TOXICOLOGY.

(Gr. toxikon-poison' logos- study)

- τ It is the qualitative and quantitative study of the adverse effect of chemicals and other anthropogenic material / xenobiotic on organisms.
- τ Environmental toxicology is concerned with the harmful effect of chemicals that are encountered by man either directly or indirectly because they are in atmosphere, hydrosphere, lithosphere/ biosphere/ by contact during occupational / recreational activities / by ingestion as food additives/food residues.

TOXINS-These are hazardous substances which have the properties like toxicity, persistence and bioaccumulation. Toxic substances are divided into:

i) **Inorganic contaminants (heavy metals)**
ii) **Heterogeneous group of organic compounds**.

- τ Chemicals that cause effect on environment are called **xenobiotics.**
- τ Toxic chemicals cause different kinds of effect on living organisms based on nature of the effects on organisms, these are classified as:

1. **Teratogens**- These cause birth defects during embryonic growth and development. Ex; usage of sedative thalidomide and alcohol during pregnancy results in abnormal foetal development
2. **Carcinogens**- These are pollutants, heavy metals, pesticides, tobacco etc. which causes cancer.
3. **Mutagens**- These cause sudden changes in the genetic material.
   Ex: Pesticides
4. **Estrogens**- These have adverse effect on human reproductive system.
   Ex: Xenobiotics, phthalates, alkyl phenols, organic chlorine compounds etc.

INSECTICIDES.

- τ These are biologically active chemicals used for pest control but their spectrum of activity extends far beyond the pests. A major source of pesticides in the rivers, streams and lakes is from runoff from the agricultural fields. Some enter inland waters from pesticide manufacturing industries.
- τ Many of these chemical compounds are quite stable and some break down partially to form more toxic compounds than the original chemical compounds.
  Eg: Chlorinated hydrocarbons- DDT, aldin, dieldrin chloradane, BHC etc.
  Organophospates- Malathion, parathion, diazinon, guthion etc.
  Carbamates- sevin baygon, pyrethrins, allethrin and cydethin.

CHLORINATED HYDROCARBONS.

- τ The effects of these on animals are quite varied. DDT primarily affects the CNS. Symptoms are increased excitability, muscular tremors and convulsions.
- τ DDT residues frequently accumulate in fatty tissues like sub cutaneous tissue, fatty tissues of mesenteries, heart, liver, thyroid gland and gonads, with the continued ingestion of contaminated foods over a long period of time, the DDT concentration gradually increases.

- When the stored fat is required as an energy source during stress, the residues may be released from these storage areas.
- Fish and other aquatic organisms are killed by organochlorines because of impaired oxygen diffusion through gill membranes. These are quite resistant to biological disintegration by bacteria in either water or soil.
- Some DDT molecules may remain intact in ecosystems for 25 years. It has been detected in world's rivers and oceans and even in the Arctic and Antarctic. Over 1 million tones of DDT have been used worldwide since 1947.
- In all countries very small quantities (0.1 ppm or more) of organochlorines are present in drinking water, fruits, vegetable, milk and larger amounts in meat, fish, eggs, butter and flour.
- Chloradane is absorbed through skin and other portals. It causes stimulation of the central nervous system. It is less toxic compared to aldrin and dieldrin, but effects are similar.
- Aldrin and Dieldrin act on the CNS. Several human deaths are reported due to drinking emulsions or solutions of dieldrin. These produce liver injury for a long period. In experimental animals these produced decreased effects on reproduction (fertility and viability of young ones). On long term feeding these produced tumours.
- Endosulfan is more toxic to male rats than females. Repeated administration may stimulate hepatic microsomal enzymes in rats. in experimental animals, it produces deleterious effects on embryo.

  Ex: DDT, Endrin, Dieldrin, Chloradane, Aldrin, Endosulfan, Isobenzan, Heptachlor, Heptachlor epoxide, Camphechlor (Toxaphene), Methoxychlor, Lindane, BHC etc.

ORGANOPHOSPHATES.

- These are very broad spectrum insecticides; and absorbed by skin, respiratory and gastrointestinal tract. These inhibit the production of cholinesterase, which breaks down acetylcholine at nerve synapses.
- Organophosphate pesticides cause an excessive accumulation of acetylcholine, which tends to interfere with the nerve impulse transmission.
- Symptoms of these depositions include sweating, more secretion in upper respiratory tract, discomfort in chest, muscular weakness, tremors and dizziness, nausea, vomiting and diarrhea. Fish and other aquatic organisms are less affected.

  Ex: Parathion, Malathion, Ethion, Fenthion, Trithion, Monocrotophos, Dimethoate, Phorate, Thionazin, Menazon etc.

CARBAMATES.

- These are absorbed through all portals including skin, have low dermal toxicities. These are reversible inhibitors of Ach E.

  Ex: Carbaryl, Propoxur, Aminocrab, Monuron, Carbofuran, Aldicrab etc.

RODENTICIDES.

- These are used to kill the rodents. It is highly persistent so can be transferred in food chains. **Ex: Sodium fluoroacetate, Warfarin.**
- These result in hyper-stimulation of the central nervous system and interfere with heart action.
- Warfarin acts as an anticoagulant, depressing levels of prothrombin. Repeated intake of this results in death from internal haemorrhage.

HERBICIDES.

- These are group of organic chemicals used to destroy or suppress the growth of plants. According to their mode of action these are of three types namely selective herbicides, Residual herbicides and Translocated herbicides.
- **Selective herbicides** are **Diphenyl** herbicides like **2, 4-D** and **2, 4, 5-T** are used to destroy particular unwanted plants or weeds without injury to others. Ex: Broad leaved weeds like Plantain growing amongst narrow-leaved like wheat and barley. These in man leads to fibrillary twitching of muscles, hypo-reflexia and urinary incontinence. If death is delayed, there may be myotonia, stiffness, atoxia, paralysis and coma. These may produce contact dermatitis in man, and are foetal toxic chemicals and can produce teratogenicity in mammals. 2, 4 –D has shown incidence of tumor in rats. Long term exposure may lead to hepatomas in mice and rats. Can delay the maturation of sperms and produce teratogenic effects in animals.
- **Residual herbicides** are applied to the soil at time of seeding where they remain active for several weeks and prevent the growth of weeds in competition with the emerging germinating crop.
- **Translocated herbicides** may be sprayed on to leaves and are able to move to all parts of the plants through the internal translocation mechanism.
- All three types if used before flower opening will prevent seed formation and so reduce weed spread by seed dispersal.
- Total herbicides like **Paraquat** and **Diaquat** are used as an easy way to destroy all vegetation. Paraquat causes respiratory failure and ultimately death. Diaquat if given orally causes hyper-excitability and cataract.

FUNGICIDES.

- These are used to control fungal infection in agriculture or forestry. These are of two types. The older **surface fungicides** like phenylmercury, alkylmercury, organicthiocarbamates (Thiram, ziram, maneb) etc are used to the foliage as sprays or dusts, these does not penetrate the plant surface, but kills the fungus and surface spores.
- New Systemic fungicides like Benomyl, Thiophantemethyl, Carboxin, and Triarimol are more effective. Benomyl and Thiophanates are used for the control of a wide range of pathogenic fungi.
- some organophosphoric compounds with a low mammalian toxicity like 'Dowco' and Triarimol are used for the control of powdery mildews and Carboxin is used as a seed dressing.

- All fungicides have low toxicity to plants, birds and mammals so these are not potentially hazardous in the short term. However some products contain metals which accumulate in food chains and humans in the long term.

HEAVY METALS.

- Metals are important class of toxic substances which are encountered in numerous occupational and environmental circumstances. It is very difficult to remove from the environment once these enter in it.
- These are dispersed in the environment through industrial effluents, organic wastes, refuse burning, transport and power generation. Carried to many miles away from the sources by wind depending upon their forms (gaseous / particulates). These pollutants washed out by rain into land or surface of water bodies. Industrial effluents with metals are the major sources of pollution of hydrosphere. Another means of dispersal is the movement of drainage water from catchment areas which have been contaminated by waste from mining and smelting units.

LEAD.

- Primary sources are industrial dusts and fumes, polluted food. Target organs are nervous system and kidney. It causes abdominal pain, vomiting, diarrhea, oliguria, collapse and coma. There is inflammation of gastro-intestinal tract mucosa and degeneration.
- Chronic inorganic lead poisoning occurs in three states; **i) Early stage** characterized by loss of appetite, weight loss, constipation, irritability, occasional vomiting, fatigue, weakness and anaemia. **ii) Advanced stage** marked by intermittent, vomiting, irritability, nervousness. **iii) Final Severe stage** involving persistent vomiting, encephalopathy, lethargy, delirium, convulsion and coma.

MERCURY.

- Primary sources are industrial fumes, vapours, polluted food and water. Target organs are kidney and nervous system. Mercury salts are associated with acute exposure arising from attempted suicide or accidental ingestion.
- Chronic toxicity in man varies based on chemical form of mercurial and the duration of exposure. Metallic mercury poisoning following exposure to mercury vapour results syndrome called **mercurialism**. Main symptoms of this syndrome are stomatis, parasthesia, erethism and tremor.
- Organic mercury poisoning due to methyl mercury is well defined syndrome. Hunter-Russell syndrome or new more common **Minamata disease**. The main symptoms of this are parasthesia, ataxia, dysarthria, tremor and constriction of the visual field.

CADMIUM.

- Primary sources are industrial fumes and dusts, polluted water and food. Target organs are renal, skeletal and pulmonary.
- It causes increased salivation and severe nausea and vomiting. In more severe cases it may lead to collapse with signs of shock, hematemeses, diarrhea and tinesmus.

- Chronic exposure causes **Itai-Itai** diseases, which is characterized by lumbar pain, leg myalgia and increase in pain when pressure applied to bones. There are skeletal deformation and Duck like gait, weight loss, cough and pulmonary emphysema.

ARSENIC.

- Primary sources are industrial dusts, polluted water. Target organs are pulmonary, skin and nervous system.
- It causes gastro-intestinal, liver and kidney damage and muscular weakness. Arsine gas (AsH_3) is a potent hemolytic poison which produces mortality by renal failure due to blockage of renal tubules.
- Chronic exposure leads to development of a syndrome of symptoms in several organ systems. It includes cancer of lungs, hemangiosarcoma of liver and skin.

TOXICITY.

- Toxicity is a relative term commonly used in comparing one chemical with another. It may be capacity of substance to cause injury to a living organism.
- Even very small amounts of highly toxic substance will damage an organism, but a substance of low toxicity will not produce an effect unless the amount is very large. This toxicity cannot be defined without reference to quality of a substance administered or absorbed by inhalation, ingestion or injection and distributed in time in single or repeated doses, the type of severity of injury and the time needed to produce that injury. The nature and extent of toxicity varies depends on the origin of toxicants. Origin may be natural, artificial or synthetic. Natural toxicants may be animal venoms, plant (opium, atropine, reserpine, quinine, curare, picrotoxin etc) or mineral sources.
- Toxicity can be classified into **acute, subacute** and **chronic** based on the rate of onset, the duration of symptoms and rate of uptake of chemicals.

MECHANISM OF TOXICITY.

- **Caustics, alkalis** and **mineral acids** are **local irritating poisons**; irritate the tissues with which they come in contact. This action may be severe and cause tissue destruction. Many **locally acting** chemicals like **weak alkalis, acids** or **neutral** substances exert a mild local effect which usually consists of skin irritation or dermatitis during the period of contact.
- The xenobiotics or toxins enter the body through gastrointestinal tract, skin and lungs and parenteral routes in experiments are intra-peritoneal, subcutaneous and intravenous.
- These toxins are absorbed into the blood stream systematically and carried to the site of action. These penetrate into the various fluid compartments like plasma, interstitial fluid, transcellular fluid and cellular fluids. Non-ionised lipid soluble fractions penetrate most readily. Equilibrium takes place in most tissues rapidly, but it is of longer time in bone and adipose tissues with poor blood supply. Some chemicals may accumulate in various areas as a result of binding or due to their affinity for fat.
- One or more tissues may be affected in a biological system. Physiological and biochemical stages of an organism at systemic, tissue, cellular and sub-cellular

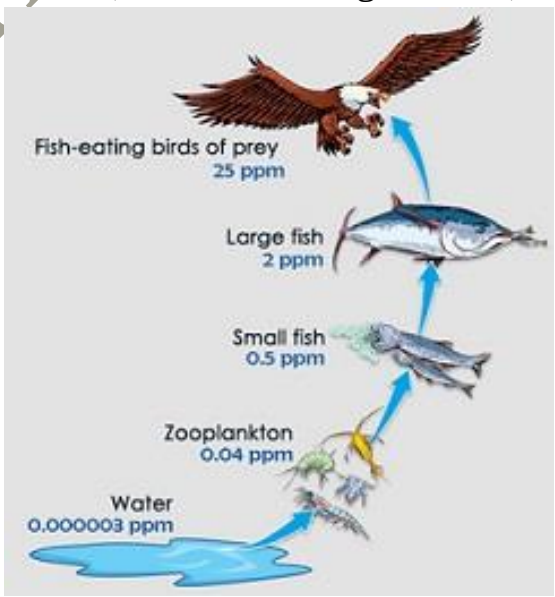
level have a great influence on the final outcome by determining the amount of toxin reaching at site of action, the rates of its accumulation, biotransformation and elimination from the body.

- The xenobiotics and their metabolites are finally eliminated via urine and bile, but they may also be excreted in the expired air, sweat, milk, saliva, vaginal secretions and by secretion into the stomach and other parts of gastrointestinal tract.

BIOMAGNIFICATION.

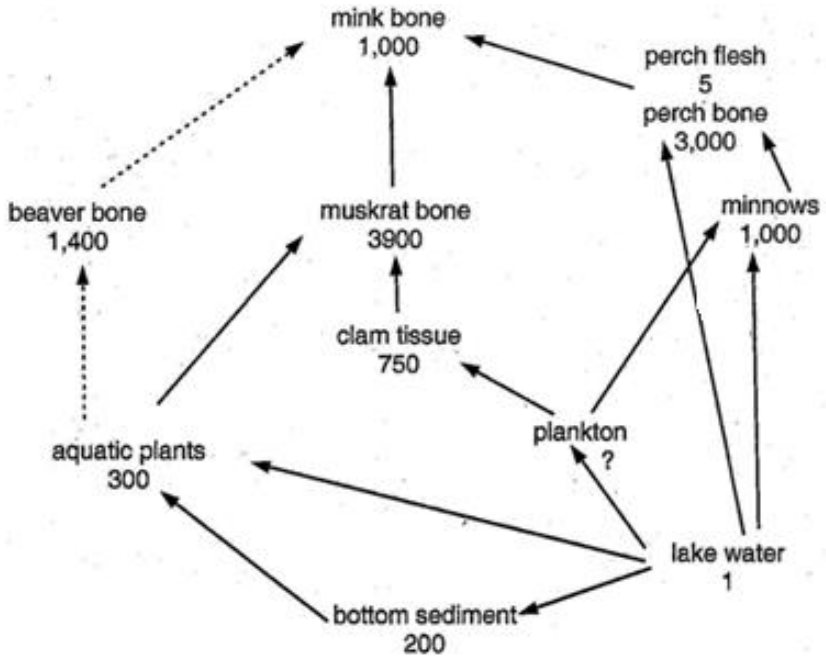
- It is defined as the accumulation of a pesticide in an animal at any particular trophic level at a concentration greater than in its food or the preceding trophic level so that eventually animals at the top food chains accumulate the maximum residues.
- Ex 1: Pesticides like DDT, BHC and PCBs residues may be found in air, soil and water. If DDT enters a pond / lake, that is absorbed by plants and other producers of pond, then reaches to successive consumers zooplanktons feeding on plants, then to minnows eating the zooplanktons, then to fish which eats minnows and finally in the body of the top consumer, the bird who eats the fish. DDT levels were found as high as upto 32/b/acre in a land marsh sprayed for 20 years to control mosquitoes; more than 5 billion of DDT is circulating in the biosphere. Even if it is never used again in future it would still be there for many years. it may be very low in water but the aquatic plants contain an average value about 5.5 ppm, about 265 times increase over the concentration used in initial application of DDT plants and animals accumulate DDT in much higher concentration in their bodies. The herbivores, fish and insects feeding on these plants may accumulate DDT in still higher concentrations and at the top carnivore level, fish eating birds, concentration may reach at a very high value.

  NOTE: Some oysters accumulate DDT 70,000 times the original concentration, frogs 2,000 times, sunfish 12,000 times and grebes 80,000 times.



Biomagnification of DDT.

- Ex 2: Some metals like lead, mercury and copper show biomagnifications in a food chain. Some radioactive substances like strontium-90, iodine-131, caesium-137 accumulate in body tissues and lead to biomagnifications.



Concentration of strontium-90 in various parts of a food web of a lake receiving atomic wastes. Average concentration factors are shown in terms of lake water = 1.

BIOTRANSFORMATION.

- It is defined as "The biologically catalyzed conversions of chemicals, other than the normal body constituents like xenobiotics into other chemicals" OR "Enzyme-catalyzed conversion of one xenobiotic compound to another". It should be differentiated from purely physical and chemical processes and metabolism.
- General principles of biotransformation are conversion of;
  - ✓ An active compound to an inactive compound.
  - ✓ An inactive compound to an active compound.
  - ✓ An inactive compound to another inactive compound.
  - ✓ One active compound to another active compound.
  - ✓ One toxic compound to another more toxic compound (bioactivation).

TYPES.

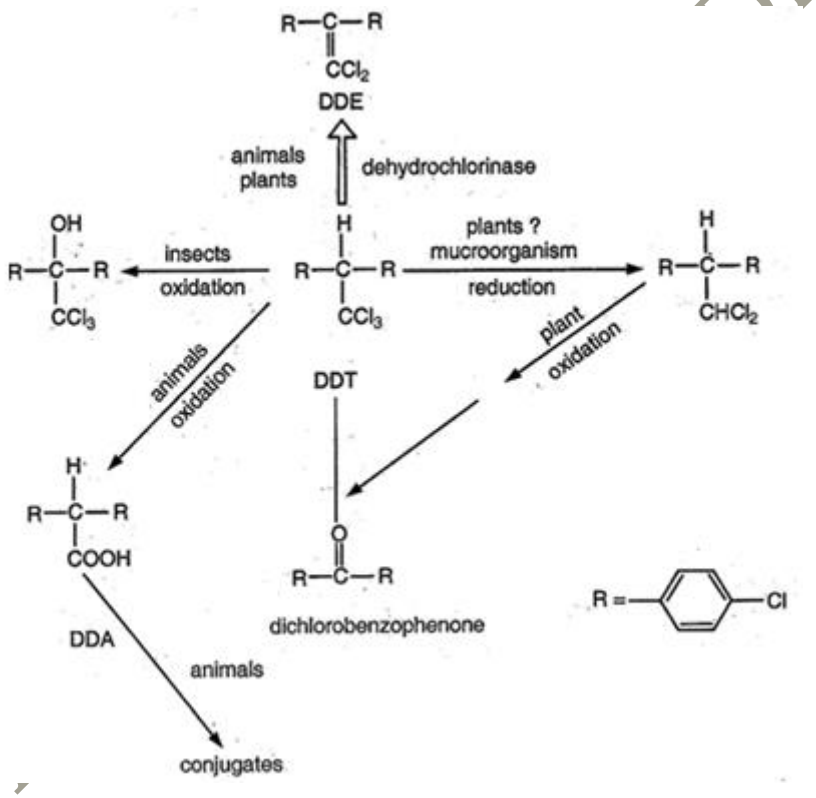
- Enzymatic biotransformation reactions may be broadly divided into two types, **Phase I. Non synthetic reactions** involving oxidation, reduction and hydrolysis. **Phase II. Synthetic reactions** involving conjugation.

BIOTRANSFORMATION OF DDT.

- Dichlorodiphenyltrichloroethane (DDT) absorbed from the intestinal tract and if it occurs in air in the form of fine aerosol or dust, it may enter the alveoli of the lung from which it is absorbed readily. It may also absorb through skin only in solutions. Fats and oils increase DDT absorption by intestine.
- DDT and one of its major primary metabolite products called DDE (1,1′ - dichloro-2,2′ - bis (chlorophenyl) ethylene, have a high fat/water coefficients

hence accumulate in adipose tissue. DDT lowers the concentration of potassium ion in fluid surrounding the nerve. It inhibits Na^+, K^+ and Mg^{2+} adenosine triphosphatase activity in the nerve ending fraction in vitro.

- τ In animals and plants, DDT is transformed by dehydrochlorination reaction which is catalysed by DDT dehydrochlorinase which yields nonpolar and persistent metabolite DDE initially.
- τ Plant tissues can convert DDT into DDE within one week. After prolonged exposure it is reductively dechlorinated to DDD, further hydroxylated and oxidized to dichlorobenzophenon. The reductive dechlorination of DDT and DDD is associated with anaerobic peroxidation of unsaturated fat by non porphyrin enzymes.
- τ In mammals oxidation of DDT to DDA (2,2′ - bis (chlorophenyl) acetic acid) and the resultant conjugates are the major metabolites present in the urine.
- τ In insects there is unusual biotransformation of DDT to dicofol (Kelthane).



Biotransformation of DDT in plants, mammals and insects.