishing population.
- ❖ **Polychlorinated Bi-phenyls Poisoning:** The **Yusho** (oil disease) epidemic affected up to 1850 people on the island of Kyusho, Japan in 1968. Rice oil was contaminated by polychlorinated biphenyls during its manufacture. The syndrome was probably caused by related polychloroquarterphenyls and polychlorodibenzofurans which formed when the oil was fried. The predominant symptoms were chloracne. Some children born to affected mothers showed evidence of contamination with stained skin and low birth weights; however overall mortality of those exposed over the next 15 years did not increase significantly.

Scientists Associated with Toxicology



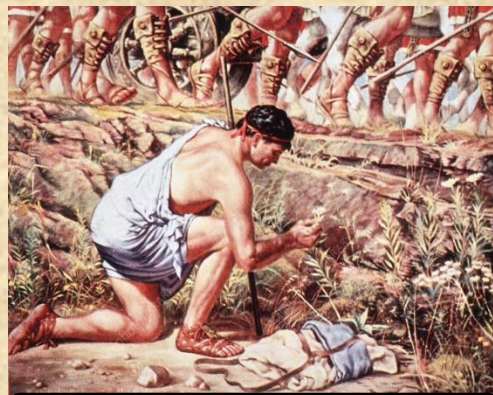
Credit: Science History Institute, USA

❖ **Paracelsus:** Paracelsus (*Philippus Aureolus Theophrastus Bombastus von Hohenheim*) determined that specific chemicals were actually responsible for the toxicity due to a plant or animal poison. He documented that the body's response to those chemicals was based on the dose received studies. He also revealed that small doses of a substance might be harmless or beneficial whereas larger doses could be toxic, thus explaining the dose-response relationship, a major concept of toxicology. He is often quoted for his statement "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy". His views which hold good even today include:

- ✓ Experimentation is essential in the examination of responses to chemicals
- ✓ One should make a distinction between the therapeutic and toxic properties of chemicals
- ✓ These properties are sometimes but not always indistinguishable except by dose
- ✓ One can ascertain a degree of specificity of chemicals and their therapeutic or toxic effects.

❖ **Emil Mark** has also stated that "There are no harmless substances. There are only harmless ways of using substances."

❖ **Pedanius Dioscorides (40-90 AD):** Dioscorides was a Greek physician, pharmacologist, botanist, and author of *De materia medica*, a 5-volume Greek encyclopedia about herbal medicine and related medicinal substances ((a pharmacopeia) which made a significant contribution to toxicology by classifying poisons as animal, plant or mineral. He also recognized the value of emetics in the treatment of poisoning.



Credit: National Library of Medicine / Science Photo Library, USA



Credit: National Library of Medicine, USA

❖ **M.J.B Orfila:** Mathieu Joseph Bonaventure Orfila, a Spanish physician, is often referred as founder of modern toxicology. It was Orfila who first prepared a systematic correlation between the chemical and biological properties of poisons of the time. He demonstrated effects of poisons on specific organs by analyzing autopsy materials for poisons and their associated tissue damage and also laid the base for forensic toxicology.

❖ **Francois Megendie:** Megendie, M.J.B. Orfila and Bernard promoted experimental toxicology. Orfila laid the foundation for forensic toxicology. Megendie discovered the mechanism of action of emetine, strychnine and arrow poisons.

❖ **Claude Bernard** discovered the mechanism of action of curare and carbon monoxide.

Incidents of Importance in History of Toxicology

- ❖ The early cave dweller recognized poisonous plants and animals and used their extracts for hunting or in warfare.
- ❖ By 1500 B.C, written recordings like *Ebers papyrus* indicated that hemlock, opium, arrow poisons and certain metals were used to poison enemies or for state executions.
- ❖ Poisons such as arsenic, aconite and opium were also known to Hindu medicine as recorded in the Vedas.
- ❖ The ancient Chinese used aconite as an arrow poison.
- ❖ Greeks, Romans and Italians used poison for execution and murder of their political opponents.
- ❖ Socrates was charged with religious heresy and corrupting the morals of local youth and was executed with extract of hemlock (*Conium maculatum*) and Greeks recognized hemlock as the state poison. The active chemical in hemlock was the alkaloid coniine which, when ingested causes paralysis, convulsions and eventually death.



The Death of Socrates (Socrates drinking poison Hemlock); Credit: Jacques-Louis David, 1787

- ❖ Demosthenes committed suicide by consuming a poison hidden in his pen.
- ❖ Cleopatra, the Queen of Egypt experimented with strychnine and other poisons on prisoners and poor. She committed suicide with Egyptian Asp (Egyptian cobra sometimes used in executions).



Cleopatra - Queen of Egypt (69-30 BC); Credit: Gerard de Lairese (1640-1711)

- ❖ King Nero used poisons to eliminate his stepbrother Britannicus and employed his slaves as food tasters to differentiate edible mushrooms from their more poisonous kin.



Mithridates VI Eupator, King of Pontus; Credit: Dr. Peter Heather

- ❖ King Mithridates VI of Pontus, was afraid that he would be assassinated by his enemies. He used his prisoners as guinea pigs to test the poisons. He started taking antidotes for many poisons. He consumed a mixture containing about 36 ingredients. But, when he was caught by his enemies and wanted to commit suicide, he could not do so and he took the help of one of his slaves to stab himself to death. The term mithridatic (meaning antidote) is derived from his name.

- ❖ A lady named *Toffana* prepared arsenic containing perfumes and such cosmetics were named as **Aqua toffana**. These perfumes were used to kill enemies.
- ❖ In France, a lady named *Catherine de Medici* along with *Marchioners de Brin villen* used most effective poisons in the name of providing treatment to sick and poor people. Later she was imprisoned for killing 2000 infants.

Historical Developments

❖ Historical developments in toxicology during various periods

- ✓ Antiquity
- ✓ Middle Ages
- ✓ Age of enlightenment
- ✓ Modern Toxicology
- ✓ After World War II

Antiquity / Ancient Past



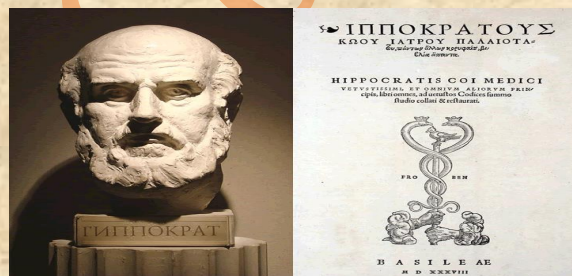
Illustration of Shen Nung, produced in the 18th century AD;
Credit: Junzi Lan, Minghui.org

❖ **Shen Nung** (2696 BC) the father of Chinese medicine which can be variously translated as "Divine Farmer" or "Divine Peasant", "Agriculture God", also known as the **Wugu Shen** is noted for tasting 365 herbs and he died of a toxic dose and wrote treatise on 'Herbal Medical Experiment Poisons'.

Homer (about 850 BC) wrote of the use of arrows poisoned with venom in the epic tale of 'The Odyssey' and 'The Iliad'.



Homer 850 BC; Credit: Biography.com



Credit: <https://medicalltourismgreece.com/hippocrates>

❖ **Hippocrates** (460-337 BC) in his writings (400 BC) showed that the ancient Greeks had a professional awareness of poisons and of the principles of toxicology, particularly with regard to the treatment of poisoning by influencing absorption.

- ❖ **Theophrastus** (370–286 BC), a student of Aristotle, included numerous references to poisonous plants in '*De Historia Plantarum*'.
- ❖ **Nicander of Colophon** (185-135 BC), physician to Attalus, King of Bythnia, was allowed to experiment with poisons using condemned criminals as subjects. As a result of his studies he wrote a treatise on '*antidotes to poisonous reptiles and substances*' and mentioned 22 specific poisons including white lead, lead oxide, aconite, cantharides, hemlock, hyoscyamus and opium. He recommended linseed tea to induce vomiting and sucking the venom from the bite of a venomous animal as treatments.
- ❖ **Sulla** (82 BC): The first known law against poisoning was issued in Rome by Sulla in 82 BC to protect against careless dispensing. The law prevented people from buying, selling or processing poisons.



Credit: <http://beaverland.web.fc2.com/hist/glance/sulla.html>



Credit: <http://exhibits.hsl.virginia.edu/treasures/>

- ❖ **Pedanius Dioscorides** (40-90 AD): The Greek physician *Dioscorides* made a particularly significant contribution to toxicology by classifying poisons as animal, plant or mineral and recognizing the value of emetics in the treatment of poisoning. The classification was accompanied by descriptions and drawings.

Middle Ages

- ❖ The writings of **Maimonides** (AD 1135–1204) included a treatise on the treatment of poisonings from insects, snakes and mad dogs. His '*Treatise on Poisons and Their Antidotes*' is an early toxicology textbook that remained popular for centuries. Maimonides also refuted many of the popular remedies of the day and stated his doubts about others.
- ❖ During the middle ages more of misuse of poisons to kill enemies was on the rise.

Age of Enlightenment

- ❖ More recently, in 1945, Sir Rudolph Peters studied the mechanism of action of arsenical war gases and so was able to devise an effective antidote known as British Anti-Lewisite for the treatment of soldiers exposed to these gases.

Modern Toxicology

- ❖ It is a continuation of the development of the biological and physical sciences in the late nineteenth and twentieth centuries.
- ❖ During this period the world witnessed an explosion in science that paved way for the beginning of the modern era of various aspects of science.
- ❖ The introduction of ether, chloroform, and carbonic acid led to several iatrogenic deaths.
- ❖ These unfortunate outcomes spurred research into the causes of the deaths and early experiments on adverse and toxic effects.

After World War II

- ❖ The 20th century is marked by an advanced level of understanding of toxicology.
- ❖ DNA (molecule of life) and various biochemicals that maintain body functions were discovered.
- ❖ Our level of knowledge of toxic effects on organs and cells is now being revealed at the molecular level.
- ❖ It is recognized that virtually toxic effects are caused by changes in specific cellular molecules and biochemical moiety.