ACUTE TOXICITY

MECHANISMS

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Toxicity

- Toxicity is a relative term generally applied in comparing one chemical with another.

- According to Theophrastus Phillipus,
  " All chemical substances are poisons, there is no chemical substance that is not poison"

- Toxicity of a chemical may be defined as the capability to cause injury in a living organism. A highly toxic substance is that which causes damage to an organism if administered in a very small amount. But a substance of low toxicity will not produce an effect unless the amount is very large.

- Toxicity can be of two types : Acute Toxicity and Chronic Toxicity

Acute Toxicity

Acute Toxicity is defined as "the adverse effect occuring at any time within the duration of 72 hours after the intake of any drug or as a result of short term exposure to a toxicant".
Newly developed drug, acute toxicology testing may be performed in animals, Data generated from such studies can be used to determine and identify the potential toxicity of a chemical to human.

- The acute toxicity of a chemical is commonly quantified as the **LC50** or **LD50**.
- However, **LC50** and **LD50** values do provide statistically sound, reproducible measures of the relative acute toxicity of chemicals.
- Acute toxicity of environmental chemicals is determined experimentally with select species that serve as representatives of particular levels of trophic organization within an ecosystem (i.e., mammal, bird, fish, invertebrate, vascular plant, algae).

LD50 and LC50

LD50 : LD stands for **"Lethal Dose"** is the statistically derived single dose of substance I.e., estimated to cause death in 50% of the population of animals who were exposed to that substance.

- **LD50** is one way to measure the short term poisoning potential (acute-toxicity) of a material.
- In 1927, J W Trevan attempted to find a way to estimate the relative poisoning potency of drugs and medicines used at that time
- Most often testing is done with rats and mice.
- Usually expressed as the amount of chemical administered(eg., miligrams) per 100 grams (for smaller animals) or per kilograms (for bigger test subjects) of the body weight of the test animal.
- LD50 can be found for any route of entry or administration but dermal (applied to the skin) and oral (given by mouth) administration methods are the most common.

LC50 : LC stands for **"Lethal Concentration"** values usually refer to the concentration of a chemical in air but in environmental studies It can also mean the concentration of a chemical in water.

- According to the OECD, guidelines for the testing of chemicals, a traditional experiment involves groups of animals exposed to a concentration for a set period of time (usually 4 hours).
- The animals are clinically observed for upto 14 days
- The concentration of the chemicals in air that kills 50% of the test animals during the observation period is the LC50 value

Mechanisms of Acute Toxicity

Mechanisms that are particularly relevant to the types of chemicals that are more commonly responsible for acute toxicity in the environment at the present time.

- **Cholinesterase Inhibition**
- **Narcosis**
- **Simple asphyxiants**
- **Chemical asphyxiants**
- **Central Nervours System (CNS) Depressants**
- **Skin Effects**
- **Chemical Sensitisation**
- **Lungs Sensitisation**
- **Eye Effects**

Cholinesterase Inhibition

- The inhibition of cholinesterase activity is characteristic of acute toxicity associated with organophosphate and carbamate pesticides.
- 40 to 80% inhibition of brain cholinesterase activity is typically reported in lethally poisoned fish.
- Acute toxicity resulting from cholinesterase inhibition is relatively common among incidents of acute poisoning of fish and birds due to the high volume usage of organophosphates and carbamates in applications such as lawn care, agriculture, and golf course main tenance.
- Cholinesterase inhibition in fish may occur following heavy rains in aquatic habitats adjacent to areas treated with the pesticides and subject to runoff from these areas.
- Acute toxicity to birds commonly occurs in birds that feed in areas following application of the pesticides.

Narcosis

- A common means by which industrial chemicals elicit acute toxicity, par- ticularly to aquatic organisms, is through narcosis.
- Narcosis occurs when a chemical accumulates in cellular membranes interfering with the normal function of the mem- branes.
- Typical responses to the narcosis are decreased activity, reduced reaction to external stimuli, and increased pigmentation (in fish).
- The effects are reversible, and nonmoribund organisms typically return to normal activity once the chemical is removed from the organism’s environment. Prolonged narcosis can result in death.
- Approximately 60% of industrial chemicals that enter the aquatic environment elicit acute toxicity through narcosis. Chemicals that elicit toxicity via narcosis typically do not elicit toxicity at specific target sites and are sufficiently lipophilic to accumulate in the lipid phase or the lipid-aqueous interface of membranes to sufficient levels to disrupt membrane function.
- Chemicals that induce narcosis include alcohols, ketones, benzenes, ethers, and aldehydes.

Simple asphyxiants

- The mechanism of toxicity for inert gases and some other non-reactive substances is lack of oxygen (anoxia)
- These chemicals, which cause deprivation of oxygen to the central nervous system (CNS), are termed **simple asphyxiants**
- If a person enters a closed space that contains nitrogen without sufficient oxygen, immediate oxygen depletion occurs in the brain and leads to unconsciousness and eventual death if the person is not rapidly removed.
- In extreme cases (near zero oxygen) unconsciousness can occur in a few seconds. Rescue depends on rapid removal to an oxygenated environment.
- Survival with irreversible brain damage can occur from delayed rescue, due to the death of neurons, which cannot regenerate.

Chemical asphyxiants

- Carbon monoxide (CO) competes with oxygen for binding to haemoglobin (in red blood cells) and therefore deprives tissues of oxygen for energy metabolism; cellular death can result.
- Intervention includes removal from the source of CO and treatment with oxygen. The direct use of oxygen is based on the toxic action of CO.
- Another potent chemical asphyxiant is cyanide. The cyanide ion interferes with cellular metabolism and utilization of oxygen for energy.
- Treatment with sodium nitrite causes a change in haemoglobin in red blood cells to methaemoglobin.
- Methaemoglobin has a greater binding affinity to the cyanide ion than does the cellular target of cyanide.
- Consequently, the methaemoglobin binds the cyanide and keeps the cyanide away from the target cells. This forms the basis for **antidotal therapy**

Central Nervours System (CNS) Depressants

- Acute toxicity is characterized by sedation or unconsciousness for a number of materials like solvents which are not reactive or which are transformed to reactive intermediates.
- It is hypothesized that sedation/anaesthesia is due to an interaction of the solvent with the membranes of cells in the CNS, which impairs their ability to transmit electrical and chemical signals.
- While sedation may seem a mild form of toxicity and was the basis for development of the early anaesthetics, “the dose still makes the poison”.
- If sufficient dose is administered by ingestion or inhalation the animal can die due to respiratory arrest.
- If anaesthetic death does not occur, this type of toxicity is usually readily reversible when the subject is removed from the environment or the chemical is redistributed or eliminated from the body.

References

- https://www.iloencyclopaedia.org/part-iv-66769/toxicology-57951/mechanisms-of-toxicity