

Toxicology: toxico = poison

Logy = science

Is the study of the adverse effects of xenobiotics on living systems; or simply it can be defined as the science that deals with poisons.

The toxicologist is trained to examine the nature of these adverse effect & the probability of their occurrence

Poison: is any chemical substances or compounds that affect the living organisms & cause changes in the function, morphology & may cause death of the cells.

Toxin: is a poisonous substance that is a specific product of the metabolic activities of a living organism and is usually very unstable, notably toxic when introduced into the tissues, and typically capable of inducing antibody formation.

venoms are toxins which are injected by a bite or sting (this is exclusive to animals).

Note that the differences between venom and other poisons is the method of delivery.

side effects: are nontherapeutic reactions to a drug that are transient and may not require any nursing intervention.

adverse effects: are nontherapeutic effects that may be harmful to the patient and that requires lowering the dosage or discontinuing the drug.

Hazard: a potential danger of a compound or process.

Risk: is the probability that the adverse effect of a chemical response (the hazard) will occur.

risk assessment depends on two important aspects:

- 1) Hazard characterisation: including qualitative and quantitative characterisation of the effects of the chemical.
- 2) Exposure assessment: Defining the actual exposure levels.

Classification of toxicology (the different areas of toxicology)

The activities of toxicologist can be classified in to:

- 1. Descriptive toxicologist:** concerned directly with toxicity testing. The appropriate toxicity test in experimental animals are designed to yield

information that can be used to evaluate the risk posed to man & the environment by exposure to specific chemicals.

- 2. Mechanistic toxicologist:** concerned with elucidating the mechanism by which chemicals exert their toxic effect on living organisms.
- 3. Regulatory toxicology:** has responsibility of deciding (on the basis of data provided by the descriptive toxicologist) whether or not a drug or chemical has a low enough risk to be marketed for described purpose.
- 4. Forensic toxicology:** it aids in establishing the cause of death & elucidating its circumstances in a postmortem investigation.
- 5. Clinical toxicology:** concerned with diseases caused by or associated with toxic substances.
- 6. Environmental toxicology** deals with the effects of chemical pollutants in the environment on nonhuman biological organisms, such as fish, birds.
- 7. Developmental toxicology** is the study of adverse effects on the developing organism that occur any time during the life span of that organism that may result from exposure to chemical or physical agents. **Teratology** is the study of defects induced during development between conception and birth.
- 8. Reproductive toxicology** is the study of the occurrence of adverse effects on the male or female reproductive system that may result from exposure to chemical or physical agents.

In addition to the subfield of Food toxicology: this sub-field deals with chemicals in food including additives, contaminants and substances that are naturally present in the food.

Classification of toxic agents:

Can be classified according to:

- 1. their target organ** : like liver, kidney, hematopoietic system poison,..... etc.
- 2. their use:** like pesticide, solvents, food additivesetc .
- 3. their source:** like animal and plant toxin
- 4. their effects:** like carcinogens ,mutagens.....etc.
- 5. their physical state:** like gases ,dusts ,metals.
- 6. their labeling requirements:** explosive ,flammable ,oxidizer.

7. their chemistry : aniline derivatives, halogenated hydrocarbonsetc .

8.their poisoning potential: extremely toxic, very toxic.....ext.

9.biochemical mechanism of action: sulfhydryl inhibitors .methemoglobin producers

Factors affecting the toxicity of toxic agents:

1. the concentration of the toxic agent, duration & frequency of exposure & route of administration.
2. the chemical & physical properties of the agent .
3. the susceptibility of biologic system or subject.
4. some of the toxicity influencing factors related to person (age, sex , nutritional statusetc),& the various kinetic factors that influence toxicity (absorption , distribution , metabolism & excretion)

Route & site of exposure:

The major routes by which toxic agents gain access to the body are through

- *GIT (ingestion)
- * Lung (inhalation)
- * Skin (topical percutaneous, or dermal).
- * parenteral administration

Toxic agents greatly exhibit the greatest potency & produce the most rapid response when given by intravenous route & an approximate descending order of effectiveness for the other routes would be: inhalation, intraperitoneal , subcutaneous , intramuscular , intradermal , oral ,& topical.

Industrial exposure to toxic agents occurs most frequently by inhalation & topical exposure, while accidental & suicidal poisoning occurs most frequently through oral ingestion. For many agents the lethal dose for topical exposure is about ten times the lethal dose for oral administration, which in turn is about ten times the lethal dose with intravenous administration. In those situation when the lethal dose for oral or topical administration is close to the lethal dose for IV. Administration it usually means that the toxic agent is absorbed rapidly and easily.

Duration & frequency of exposure:

Toxic effect may be produced by acute & /or chronic exposure to chemical agents:

- **_acute exposure:** is defined as a single exposure or multiple exposure to a chemical occurring within short time (24hrs or less).
- **Subacute exposure:** refers to repeated exposure to a chemical for 1 month or less.
- **Subchronic exposure:** exposure for 1-3 months.
- **Chronic exposure:** is defined as exposure to a chemical agents for more than 3months.

the frequency of administration is other related factor , in general fractionation of the dose reduces the effect. a single dose of a test substance that produces an immediate server effect might reduce less than half of the effect when given in two divided doses & no effect when given in ten doses over a period of several hours or days.

Lethal dose (LD50):

Is the dose of chemical needed to produce death in 50% of the dosed animal, it is expressed as mg/kg body weight. Categories of toxicity have been devised according to the LD50.

| | |
|--------------------------|------------------|
| 1. Practically non toxic | LD50 > 15 g/kg |
| 2. Slightly toxic | 5 ___ 15 g/kg |
| 3. Moderately toxic | 0.5___ 5 g/kg |
| 4. Very toxic | 50 ___ 500 mg/kg |
| 5. Extremely toxic | 5 ___ 50 mg/kg |
| 6. Super toxic | < 5 mg/kg |

Effective dose ED50: Dose effective in 50% of population.

NOAEL : No Observed Adverse Effect Level. (Highest data point at which there was NOT an toxic or adverse effect).

LOAEL : Lowest data point at which there was an observed toxic or adverse effect.

Therapeutic index: $=LD_{50}/ED_{50}$

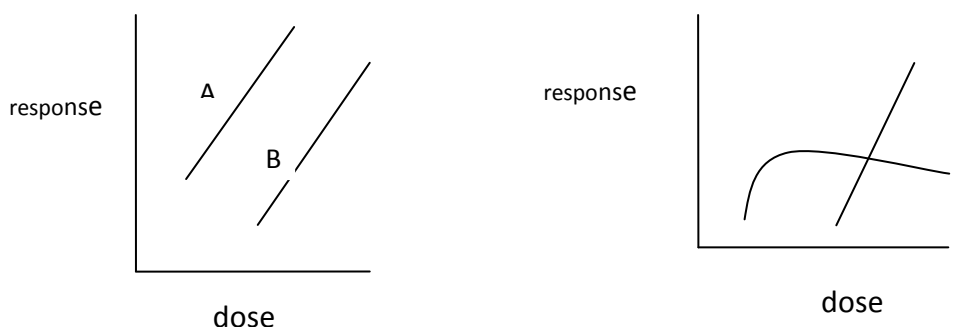
Therapeutic index refers to the safety of the drug or compound. The larger the ratio, the greater the relative safety.

Margins of Safety and Exposure:

For nondrug chemicals, the term margin of safety is an indicator of the magnitude of the difference between an estimated "exposed dose" to a human population and the NOAEL (no observable adverse effect level) determined in experimental animals.

It is an index of a drug's effectiveness and safety. It is calculated as the amount of drug that is lethal to 1% of animals (LD₁) divided by the amount of drug that causes a beneficial effect in 99% of the animals (ED₉₉). $=LD_1/ED_{99}$

Potency: Refers to the range of chemical doses produces increasing response



A is more potent than B, C is more potent than D.

Efficacy: Refers to the limit of the dose _response relationship on the response axis to a certain chemical. A has more efficacy than B, D has more efficacy than C.

Dose Response relationship

Is the relationship between the degree of response of the biological system and the amount of toxicant administered.

Toxic receptor: the molecular structure affected by the toxic agent (DNA, protein like enzyme, ion channel).

Types of Reactions

The toxicant may bind to the target molecules by different types of reactions:.

Noncovalent Binding its usually reversible because of the low bonding energy.

Covalent Binding

Being practically irreversible, covalent binding permanently alters endogenous molecules. The electrophilic toxicants react with nucleophilic atoms that are abundant in biological macromolecules, such as proteins and nucleic acids..

Hydrogen Abstraction

Neutral free radicals can readily abstract H atoms from endogenous compounds, converting those compounds into radicals. Radicals also can remove hydrogen from proteins and form cross-links with DNA or other proteins.

Electron Transfer

Chemicals can exchange electrons to oxidize or reduce other molecules, leading to the formation of harmful by-products. For example, chemicals can oxidize Fe(II) in hemoglobin to Fe(III) in methemoglobinemia.

Enzymatic Reactions

A few toxins act enzymatically on specific target proteins.

Undesired effects

1. **Allergic reaction:** chemical allergy is an adverse reaction to chemical resulting from previous sensitization to that chemical or to a structurally similar one, this involves skin including dermatitis , urticaria & itching, or eye including conjunctivitis .

2. **idiosyncratic reaction :** chemical idiosyncrasy is genetically determined abnormal reactivity to a chemical, the response observed is qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemicals .eg. patients who exhibit prolonged muscular relaxation & apnea lasting several hours after a standard dose of succinyl cholin which is usually produces skeletal muscle relaxation of only a short duration because of its very rapid metabolic degradation by pseudocholinesterase of the plasma such patients have an atypical pseudocholinesterase .

3. **immediate & delayed toxicity :** immediate toxicologic effects can be defined as those that occur or develop rapidly after a single administration of a substance.

Delayed effects are those that occur after a period of time

eg. carcinogenic effect of chemicals usually have a long period often 20_30 years before tumors are observed .

5. local & systemic toxicity : Local effects refer to those that occur at the site of first contact between the biologic system & toxicant eg. Ingestion of caustic substances or inhalation of irritant materials.

Systemic effects are those that require absorption & distribution of the toxicant to a site of action most substances except highly reactive materials produce systemic effect .for some materials both effects can be noted .

Occurs when two or more chemicals given together:

Is situation in which the combined effect of two chemical is equal to the sum of the effect of each agent given alone (example: $2+3=5$) eg. when 2 organic phosphate insecticides given together the cholinesterase inhibition is usually additive.

Is the situation in which the combined effect of 2 chemicals is much greater than the sum of the effect of each agent given alone (example: $2+3=8$) eg. Ethanol +carbon tetrachloride CCL₄(both are hepatotoxic agents).

Is a situation in which one substance does not have a toxic effect on a certain organ or system but when add to another chemical it makes the latter much more toxic (example: $0+2=10$).

4. antagonism:

Is the situation in which two chemicals when given together , interfere with each others action or one interferes with the action of the other chemical (example: $4+6=8$, $4+(.4)=0$).

a. functional antagonism :is when two chemicals counterbalance each other by producing opposite effect on the same physiologic function .eg. barbiturate decrease blood pressure while vasopressor agent like nor epinephrine increase B.P.

b.chemical antagonism :

a reaction between two chemicals to produce a less toxic product. eg. heparin + protamine sulphate.

c. dispositional antagonism:

is the situation in which the disposition (that is the absorption ,distribution ,metabolism or excretion) of the chemical is altered so that less amount of the toxic compound reaches the target or the duration at the target organ is less . eg. The prevention of absorption of a toxicant by ipecac or charcoal

d. receptor antagonism:

is where two chemicals bind to the same receptor they produce less of an effect than the addition of their separate effects .(example: $4+6=8$).receptor antagonist often termed blocker . eg. Opioid +naloxone , organ phosphorous +atropine .

Selective toxicity

Means that a chemical produces injury to one kind of living matter without harming some other kinds, even though the two may be in contact .eg. some drugs have toxic effect on the liver , other than on other organs as kidney ,lungetc .

Tolerance:

Is the state of decreased responsiveness to a toxic effect of a chemical resulting from prior exposure to that chemical or to a structurally related chemical .two major mechanisms for tolerance:

1. due to a decreased amount of toxicant reaching the site where the toxic effect is produced (dispositional tolerance).
2. due to decreased responsiveness of a tissue to the chemical.