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1. Learning Outcomes

After studying this module, you shall be able to know that –

- About Pesticides and their classification.
- Learn about the mode of action of Pesticides
- Learn about the Toxicokinetics

2. Introduction to Pesticides

Chemicals have been used to exterminate or control pests for centuries and thus known as "Agricultural Chemicals". The term "agricultural chemicals" has largely been replaced by the term "pesticides," defined as economic poisons, regulated by national and municipal laws that are used to control, eradicate, or repel pests.

From the past history, it is well established that the Chinese were familiar with the use of Arsenic to control insects while the early Romans used common salt to control weeds and sulphur to control insects. In the eighteenth century, a compound named Pyrethrin having insecticidal properties was found present in the flowers of the chrysanthemum (*Pyrethrum cineraefolium*). The Chinese and South American citizens learnt to use the roots of various Derris plant species as a fish poison. In the period in-between, Rotenone was discovered in 1895 and used for insect regulator. During this decade, Paris- Green, a combination of copper and Arsenic salts, was discovered so as the Bordeaux mixture, a combination of lime and Copper Sulphate.

During 1940s, chlorinated hydrocarbon insecticides such as DDT, the phenoxy acid herbicides such as 2, 4- D, Natural compounds like Red Squill, extracted from the bulbs of Red Squill or *Urginea (Scilla) maritima*, effective in controlling rodents were introduced. Atrazine, a Triazine herbicide, introduced in the late 1950s, ruled the world herbicide market for years. Synthetic pyrethrins or pyrethroid insecticides (e.g., resmethrin) became and extensively used insecticides because of their low noxiousness, increased perseverance in respect to to the pyrethrins and less used. Pesticides are rare amongst environmental pollutants in that they are used intentionally for the purpose of assassination some kind of life. Ideally pesticides should be highly selective, abolishing objective organism though leaving non target organisms unhurt. In reality, most pesticides are not so selective. Depending on what a substance is formed to do, pesticides have been sub classified into a several of categories. The major classes of pesticides in use today are fumigants, fungicides, herbicides, and insecticides.

3. Forensic Issues

From the time when number of organchlorine pesticides has been banned, the case of poisoning involving these compounds has been declined. However, cases of accidental deaths are still reported due to surreptitious use of pesticides. Today, many household insecticides consist of carbamates and pyrethroids and hence poisoning involving them are on the rise, particularly among children. Poisoning due to other pesticides is comparatively rare except among individuals who are occupationally exposed. Owing to easy availability, pesticides such as organophosphates and carbamates have always been extremely popular in India for the purpose of committing suicide. In current scenario, aluminium phosphide has initiated to find increasing favour and has in fact edged out the other insecticides from the top spot in some states.

Homicidal poisoning comprising pesticides has always been unusual owing to disagreeable odour/taste, which most of these substances possess. Significant exceptions include thallium and arsenical compounds. However, cases have been reported even with other pesticides.

Pesticide poisoning is a menace in Indian subcontinent and is a reason behind most of the cases reported of accidental, homicide or suicide in the forensic laboratories. The rate of their abuse is high because of their readily and easy availability in the markets. They are also present in most of the insect and mosquito repellents which are over the counter articles. Detection of the pesticide is not easy because of the wide diversity and huge amount of examples available presently in India e.g., according to Insecticide Act, 1968, there are 186 chemical Pesticides registered for use in India under section 9(3) as on 7th March 2005 and 31 formulations banned and 7 as restricted to be used in India only.

India is principally a rural oriented country which consists more graphical rural area in comparison to the urban areas and unfortunately the literacy rate is in very poor condition, so it could be understood about pesticide poisoning by an example as the agriculture needs pesticides for the purpose of good yield of crops by killing pests, the person (farmer) comes in the contact of that pesticide which is of course accidentally happens could result the death of that person.

4. Classification of Pesticides

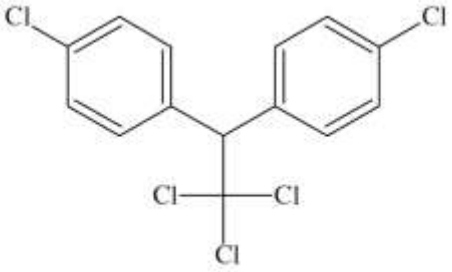
Pesticides can be categorized as per to their chemical structure. Pesticides with analogous structures have alike features and generally have a same method of action. Most pesticides are active ingredients either inorganic or organic. From a technical interpretation, inorganic pesticides do not comprise carbon and are generally extracted from mineral ores extracted from the earth. Examples of inorganic pesticides comprise Copper Sulphate, Ferrous Sulphate, Copper and sulphur. On the other hand Organic pesticides include carbon in their chemical structure. Most **organic compounds are** made from several combinations, but a few are extracted from plant material and are known as 'botanicals'. Examples of organic pesticides include captan, pyrethrin, and glyphosate.

4.1 ORGANOCHLORINE PESTICIDES

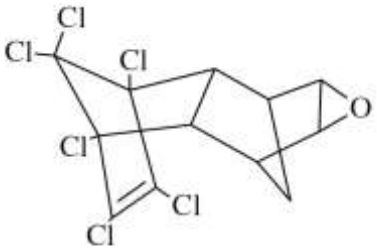
The chlorinated hydrocarbon insecticides were introduced in the 1940s and 1950s and comprise conversant insecticides such as DDT, methoxychlor, chlordane, heptachlor, aldrin, dieldrin, endrin, toxaphene, mirex, and lindane. Though DDT was manufactured in 1874, its insecticidal properties were not noted until 1939, when Dr. Paul Mueller, a Swiss chemist, discovered its efficiency as an insecticide and was given a Nobel Prize for his effort. During World War II the United States used large amount of DDT to control vector-borne diseases, like typhus and malaria, to which US troops were uncovered. After the war DDT use turn out to be widespread in agriculture, public health, and households. Its persistence, originally called as a desirable attribute, later turn into the basis for public anxiety and ultimately led to the prohibition of DDT and other chlorinated insecticides. These combinations are available as dusting powders, wettable powders, emulsions, granules and solutions.

There are four distinct categories of these pesticides:

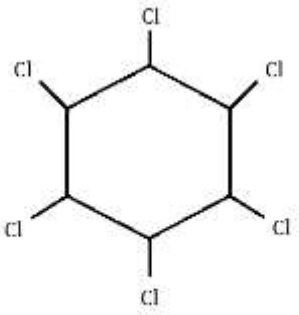
1. **DDT and analogues:** DDT (dichlorodiphenyltrichloroethane), methoxychlor
2. **Benzene hexachloride group:** benzene hexachloride (BHC), gamma-hexachlorocyclohexane (lindane)
3. **Cyclodienes and related compounds***:* aldrin, dieldrin, endosulfan (thiodan), endrin, isobenzan, chlordane, chlordecone (kepone), heptachlor, mirex (dechlorane)
4. **Toxaphene and related compounds:** toxaphene



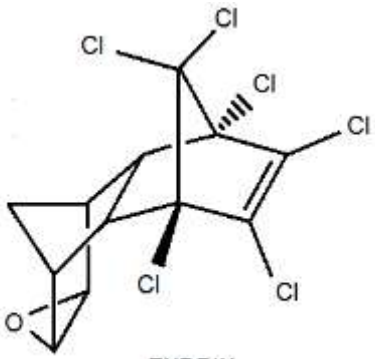
DDT



Dieldrin



BHC



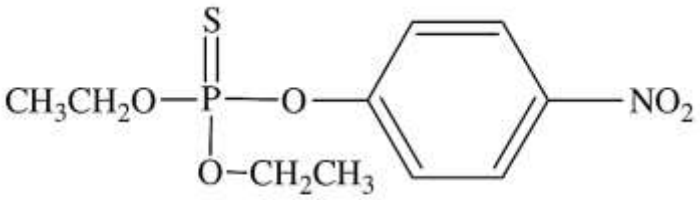
ENDRIN

❖ **Fatal Dose**

Dieldrin is placed in the "extremely toxic" category **(LD_{50}: 1 to 50 mg/kg),** while DDT, endosulfan, and lindane are considered "highly toxic" **(LD_{50}: 51 to 500 mg/kg).**

4.2 ORGANOPHOSPHORUS PESTICIDES

Also known as Organophosphates are among the most widely used insecticides in India as well as in the whole world. Organophosphates are Phosphoric Acid Esters or Thiophosphoric Acid Esters and are among the most widely used pesticides. During the decade of 1930- 1940, Gerhard Schrader and his co-workers realized the insecticidal properties of these compounds and by the end of the World War II they were successful to make many of the insecticidal Organophosphates used at present. Chlordane, a cyclodiene insecticide, was used extensively as termiticide in the 1980s but was removed from the market due to calculable residue levels allegedly causing health problems. These compounds are available as dusts, granules, or liquids. Some products need to be diluted with water before use, and some are burnt to make smoke that kills insects.



Parathion

❖ **Fatal Dose**

Extremely toxic (LD_{50}: 1 - 50 mg/kg) to highly toxic (LD_{50}: 51 to 500 mg/kg) - Chlorfenvinphos, Chlorpyriphos, Demeton, Diazinon, Dichlorvos, Dimethoate, Disulfoton, Ediphenphos, Ethion, Fenitrothion, Fensulfothion, Fenthion, Fonophos, Formothion, Methyl Parathion, Mevinphos, Monocrotophos, Oxydemeton Methyl, Phenthoate, Phorate, Phosphamidon, Quinalphos, TEPP and Thiometon.

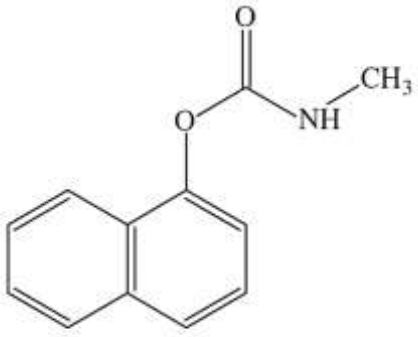
Moderately toxic (LD_{50}: 501 to 5000 mg/kg) to slightly toxic (LD_{50}: >5000mg/kg) - Abate, Acephate, Coumaphos, Crufomate, Famphur, Glyphosate, Malathion, Phenthoate, Primiphos Methyl, Ronnel, Temephos, Triazophos, and Trichlorphon.

❖ **Fatal Period**

In fatal doses symptoms starts within half an hour and death occurs within three hours. In non-fatal cases, effects last for 36 hours and fade off in 48 - 72 hours to 3 weeks.

4.3 CARBAMATE PESTICIDES

Carbamates are as popular as organophosphates in their role as insecticides (and fungicides) and share a number of resemblances. Carbamates are the group of insecticides which are derived from Carbamic Acid (mono amide of carbon dioxide) Aryl or Alky Ester derivatives of Carbamic Acid. Besides them an additional group of carbamates insecticides also exist which are derivatives of aliphatic oxime rather than esters, resembling aldehydes or ketones collectively known as methylcarbamyloximes.



Carbaryl

❖ **Fatal Dose**

Extremely toxic (LD_{50}: 1 to 50 mg/kg) to highly toxic (LD_{50}: 51 to 500 mg/kg) - Aminocarb, Bendiocarb, Benfuracarb, Carbaryl, Carbofuran, Dimetan, Dimetilan, Dioxacarb, Formetanate, Methiocarb, Methomyl, Oxamyl, Propoxur.

Moderately toxic (LD_{50}: 501 to 5000mg/kg) to slightly toxic (LD_{50}: >5000 mg/kg) - Aldicarb, Bufencarb, Isoprocarb, MPMC, MTMC, Pirimicarb.

4.4 PYRETHROID PESTICIDES

Pyrethrins are active extracts of the chrysanthemum plant (*Chrysanthemum cinerariaefolium*), and include pyrethrum and piperonyl butoxide. They are esters of pyrethric and chrysanthemic acids formed by the keto alcohols pyrethrolone, cinerolone, and jasmololone. Pyrethrin I and pyrethrin II are two of the most insecticidally potent pyrethric and chrysanthemic esters. Pyrethroids are synthetic analogues and number over 1000 varieties which are used as insecticides to incapacitate or "knock out" insects. Most mammals are resistant since they can rapidly metabolise and detoxify these agents.

These compounds are used as household insect repellents and insecticides. They are sold as liquids, sprays, dusts, powders, mats, and coils. They are also used to prevent pest infestation in granaries and in agriculture as pesticides. Pyrethrum extract is effective for treating pediculosis of the head, body and pubic area.

❖ **Fatal Dose**

Pyrethrum has an **LD_{50}** of over **1 gm/kg**. However, the minimal lethal dose of pyrethrum is not clearly established, though it is probably in the range of **10** to **100 grams**. Most cases of toxicity are actually the result of allergic reactions.

5. Mode of Action of Pesticides

❖ **Organochlorines:**

All the Organochlorines can be absorbed transdermally, orally, and by inhalation. Gastrointestinal absorption of these agents is generally efficient, particularly in the presence of absorbable lipid (animal or vegetable) fat. DDT is the least well absorbed transdermally, while dieldrin is very well absorbed. Many of these compounds are metabolised slowly and persist in tissues (especially fat) for prolonged periods. High residue levels from Organochlorine insecticide poisonings are found in adipose tissue. However, unlike other Organochlorine pesticides, methoxychlor does not substantially accumulate in fatty tissues of humans.

❖ **Organophosphorus:**

Organophosphates are powerful inhibitors of acetylcholinesterase which is responsible for hydrolysing acetylcholine to choline and acetic acid after its release and completion of function (i.e. propagation of action potential). As a result, there is build-up of acetylcholine with continued stimulation of local receptors and ultimately paralysis of nerves or muscles. Although organophosphates differ structurally from acetyl choline, they can bind to the acetylcholinesterase molecule at the active site and phosphorylate the serine moiety. When this occurs, the consequential conjugate is infinitely more stable than the acetylcholine- acetylcholinesterase conjugate, although endogenous hydrolysis does occur. Depending on the amount of stability and charge distribution, the time to hydrolysis is increased. Phosphorylated enzymes degrade very slowly over days to weeks, making the acetylcholinesterase essentially inactive. Once the acetylcholinesterase is phosphorylated, over the next 24 to 48 hours an alkyl group is eventually lost from the conjugate, further exacerbating the situation. As this occurs, the enzyme can no longer spontaneously hydrolyse and becomes permanently inactivated. Apart from acetylcholinesterase, organophosphates exert powerful inhibitory action over other carboxylic ester hydrolases such as chymotrypsin, butyrl cholinesterase (pseudo cholinesterase), plasma and hepatic carboxyl esterases, paraoxonases, and other non-specific proteases.

❖ **Carbamates:**

Like the Organophosphate insecticides, the mode of action of the carbamates is acetylcholinesterase inhibition with the important difference that the inhibition is more rapidly reversed than with Organophosphate compounds. This is a reversible type of binding and hence symptoms are less severe and of shorter duration. As a result both morbidity and mortality are limited when compared to organophosphate poisoning. Also, since carbamates do not penetrate the CNS to the same extent as organophosphates, CNS toxicity is likewise much less. With respect to all other clinical manifestations, there is general similarity between carbamates and organophosphates. Carbamates are rapidly metabolised. They are rapidly hydrolysed by liver enzymes to methyl carbamic acid and a variety of low toxicity phenolic substances. These metabolites may sometimes be measured in urine as long as 2 to 3 days after significant pesticide absorption.

❖ **Pyrethroids:**

Low toxicity in mammals is probably due to rapid metabolic breakdown in the liver: pyrethrum is broken down mainly by oxidation of the isobutenyl side chain of the acid moiety and of the unsaturated side chain of the alcohol moiety with ester hydrolysis playing a role. Pyrethrins affect nerve membranes by modifying the sodium and potassium channels, resulting in depolarization of the membranes. Formulations of these insecticides frequently contain the insecticide synergist piperonyl butoxide, which acts to increase the efficacy of the insecticide by inhibiting the Cytochrome P450 enzymes responsible for the breakdown of the insecticide.

6. Toxicokinetics of pesticides

❖ **Organochlorines:**

Excretion of organochlorine compounds does not follow first order kinetics. As body stores get lower, the half-life for the remaining store increases dramatically. This is probably due to complex lipoprotein binding, wherein different bound forms exhibit different dissociation characteristics.

❖ **Organophosphates:**

Organophosphates can be absorbed by any route including transdermal, trans-conjunctival, inhalational, across the GI and GU mucosa, and through direct injection. Appearances usually begin within a few minutes to few hours, but may be delayed upto 12 hours or more in the case of certain compounds (e.g. fenthion, parathion).

❖ **Carbamates:**

Carbamates being highly volatile have various mode of absorption in case of occupational poisoning but the most likely is through skin i.e. dermal toxicity. The lipophility of this class of agents and presence or organic solvents and emulsifier insure a rapid dermal penetration and absorption into the systemic circulations. Carbamates are readily absorbed in the gastro intestinal tract and the efficacy of absorption is guided by the vehicle in which it is administered. The excretion of water soluble by products of detoxification occurs relatively rapid through the urine and / or faeces in most vertebrate species. Glucoronide and sulphate derivatives of the aryl substituent are the major products found in the urine. Small amount of the parent carbamates may be excreted in the urine.

❖ **Pyrethroids:**

Structurally, pyrethroids are of two types-

1) **Type I** pyrethroids do not contain a cyano group, e.g. permethrin.
2) **Type II** pyrethroids contain a cyano group, e.g. deltamethrin, cypermethrin, fenpropathrin, fenvalerate, etc.

Like DDT, pyrethroids extends the inactivation of the sodium channel by binding to it in the open state. Type II agents are more potent in this regard, and also act by inhibiting GABA-mediated inhibitory chloride channels.

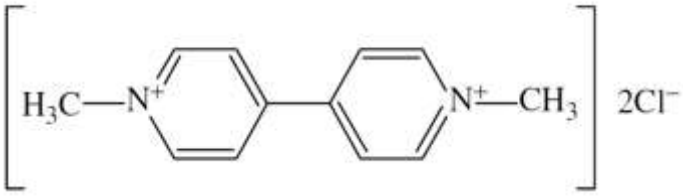
7. Introduction to Herbicide (Weedicides)

These are compounds which kill weeds. They are also known as Weedicides. The main examples of herbicides are acrolein, dalaphon, paraquat, Diquat, glyphosate, atrazine, propazine, simazine, nitrofen, Trichloroacetic Acid and chlorophenoxy compounds. Some important Weedicides are discussed as under:

7.1 PARAQUAT AND DIQUAT

Paraquat and Diquat are widely used herbicides which belong to the bipyridyl group. Paraquat is 1, 1- dimethyl- 4, 4-bipyridyliumdichloride, and was first synthesized in 1882, but began to be used as an herbicide only since the 1960s. It is available either in granular form (25–80 gm/kg) or as water soluble concentrate which is an odourless brown liquid (100–200 gm/L). The granular form is available as colourless crystals (dichloride salt) or a yellow solid [*bis* (methyl sulphate) salt]. In India, most of the concentrates of paraquat are available as 10 –20% solutions, and therefore 10 ml of a 20% solution can contain about 2 grams of paraquat. Common brand names include Weedol, Gramoxone and Uniquat.

Diquat is 1, 1- ethylene-2, 2- dipyridylium dibromide, and is less commonly used than paraquat. It has the same indications and mode of action as paraquat but produces much less severe pulmonary lesions.



Paraquat

❖ **Fatal Dose**

The fatal dose of Paraquat and Diquat is approximately **4 mg/kg.**

❖ **Fatal period**

Usually the Fatal Period is 3-5 days but may vary with the intervening factors.

❖ **Mode of Action**

Paraquat is a rapidly-acting herbicide. It kills the tissues of green plants by contact action with foliage and by some amount of translocation to the xylem.

❖ **Toxicokinetics**

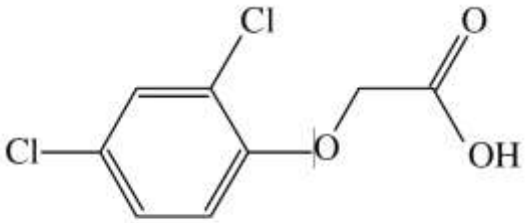
Absorption through inhalation, skin contact, or eye contact is minimal, though prolonged contact can be hazardous. On ingestion, paraquat solution is much more rapidly absorbed than the granular form. After absorption it tends to accumulate in the lungs and kidneys. Paraquat has a large volume of distribution (1.2 to 1.6 L/kg). More than 90% of an absorbed dose is excreted by the kidneys as the parent compound within12 to 24 hours. Paraquat is distributed into all organs. Highest concentrations are found in kidney and lung; paraquat also accumulates in muscle tissue, which may represent a reservoir, explaining prolonged detection of plasma or urine paraquat weeks or months following ingestion.

7.2 CHLOROPHENOXY COMPOUNDS

Chlorophenoxyacetate herbicides include the following:

- MCPA (4- chloro-2- methylphenoxyacetic acid)
- MCPP (2- methyl-4- chlorophenoxypropionic acid)
- DCPP (2,4- dichlorophenoxypropionic acid)
- 2,4D (2,4- dichlorophenoxyacetic acid)
- 2,4,5-T (2,4,5- trichlorophenoxyacetic acid)

These herbicides are used to kill broad-leaved weeds in cereal crops, grassland parks and gardens, and weeds in ponds, lakes, and irrigation canals. Common brands of Chlorophenoxy compounds are 2, 4-D, Fennoxone, Weednash.



2,4-D

❖ **Mode of Action**

Rapid and complete absorption of chlorophenoxy compounds from the GI tract has been reported. Dermal absorption is limited. Chief organs of deposition are kidneys, liver, central and peripheral nervous systems, and the gastrointestinal tract.

❖ **Toxicokinetics**

They are highly protein bound. Phenoxy acid esters and salts are primarily metabolised by acid hydrolysis; a minor amount is conjugated. They are primarily eliminated unchanged (90%) by the kidneys via the renal organic anion secretory system.

7.3 GLYPHOSATE

Glyphosate, an aminophosphonate is used as an herbicide. It is an odourless, colourless to white crystalline powder and is weakly acidic. Glyphosate herbicides are commonly applied in spray form and primarily formulated as either a water-soluble liquid or concentrate solution, or a solution made with a water-soluble powder and other ingredients.

❖ **Fatal Dose**

Ingestion of > 200 ml is likely to produce severe toxicity.

❖ **Mode of Action**

The surfactant present in commercial solution, polyoxyethyleneamine, an anionic surfactant, may be responsible for many of the toxic effects of glyphosate. Surfactants alone may cause circulatory failure, respiratory failure, seizures, generalised oedema and gastric erosion. Glyphosate appears to undergo minimal metabolism. Results from animal studies indicate that essentially no toxic metabolites are produced and nearly 100% of the body burden is parent compound.

8. Summary

- Acute pesticide poisoning is a serious global problem accounting for an estimated 3 million cases of severe poisoning worldwide each year, with approximately 220,000 deaths.
- More than 90% of these cases are reported from developing countries such as India.
- Apart from that Pesticides are a major source of concern as water and soil pollutants.
- Because of their stability and persistence, the most hazardous pesticides are the organochlorine compounds such as DDT, aldrin, dieldrin, and chlordane.
- Persistent pesticides can accumulate in food chains. This bioaccumulation has been well documented with the pesticide DDT, which is now banned in many parts of the world.
- In contrast to the persistent insecticides, the organophosphorus pesticides, such as Malathion, and the carbamates, such as carbaryl, are short-lived and generally persist for only a few weeks to a few months.
- Thus these compounds do not usually present as serious a problem as the earlier insecticides.