CHAPTER FOUR

PESTICIDE POISONING

Pesticide Poisoning

- Objectives
- Insecticides
- Herbicides
- Fungicides
- Fumigants
- Rodenticides

Objectives

At the end of this chapter students will be able to:

- Discuss the toxicity of Insecticides
- Discuss the toxicity of Herbicides
- Discuss the toxicity of Fungicides
- Discuss the toxicity of Fumigants
- Discuss the toxicity of Rodenticides

1. Insecticides

Organophosphate and Carbamate Insecticides

- Organophosphate compounds have become widely used pesticides as replacements for the more persistent **organochlorine** insecticides
- Organophosphate insecticides do not **bioaccumulate** in tissues and organisms or accumulate in the environment as do the organochlorines
- Chlorpyrifos, an organophosphate compound, has become a widely used termiticide, serving as a substitute for the more persistent organochlorine compounds

Insecticides cont'd

Mechanism of Action

- Both organophosphate and carbamate have the same mechanism of action in insects as well as in mammals (including humans): the inhibition of the enzyme **acetyl cholinesterase**
- The inhibition of acetyl cholinesterase is responsible for the acute symptomatology
- Acetyl cholinesterase is an enzyme located in the synaptic cleft and its function is the breakdown of acetylcholine

Insecticides cont'd

- Acetylcholine is the neurotransmitter present:
  - Postganglionic parasympathetic nerves
  - Somatic motor nerves endings in skeletal muscle
  - Preganglionic fibers in the parasympathetic and sympathetic nerves
  - In some synapses in the central nervous system

Insecticides cont'd

- Organophosphate and carbamate insecticides by inhibiting the acetyl cholinesterase at its site, resulting accumulation of the acetylcholine in nerve tissue and at the effector organ
- The accumulation results in the continued stimulation of cholinergic synapses and at sufficient levels leads to the signs and symptoms associated with overexposure to these compounds

Acute Effects of Organophosphate and Carbamate Insecticides

- The effects of organophosphate and carbamate insecticides can be either local (e.g., sweating from localized dermal exposure) or systemic
- Signs and symptoms of overexposure to the compounds occur beginning from 5 min to 12 h after exposure
- The acute signs and symptoms are related to the degree of inhibition of acetyl cholinesterase in the individual
- The clinical manifestation is a result of muscarinic, nicotinic, and CNS symptoms

Acute Effects of Organophosphate and Carbamate Insecticides cont'd

- In systemic intoxications resulting the muscarinic effects are generally the first effects to develop
- Signs and symptoms resulting from overexposure to these organophosphate and carbamate compounds are:
  - Diarrhea, Urination, Meiosis (pinpoint pupils), Bronchospasm, Emesis (vomiting), Lacrimation (tearing), and Salivation
- Signs and symptoms do not occur unless acetyl cholinesterase activity is approximately 50 percent or less of normal activity

Acute Effects of Organophosphate and Carbamate Insecticides cont'd

- Signs and symptoms in cases of mild to moderate organophosphate intoxication typically resolve within days to weeks following exposure.
- In cases of severe organophosphate intoxication, it can be 3 months or so before cholinesterase red blood cell levels return to normal.
- Death from organophosphate intoxication is usually due to:
  - Respiratory failure from depression of the respiratory center in the brain
  - Paralysis of the respiratory muscles, and excessive bronchial secretions, pulmonary edema, and bronchoconstriction

Acute Effects of Organophosphate and Carbamate Insecticides cont'd

- Carbamate intoxication presents similar to that of organophosphate intoxication
- Carbamate intoxication resolve quickly than organophosphate, due to the rapid **reversal** of acetyl cholinesterase enzyme as well as to the rapid **biotransformation** in vivo

Chronic Effects of Organophosphate and Carbamate Insecticides

- The main chronic effect that may result from exposure to organophosphate insecticides is delayed neuropathy
- Organophosphate-induced delayed neuropathy has been associated with exposure to only a few organophosphate compounds, with cases occurring almost exclusively at near-lethal exposure levels.

Organochlorine Insecticides

- Organochlorine insecticides had widespread use in the 1940s through the mid-1960s in agricultural and malarial control programs
- Because of their environment effects, their use has become almost completely discontinued
- Organochlorine insecticides that were commonly used in the past include:
  - Toxaphene (Toxakil)
  - Endrin (Hexadrin)
  - Aldrin (Aldrite)
  - Endosulfan (Thiodan)

Organochlorine Insecticides cont'd

- Organochlorine insecticides that were commonly used in the past include …..:
  - BHC (hexachlorocyclohexane)
  - Dienoclor (Pentac)
  - Heptachlor (Heptagran)
  - Dicofol
  - Mirex (Declorane)
  - Chlordane
  - DDT

Organochlorine Insecticides cont'd

- Organochlorine compound that is still in use today is lindane
- lindane is used in the medicinal product for human ectoparasite disease (as well as in products for use in the home and garden and on animals, e.g., Acitox, Gammex)
- It is also used as insecticides in agricultural and forestry settings
- Organochlorine compounds were also used as structural protection against termites in the past

Acute and Chronic Health Effects of Organochlorine Insecticides

- The principal adverse effect associated with over-exposure to organochlorine insecticides is:
  - Nervous system hyperactivity (e.g., headache, dizziness, paresthesias, tremor, incoordination, or convulsions)
  - Nausea and vomiting, headache, tremor, and mental disturbances
- Myoclonic movement and convulsions are sometimes seen in severe cases of poisoning

Acute and Chronic Health Effects of Organochlorine Insecticides cont'd

- It should be noted that with overexposure to the toxaphene and cyclodiene compounds (e.g.,aldrin, endrin, chlordane, and heptachlor) the first sign seen is convulsions, in the absence of the early symptoms just mentioned

Insecticides of Biological Origin

- Many compounds are present in nature that have insecticidal qualities, including extracts from the chrysanthemum flower and from the *Legumionocae* genera (e.g., rotenone)
- Trade names of insecticides in this classification include Pyrocide (pyrethrum) and Prentox (rotenone)

Pyrethrum and Pyrethrins

- Pyrethrum is an extract from the chrysanthemum flower, *Pyrethrum cinerariaefollium* (“Dalmatian insect flowers”) and other species
- This extract contains approximately 50 percent natural pyrethrins, the insecticidal component of the extract

Insecticides of Biological Origin cont'd

- The pyrethrins jasmolins I and II, cinerins I and II, and pyrethrins I and II are extracted from the powder for formulation into commercial aerosols and spray products
- This class of compounds are commonly used in household insecticides and in pet products (e.g., flea and tick dips and sprays)
- Pyrethrins and pyrethrum are very rapidly metabolized and excreted from humans and have very low mammalian toxicity

Insecticides of Biological Origin cont'd

Rotenone

- Rotenone (Noxfish) occurs naturally in several plants species (e.g., the *Leguminocae* genera) and is used mainly as an insecticide as well as to eliminate fish in lakes and ponds
- The mechanism of action is respiratory toxin, blocking **electron transport** at ubiquinone, preventing oxidation of NADH
- Rotenone seems to have low toxicity in man, and few reports of serious injury appear to have been reported
- Occupational exposure to the powder of the plant that contains rotenone has reportedly caused dermal and respiratory tract irritation and numbness in mouths of workers

2. Herbicides

Chlorophenoxy Herbicides

- The most commonly recognized chlorophenoxy herbicides are 2,4-dichlorophenoxy acetic acid (2,4-D) and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T)
- These compounds exert their action in plants by acting as **growth hormones**, but have no such hormonal action in animals or humans
- The primary routes of exposure to chlorophenoxy herbicides are dermal and inhalation
- Chlorophenoxy compounds act by **uncoupling oxidative phosphorylation** and decreasing oxygen consumption in tissue

Herbicides cont'd

- These compounds are fairly rapidly excreted and do not accumulate in the body
- These compounds are excreted via the urine primarily, and apart from conjugation of acids, little biotransformation occurs in the body
- Following ingestion, the acute toxicity of chlorophenoxy herbicides includes irritation of the mucous membranes and gastrointestinal linings
- Large intentional overdoses with chlorophenoxy acids have resulted in symptoms of coma, metabolic acidosis, myotonia, mucous membrane irritation, and myalgias

Herbicides cont'd

Bipyridyl Compounds: Paraquat and Diquat

- Paraquat (1,1′-dimethyl-4,4′-dipyridylium) and diquat (1,1′-ethylene-2,2′- bipyridylium) are bipyridylium herbicides
- The common trade names are Gramoxone (paraquat) and Aquacide (diquat)
- A majority of toxicity associated with both paraquat and diquat are seen in cases of accidental or intentional (suicidal) ingestion, with paraquat having greater toxicity than diquat

Herbicides cont'd

- Paraquat poisoning (e.g., from suicide attempts) can lead to multi organ toxicity (e.g. gastrointestinal tract, kidney, heart, and liver) including pulmonary fibrosis
- **Early deaths** occurring after intoxication with paraquat result from **acute pulmonary edema, oliguric** renal failure, and hepatic failure
- Deaths occurring **one to three weeks** following an intoxication episode are typically the **result of pulmonary fibrosis**
- Sufficient dermal exposure to paraquat can also cause dermal irritation, blistering, and ulceration
- **Inhalation is not believed to be a toxic route of exposure**

Herbicides cont'd

- Diquat causes less dermal irritation and injury than does paraquat, and diquat is not selectively concentrated in pulmonary tissue like paraquat
- Diquat, in contrast to paraquat, causes little to no injury to the lungs; however, diquat has an effect on the **central nervous system**, whereas paraquat does not
- The mechanism of action of diquat is thought to be similar to that of paraquat, involving the production of **superoxide radicals** that cause lipid membrane destruction
- Dermal exposure to sufficient levels of diquat can cause fingernail damage and irritation of the eyes and mucous membranes

Herbicides cont'd

- Intoxication by diquat via the oral route has reportedly caused gastrointestinal irritation, nausea, vomiting, and diarrhea
- Both paraquat and diquat are reportedly associated with renal toxicity

Glyphosate (Round-Up) [*N*-(phosphonomethyl) glycine]

- It is a widely used herbicide that interferes with amino acid metabolism in plants
- Glyphosate is moderately absorbed through the gastrointestinal tract, undergoes minimal biotransformation, and is excreted via the kidneys

Herbicides cont'd

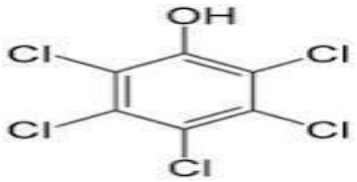
- It may cause various signs and symptoms include gastrointestinal irritation and damage, as well as dysfunction in several organ systems (e.g., lung, liver, kidney, CNS, and cardiovascular system)

Triazines

- Triazine and triazole herbicides include:
  - Atrazine (2-chloro-4-ethylamino-6-isoproplyamine-*s*-triazine),
  - Propazine,
  - Simazine [2-chloro-4,6-bis(ethylamino)-*s*-triazine], and
  - Cyanazine [2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-*s*-triazine]
- Triazine herbicides have relatively **low toxicity and no cases of systemic poisoning**

3. Fungicides

- Fungicides are used to control the growth of fungi
- Pentachlorophenol is one of known fungicide



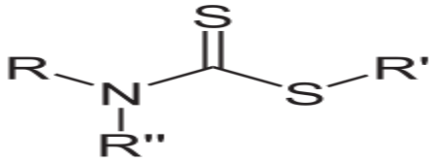
- It is also called penta, and used as a wood preservative for fungus decay or against termites, as well as a molluscicide
- Trade names of pentachlorophenol include: Pentacon, Penwar, and Penchlorol
- Pentachlorophenol is absorbed via the skin, lung, and gastrointestinal tract
- Pentachlorophenol and its biotransformation products are excreted primarily via the kidneys

Fungicides cont'd

- The biochemical mechanism of action is through an increase in oxidative metabolism from the uncoupling of oxidative phosphorylation
- This increase in oxidative metabolism in poisonings can lead to an increase in body temperature
- In fatal cases of poisoning from pentachlorophenol, body **temperatures increases** as high as 41.8 °C (107.4 °F)
- Severe overexposure to pentachlorophenol can cause delirium, flushing, pyrexia, diaphoresis, tachypnea, abdominal pain, nausea, and tachycardia

Fungicides cont'd

Dithiocarbamates/Thiocarbamates



- The dithiocarbamates and the thiocarbamates are used as fungicidal compounds and have little insecticidal toxicity, unlike the *N*-methyl carbamates, Thiocarbamate fungicides include:
    - Thiram (AAtack),
    - Metam-sodium (Vapam),
    - Ziram (Ziram 76),
    - Ferbam, and
    - Ethylene bis dithiocarbamate (EBDC) compounds-maneb, zineb, and mancozeb
    - The thiocarbamate class of fungicides has low acute toxicity

Fungicides cont'd

- Thiram dust may cause eye, skin, and mucous membrane irritation, with contact dermatitis and sensitization
- Thiram, like disulfiram, is not a cholinesterase inhibitor, but does cause inhibition of the enzyme **acetaldehyde dehydrogenase** (responsible for the conversion of acetaldehyde to acetic acid)
- Exposure to ziram, ferbam, and the EBDC compounds have been associated with skin, eye, and respiratory tract irritation in humans
- Maneb and zineb have been associated with cases of chronic dermatological disease, possibly due to dermal sensitization to these compounds in workers

Fungicides cont'd

Chlorothalonil

- Chlorothalonil (Bravo, Daconil) (2,4,5,6-tetrachloro-1,3-benzenedicarbonitrile) has been reported to cause dermal and mucous membrane irritant effects
- Chlorothalonil appears to have low potential for toxicity in humans

Copper Compounds

- Exposure to dust and powder formulations of copper-based fungicides has been reported to cause irritation of the skin, eyes, and respiratory tract
- Systemic intoxication in humans by copper fungicides has been rarely reported

Fungicides cont'd

- Ingestion of the compound cause:
  - Gastrointestinal irritation, nausea, vomiting, diarrhea
  - Headache, sweating, weakness
  - Hemolysis
  - Albuminuria
  - Methemoglobinemia & Hemoglobinurina
  - Liver enlargement
  - Occasionally renal failure

4. Fumigants

- The fumigants are volatile in nature; some exist in a gas phase at room temperature while others are liquids or solids
- Fumigants are in general readily absorbed via dermal, respiratory, and ingestion routes

Methyl Bromide

- Methyl bromide (Brom-O-Sol, Terr-O-Gas) has been in use as a fumigant since 1932
- It is a colorless and practically odorless compound (at low levels), with its low warning potential contributing to its toxicity
- At higher concentrations, the odor of methyl bromide is similar to chloroform

Fumigants cont'd

- Methyl bromide has been used to treat dry packaged foods in mills and warehouses as well as used as a soil fumigant to control nematodes and fungi
- Methyl bromide is very irritating to the lower respiratory tract
- The parent compound is responsible for the toxicity of the methyl bromide, with the mechanism of toxicity to bind with **sulfhydryl enzymes**
- Exposure to high concentrations of methyl bromide can lead to pulmonary edema or hemorrhage

Fumigants cont'd

- Symptoms of acute intoxication include headache, dizziness, nausea, visual disturbances, vomiting, and ataxia
- Exposure to very high concentrations can lead to unconsciousness and death
- Death typically occurs within 4–6 h to 1–2 days post exposure; due to respiratory or cardiovascular failure resulting from pulmonary edema
- Dermal exposure to liquid methyl bromide can cause skin damage in the form of burning, itching, and blistering

Fumigants cont'd

Ethylene Oxide

- Ethylene oxide, also known as epoxyethane (ETO)
- It is a sterilant and fumigant that exists as a colorless gas and which has a high odor threshold
- Ethylene oxide also is a severe mucous membrane and skin irritant
- Dermal exposure at sufficient levels can result in edema, burns, blisters and frostbite
- Acute intoxications can result in CNS depression characterized by headache, nausea, vomiting, drowsiness, weakness, and cough
- Exposure to extreme concentrations of ethylene oxide can cause the development of pulmonary edema and cardiac arrhythmias

Fumigants cont'd

Sulfuryl Fluoride

- Sulfuryl fluoride (Vikane) (SO_2F_2), a colorless and odorless gas, is used as a structural fumigation
- Fatalities have been reported from individuals entering buildings recently fumigated with sulfuryl fluoride before reentry was allowed
- The acute toxic effects from sulfuryl poisoning include mucous membrane irritation, nausea, vomiting, dyspnea, cough, severe weakness, restlessness, and seizures

5. Rodenticides

- The rodenticides are a class of compounds designed specifically to target rodents
- The most efficient route of exposure of these compounds is via ingestion
- The rodenticides acts by depression of the vitamin K synthesis of the blood clotting factors II (prothrombin), VII, IX, and X
- This anti-coagulant property manifests as diffuse internal hemorrhaging occurring typically after several days of rodenticide bait ingestion
- Warfarin is a commonly used coumarin rodenticide

Rodenticides cont'd

- It causes toxic effects by inhibiting the formation of prothrombin and the inhibition of vitamin K–dependent factors in the body
- Other anticoagulant rodenticides include: coumafuryl, brodifacoum, difenacoum, and prolin
- Warfarin is known to be absorbed both dermally and from ingestion
- Signs and symptoms of intoxication include: epistaxis, hemoptysis, bleeding gums, gastrointestinal tract and genitourinary tract hemorrhage
- The indandiones, unlike the coumarins, cause nervous system, cardiac, and pulmonary effects in laboratory animals preceding the death from the anticoagulant effects

Rodenticides cont'd

- These types of adverse effects have not been reported in cases of human exposure
- Indandione rodenticides include diphacinone, diphacin, and chlorphacinone
- The most prominent clinical laboratory sign from the administration of these classes of compounds is an increased prothrombin time and a decrease in plasma prothrombin concentration
- Treatment of toxicity from coumarins and indandions consists of the administration of vitamin K

Rodenticides cont'd

Thallium Sulfate

- Thallium sulfate is readily absorbed via ingestion and dermally, as well as via inhalation
- The target organs of thallium sulfate are gastrointestinal tract (hemorrhagic gastroenteritis), heart and blood vessels, kidneys, liver, skin, and the hair
- Symptoms such as headache, lethargy, muscle weakness, numbness, tremor, ataxia, myoclonia, convulsions, delirium, and coma
- Death from thallium sulfate intoxication is due to respiratory paralysis or cardiovascular failure

Rodenticides cont'd

- Serum, urine, and hair thallium levels can be used to assess exposure to this compound
- There is no specific treatment for thallium sulfate poisoning, and treatment is supportive
- **Syrup of ipecac and activated charcoal can be used to decrease gastrointestinal absorption**

Sodium Fluoroacetate

- Sodium fluoroacetate is also known as 1080 (registered trademark)
- This compound is easily absorbed via ingestion as well as through inhalation and dermal routes

Rodenticides cont'd

- Fluorocitrate adversely affects cellular respiration through disruption of the tricarboxylic acid cycle (inhibiting the enzyme ***cis*-aconitase**)
- The accumulation of citrate in tissues also accounts for some of the acute toxicity associated with this compound
- The target organs of sodium fluoroacetate are:
  - The heart (seen as arrhythmias leading to ventricular fibrillation)
  - The brain (manifested as convulsions and spasms), following intoxication (typically following suicidal or accidental ingestion)

References and Suggested Reading

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