

Toxicity Testing

- Different types of testing methods are undertaken to test the toxicity of drugs and chemicals. This includes -
 - ❖ Acute toxicity
 - ❖ Subchronic toxicity
 - ❖ Chronic toxicity
 - ❖ Developmental toxicity
 - ❖ Reproductive toxicity
 - ❖ Phototoxicity,
 - ❖ Behavioural toxicity

- ❖ Hypersensitivity
- ❖ Ocular and skin irritation tests
- ❖ Mutagenicity
- ❖ Teratogenicity and
- ❖ Carcinogenicity
- In addition, toxicokinetic studies are conducted to estimate the toxicity.
- In many of these studies rodents are used as experimental animals.

Chronicity Factor

- The ratio of acute to chronic LD 50 doses is known as chronicity factor.
- Compounds with cumulative effects have a high chronicity factor.
- A chronicity factor greater than 2.0 indicates a relatively cumulative toxicant.
- Chronicity factor may be influenced by the tendency to accumulate *vs.* being rapidly eliminated or detoxified .
- It may also be influenced by cumulative and progressive damage that occurs from repeated toxic insults to a target tissue.

- A compound may have low acute toxicity, but if it has the tendency to accumulate in body tissues it can cause sub acute or chronic toxicity.
- Such toxicants are termed as cumulative poisons.
- The chronicity factor gives an indication of cumulative effects of poisons.
- However, chronicity factor may be influenced by the tendency to produce tolerance.
- The biological system may tolerate higher dose after prolonged exposure. Potassium cyanide is an example.
- Its acute LD₅₀ is 10 mg/kg, but pre-exposed animals tolerate 250 mg/kg.
- Therefore the chronicity factor is 0.04 for potassium cyanide.

Untoward Effects due to Poisonous Substances

- There are other untoward effects caused by poisonous substances irrespective of the poisoning being acute, sub-acute or chronic.
- These may be produced by certain drugs even at therapeutic dose levels.
- *Allergy* –The individual becomes sensitized to a previous dose of the same material.
- *Teratogenicity* (Greek word meaning monster) – The exposure to certain naturally occurring or man-made agents during certain stages of gestation results in malformations of the offspring. Teratogen is defined as an agent which, when administered during gestation, produces nonlethal structural or functional changes in the embryo or fetus. Some plants and drugs have been identified to cause teratogenicity. For example: plants like *Veratrum* and *Lupinus* and drugs like thalidomide and colchicine.

- *Carcinogenicity* – The agent after a considerable delay may induce neoplasia.
- The compound has the ability to transform normal cell into progressively and uncontrollably proliferating ones.
- *Mutagenicity* – The agent induces mutation or changes through a change in the genotype or genetic material of a cell by covalent modification of bases in DNA particularly generation of DNA, which passes on when the cell divides.
- Certain common terms used in toxicology studies include
- *Parts Per Million* (ppm) is the term commonly used to express the quantity of toxicant mixed within another substance (e.g., feed) $1 \text{ ppm} = 0.0001\% = 1 \text{ mg toxicant/kg feed}$.

- *Lethal concentration* (LC) is the lowest concentration of compound in feed water or even in air that causes death. It is expressed as milligrams of compound per kilogram of feed (parts per million or billion as ppm or ppb)
- *Toxic concentration* (TC) relates to the first recognition of toxic effects. The specific (threshold) toxic effects should be identified when a toxic concentration is given.
- *Highest nontoxic dose* (HNTD) is the largest dose that does not result in clinical or pathologic drug-induced alterations.
- *Toxic-dose-low* (TDL) is the lowest dose that will produce alterations; administration of twice this dose is not lethal.
- *Toxic-dose-high* (TDH) is the dose that will produce drug-induced alterations and administration of twice this dose is lethal.

- *Lethal dose* (LD) is the lowest dose that causes death in any animal during the period of observation. LD₅₀ is a commonly used measure of toxicity.
- *Median Lethal Dose* (LD₅₀) is the dose at which a toxicant causes lethality in 50% of the population or animals exposed to that particular agent/compound.
- *No observed adverse effect level* (NOEL or NOAEL) is the largest dose that will produce no deleterious effects when administered over a given period of time. This study is generally conducted in two species (rats and dogs) at three doses by the route of choice.
- *Reference dose* (RfD) is the highest dose expected to have no effect on the species of interest (often human beings) despite a lifetime of exposure. The RfD may be set at 1/10 of the HNTD or 1/10 of the NOAEL.

- *Maximum tolerated dose* (MTD) is sometimes used to indicate maximum tolerated dose (highest dose not causing death). Other times it is used to indicate minimum toxic dose (lowest dose causing any abnormality). Thus, it is best to ask what is meant by MTD.
- *Safety factor* (SF) reflects the quality of the toxicological investigation and the degree of certainty with which the results can be extrapolated to human beings.
-