TOXICOLOGY OF FUNGICIDES, PESTICIDES; ORGANOPHOSPHATES

FUNGICIDE POISONING

Fungicides are extensively used in industries, agriculture, and the home.

- **Uses:** protection of seed grain during storage, shipment, and germination; protection of mature crops, berries, seedlings, flowers, and grasses in the field, in storage, and during shipment; suppression of mildews that attack painted surfaces; control of slime in paper pulps; and protection of carpet and fabrics in the home.
- Fungicides vary enormously in their potential for causing adverse effects in humans. However, most fungicides currently in use are unlikely to cause frequent or severe systemic poisonings for several reasons:
    1. Many fungicides have low inherent toxicity in mammals and are inefficiently absorbed.
    2. Many fungicides are formulated as suspensions of wettable powders or granules, from which rapid, efficient absorption is unlikely.
    3. Methods of application are such that relatively few individuals are intensively exposed.
- Apart from systemic poisonings, fungicides as a class are probably responsible for a disproportionate number of irritant injuries to skin and mucous membranes, as well as dermal sensitization.

Examples of fungicides are:

a. Substituted Benzenes

b. Thiocarbamates

c. Ethylene bis-dithiocarbamates/EBDC compounds

d. Thiophthalimides

e. Copper compounds

f. Organomercury compounds

g. Organotin compounds

h. Cadmium compounds

i. Miscellaneous organic fungicides

- **Substituted Benzenes:**

1. **Chloroneb:** It is moderately irritating to skin and mucous membranes. The metabolite dichloromethocy-phenol is excreted in the urine. No cases of systemic poisoning in humans have been reported.
2. **Chlorothalonil**: Causes irritation of skin and mucous membranes of the eyes and respiratory tract on contact. Cases of allergic contact dermatitis have been reported.
3. **Hexachlorobenzene:** Differs chemically and toxicologically from hexachlorocyclohexane, the gamma isomer of which lindane is still a widely-used insecticide. Although this seed protectant fungicide has only slight irritant effects and relatively low single-dose toxicity, long-term ingestion of HCB-treated grain by Turkish farm dwellers in the late 1950s caused several thousand cases of toxic porphyria cutanea tarda.

   Mechanism of action: Impairs hemoglobin synthesis, leading to toxic end-products (porphyrins) in body tissues.

   Clinical Signs: Excretion of red-tinged (porphyrin-containing) urine, scarring and atrophy of skin with overgrowth of hair, liver enlargement, loss of appetite, arthritic disease, and wasting of skeletal muscle mass.

   Treatment: Wash skin with soap and water. Flush contamination from the eyes with copious amounts of water. If a large amount of the fungicide has been ingested in the last few hours, and if copious vomiting has not already occurred, activated charcoal in addition to the cathartic sorbitol can be given.

- **Thiocarbamates**

1. **Metam-Sodium:** Formulated in aqueous solutions for application as a soil biocide and fumigant to kill fungi, bacteria, weed seeds, nematodes, and insects.

Mechanism of action: Its decomposition in water yields methyl isothiocyanate, a gas that is extremely irritating to respiratory mucous membranes, the eyes and the lungs.

Clinical Signs: Severe respiratory distress, coughing of bloody, frothy sputum.

NB: Metam-sodium is not a cholinesterase inhibitor. Atropine is not an antidote.

2. **Thiram:** It is a common component of latex and possibly responsible for some of the allergies attributed to latex. Thiram dust is moderately irritating to the skin, eyes, and respiratory mucous membranes. It appears to be about 10 times as toxic as disulfiram.

Clinical Signs: Nausea, vomiting, diarrhea, mental confusion, dyspnea, chest and abdominal pain, profuse sweating and skin rash.

Treatment: Appropriate i.v fluids should be infused, especially if vomiting and diarrhea are severe. Serum electrolytes and glucose should be monitored and replaced as needed.

- **Ethylene bis-dithiocarbamates/EBDC compounds**

1. Maneb **2. Zineb**

These fungicides may cause irritation of the skin, respiratory tract, and eyes.

- **Thiophthalimides**

1. Captan **2. Captafol**

They are moderately irritating to the skin, eyes, and respiratory tract.

Clinical Signs: Laboratory animals given very large doses of captan exhibit hypothermia, irritability, listlessness, anorexia, hyporeflexia, and oliguria.

- **Copper compounds:**
    1. Organic copper compounds
    2. Inorganic copper compounds.

TOXICOLOGY OF PESTICIDES; ORGANOPHOSPHATES

- A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest.
- In other words, pesticides are any chemical, physical or biological agents that would kill or destroy unwanted plant or animal pests.
- Pesticides are used extensively as acaricides/ ectoparasiticides in veterinary medicine to control insect pests of both mammals and birds.
- Also widely used to control insect vectors of public health importance.

- **Insecticides**:

- Insecticides are a heterogeneous group of chemicals whose desired activity is killing of insects in a very selective and specific manner.
- Most insecticides are not highly selective and result in poisoning in many nontarget species including man and domestic animals.
- Insect pests are responsible for destruction and damage of one third of the world's crops.

Uses:

(i) To increase the production and quality of agricultural products

(ii) To minimize the damage caused by insects during storage of food grains

(iii) To control ectoparasites of domestic animals

(iv) To control certain vector borne diseases

(v) To repel household pests

(vi) Act as anthelmintics in livestock.

- Most insecticides affect the nervous system of insects but they also possess some activity against the mammalian nervous system.
- The hazard to man and animals occur due to percutaneous absorption or by ingestion of their immediate residues.

On the basis of their chemical nature, insecticides may be categorized as:

- Organochlorine or chlorinated hydrocarbon insecticides
- Organophosphorus insecticides
- Carbamate insecticides
- Synthetic pyrethroid insecticides

- **Organochlorine insecticides**

The chlorinated hydrocarbons are divided into four groups:

i. Dichlorodiphenylethanes e.g dichlorodiphenyltrichloroethane (DDT), methoxychlor etc.

ii. Chlorinated cyclodienes e.g aldrin, dieldrin etc.

iii. Hexachlorocyclohexanes e.g lindane.

iv. Miscellaneous group e.g mirex.

Sources of poisoning:

i) Ingestion of organochlorine contaminated feeds and water by the animals.

ii) Inhalation or absorption from the skin during topical application as ectoparasiticides.

Pharmacokinetics: They are water insoluble but soluble in oil and organic solvents. The compounds, in powder form, can easily penetrate the cuticle of insects compared to mammalian skin and intestinal mucosa which explains its greater toxicity to insects than in mammals.

In mammals, methoxychlor is rapidly degraded by liver and the non-toxic metabolite(s) is excreted in faeces. Its low toxicity and tissue accumulation is due to rapid detoxification and slow gastrointestinal absorption. Aldrin is metabolized by microsomal enzymes to diedrin which is more toxic than the parent compound. Except methoxychlor, other organochlorine insecticides are stored in the body fat. However, none of these agents are known to accumulate in vital organs.

Mechanism of toxicity: The chlorinated hydrocarbons are neuro-poisons. By virtue of their high lipid solubility, these agents can enter the neural membrane with ease and interfere with normal functioning of the nerve membrane sodium channels.

DDT acts by (1) reducing the potassium transport through pores

(2) inactivating sodium channel closure

(3) inhibiting Na^{+}-K^{+} and Ca^{2+}-Mg^{2+} ATPases

(4) inhibiting calmodulin- Ca^{2+} binding with release of neurotransmitter.

The cyclodiene compounds act on the chloride ion (Cl^{-}) transport by antagonizing the gamma amino butyric acid (GABA) receptors in the Cl^{-} channels and also inhibit the Ca^{2+}-Mg^{2+} ATPase.

Clinical symptoms: DDT poisoning cause initial stimulation of CNS followed by depression and death due to respiratory failure. In chronic poisoning, liver damage, hypoglycemia, fall in liver glycogen concentration and hyperkalemia may be noted. Symptoms of cyclodeine compound poisoning are similar to DDT poisoning but more severe in nature and are characterized by grinding of teeth, difficult respiration, snapping of the eyelids and frequent urination. Other signs include walking backwards, wall climbing, aimless jumping and violent frenzied behavior.

Post-mortem lesions: There are no specific lesions in the nervous system. However, acute aldrin poisoning may cause hepatitis and acute tubular nephrosis. Chronic DDT and methoxychlor toxicoses may produce focal centrilobular necrosis of the liver.

Diagnosis:

- History of exposure to the insecticide.
- Clinical symptoms and post-mortem lesions
- Analysis of feeds and/or biological samples like liver and kidneys in dead animals and blood and milk samples in living animals.

Differential diagnosis:

i) Salt poisoning: history and absence of hyperthermia

ii) Strychnine poisoning: convulsions are tonic and absence of behavioural abberations and locomotor disturbances.

iii) Fluoroacetate poisoning: convulsions not elicited by external stimuli

iv) Nicotine poisoning: only cholinergic signs are exhibited

v) Anticholinesterase insecticide poisoning: only parasympathetic signs, no behavioural changes or hyperthermia.

vi) Lead poisoning: no abnormal posturing.

Treatment: No specific antidote is available. Treatment is only symptomatic and supportive.

ORGANOPHOSPHOROUS INSECTICIDES

Of the various groups of insecticides used in agriculture, veterinary and public health practices, organophosphorous insecticides (OPIs) constitute the bulk. These compounds are preferred due to their high selectivity, low toxicity in mammals and their rapid degradation in animal body and ecosystem. Although, OPIs have comparatively low toxicity in mammals than in insects, much higher acute toxicity has been observed in animals from careless use or following accidental ingestion of these chemicals. Besides their acute toxic effects, OPIs are also

implicated in various disorder and disease like cancer, reproductive disorders, peripheral neuropathy, impaired immune functions and neurobehavioural changes.

Examples: Parathion, and its oxygen analogue paraoxone, Disopropyl phosphorofluoridate (DFP), diazinon, dimethoate, coumaphos, curfomate, fenchlorvos, dichlorvos and haloxon.

Classification:

1. Based on the mechanism of action:

a) **Direct acting OPIs**: These compounds act by directly inhibiting the cholinesterase enzyme e.g dichlorvos, fenchlorvos.

b) **Indirectly acting OPIs**: These insecticides as such are inactive but are biotransformed in the body to toxic metabolites which inhibit cholinesterase enzymes.

1. Based on the manner in which they exert their insecticidal action:

a) Contact poisons: e.g parathion, malathion, paraoxon etc.

b) Selective systemic insecticides: Remain active and soluble for a reasonable period and are toxic to the plant pests but not to their predators e.g dimenthoate etc.

Mechanism of Toxicity: They inhibit acetylcholinesterase enzyme.

This inhibition leads to accumulation of acetylcholine at the nerve endings thus producing symptoms of parasympathetic stimulation.The phosphorylated AChE is higly stable and inactive and is unable to hydrolyse acetylcholine.

Pharmacokinetics: highly soluble and are rapidly absorbed by practically all routes including gastrointestinal tract, skin, mucous membranes and lungs. Dermal absorption is highly influenced by the solvent used. The metabolism and excretion of OPIs is a very complex process and it is dependent on chemical nature of the compound, route of entry and the species of animals involved. OPIs are hydrolysed in the body by a group of enzymes called phosphorylphosphatases. These enzymes are widely distributed in plasma and various tissues and are not inhibited by organophosphorous compounds.

HERBICIDE AND RODENTICIDE POISONING

HERBICIDE POISONING

- Herbicides are compounds that have the potential of either killing or damaging unwanted plants or weeds.
- The biochemical differences in plants make it possible to design chemicals that have selective toxicity potential against various plants/weeds with no deleterious effects on the crops.
- More recently developed synthetic organic herbicides are quite selective for specific plants and have low toxicity for mammals; other less selective compounds e.g arsenicals are more toxic to animals.
- Most animal health problems result from exposure to excessive quantities of herbicides because of improper or careless use or disposal of containers.
- When used properly, problems are rare.

Herbicides are categorized based on their:

A. USES

- Pre-planting herbicides: mixed with the soil before seeding.
- Pre-emergent herbicides: applied before the emergence/appearance of unwanted weeds.
- Post-emergent herbicides: applied after the emergence/germination of crops and unwanted weeds.

B. CHEMICAL NATURE

- Dinitro compounds
- Bipyridium compounds/ Quaternary Ammonium compounds
- Phenoxyacetic acids
- Phenyl or Substituted ureas
- Heterocyclic compounds/Triazenes
- Carbamates and thiocarbamate compounds
- Aromatic/ Benzoic acid compounds
- Chloroaliphatic acids

- Substituted dinitroanilines

C. MECHANISM OF ACTION

- Selective herbicides
- Contact herbicides
- Translocating herbicides

ORGANIC HERBICIDES

1. Dinitro compounds [2, 4-dinitrophenol, dinitro ortho cresol (DNOC)]

Sources of poisoning:

- Accidental ingestion of DNOC-sprayed foliage by animals
- Licking of empty containers
- Malicious poisoning

Mechanism of action:

- Act by interfering with electron transport chain of energy metabolism.
- They uncouple the oxidative phosphorylation and convert the cellular energy to heat producing severe hyperthermia.
- In ruminants, the ruminal microflora reduce the dinitro compounds to diamine metabolites which induce methaemoglobinemia.

Clinical Signs:

- Fever, dyspnoea, tachycardia, convulsion followed by coma and death.

Post-mortem lesions:

- Rapid onset of rigor mortis
- Yellow - green colour to tissues and urine
- Dark blood, gastroenteritis, hyperkeratosis of skin
- Hyperplasia of urinary bladder mucosa

Diagnosis:

- History
- Clinical Signs
- Post mortem lesions

Differential Diagnosis:

- Heat stroke

- Nitrate/ Nitrite poisoning
- Carbon monoxide poisoning

Treatment:

- No specific treatment or antidote
- Remove animal from source of poisoning and keep animal in a cool and calm place.
- To control hyperthermia, use cool bath or ice-water sponging and sedatives such as diazepam.
- Gastric lavage, oxygen therapy, fluid therapy.

NB: Use of antipyretics, phenothiazines and atropine is contraindicated.

- In ruminants, methaemoglobinemia may be treated with methylene blue solution (2-4%)-10mg/kg, IV q8hrs for the first 24-48hours or ascorbic acid at 5-10mg/kg iv q8h for the first 24-48 hours.

2. Bipyridium compounds or Quaternary Ammonium Herbicides (diquat, paraquat)

- These are water soluble, non volatile, dessicant, broad spectrum herbicides.
- They act rapidly, are inactivated on soil contact by soil bacteria and rapidly decompose in light.
- Used in agriculture for preharvest of cotton and potatoes and weed control.
- They produce highly toxic effect in tissues by development of free radicals.

Sources of poisoning:

- Accidental ingestion of freshly treated vegetation by animals
- Malicious poisoning especially of dogs

Mechanism of action:

- They are caustic and irritant agents which cause ulceration and necrosis of the skin and mucous membrane in dogs, pigs and man.
- Paraquat is actively taken up by the alveolar cells via a diamine or polyamine transport system where it undergoes NADPH-dependent electron reduction to form a free radical capable of reacting with molecular oxygen which is then converted to H_2O_2 by the enzyme superoxide dismutase. This can attack polyunsaturated lipids present in cell membranes forming lipid hydroperoxides thereby damaging the

cellular membrane and reducing the intergrity of the cell. This affects efficient gas transport exchange inducing respiratory impairment.

Clinical Signs:

- Emesis, anorexia, abdominal pain, dyspnoea, jaundice and CNS depression. If the animal survives, dehydration, pallor or cyanosis, tachycardia, uremia, moist rales, pulmonary edema and emphysema ensues.

Post mortem lesions:

- Pulmonary congestion, edema and haemorrhages, progressive intra-alveolar fibrosis, atelectasis, erosions and ulceration of the buccal cavity, haemorrhagic gastroenteritis, congestion of the liver, kidney and spleen.

Diagnosis:

- History
- Clinical Signs
- Post mortem lesions
- Analysis of the urine, suspected baits or the feeding material

Differential Diagnosis:

- Pneumonia
- Alpha-naphthylthiourea poisoning
- Bovine pulmonary edema

Treatment:

- No specific treatment or antidote.
- Symptomatic and supportive therapy: Fluid therapy, gastric lavage, diuretic, antacids, NSAIDS, ascorbic acid, large quantity of adsorbent e.g activated charcoal.

NB: Oxygen therapy is contraindicated because it will act as a ready source for the formation of more superoxides.

3. **Phenoxyacetic acids [2,4- dichloro-phenoxyacetic acid (2,4-D) and 2,4,5-trichloro-phenoxyacetic acid (2,4,5-T)]**

- Chlorophenoxyacetic acids were the first commercially available herbicides in 1946.

- They are widely employed, selective herbicides with specific translocation mechanism and are useful for the control of weeds in cereal crops, grasslands and meadows.
- These compounds act as plant regulators selectively against dicotyledons.

Sources of poisoning:

- Directly by accidental ingestion of the herbicide or indirectly by ingestion of poisoned plants which have been made more palatable by the herbicide. The herbicide may increase the content of nitrate/nitrite levels in many otherwise non-toxic plants.

Mechanism of action:

- Not known. Known to be carcinogenic (hepato-carcinoma in laboratory animals), mutagenic, teratogenic, fetotoxic (able to cause reproductive toxicity in cattle)

Clinical Signs:

- Depression, anorexia, weight loss, ruminal atony, diarrhea, unthriftiness and weakness of the muscles of the hindlimbs. Abortion, irregular estrus, anoestrus and ovarian atrophy may be recorded in cattle. In laboratory animals, they are reported to cause proliferation of hepatic peroxisomes and development of hepatic carcinoma.

Treatment:

- No specific antidote.
- Symptomatic and supportive therapies include administration of diuretics and liver protectants.

4. Phenyl or Substituted ureas (diuron and isoproturon)

Sources of poisoning:

- Directly by accidental ingestion of the herbicide. Cattle, sheep and goats are frequently affected animals.

Mechanism of action:

- Not known. They induce hepatic microsomal enzymes and may alter metabolism of other xenobiotic agents.

Clinical Signs:

- Anorexia, abnormal gait, excitability followed by depression and prostration, occasional respiratory difficulties, haematuria and hypersalivation.

Post-mortem lesions:

- Congestion of the GIT, liver, kidneys and haemorrhages in the heart and lungs.

Treatment:

- No specific antidote.
- Symptomatic and supportive therapies. Animals may recover spontaneously even without any treatment.

5. Triazene compounds (atrazine and metribuzin)

- They have low mammalian toxicity potential.
- Atrazine is a selective herbicide for maize, sorghum, sugarcane and pineapple.

Mechanism of action:

- Not known.

Clinical Signs:

- Weakness, hypersalivation, ataxia, posterior paralysis after 3weeks.

Diagnosis:

- History
- Clinical signs

Treatment:

- No specific antidote.
- Symptomatic and supportive therapies

6. Carbamates and thiocarbamate compounds (thiobencarb, carboxazole)

Mechanism of action:

- Not known.

Clinical Signs:

- Lack of appetite, depression, respiratory difficulty, diarrhea, weakness and seizures.

Diagnosis:

- History
- Clinical signs

Treatment:

- No specific antidote.
- Symptomatic and supportive therapies

7. Aromatic/ Benzoic acid compounds (chloramben, dicamba)

Mechanism of action:

- Not known.

Clinical Signs:

- Depression, anorexia, weight loss, diarrhea, unthriftiness and general muscular weakness.

Diagnosis:

- History
- Clinical signs

Treatment:

- No specific antidote.
- Symptomatic and supportive therapies

8. Substituted dinitroaniline compounds (pendimethalin, trifluran)

- Plant growth regulators

Mechanism of action:

- Not known.

Clinical Signs:

- Haemolysis, methaemoglobin and immunotoxicity

Diagnosis:

- History
- Clinical signs

Treatment:

- No specific antidote.
- Symptomatic and supportive therapies