Lecture Three: Pesticides Toxicity

Lecture Three in General Toxicology

"Fourth Year Students"

Second Semester

(2023-2024)

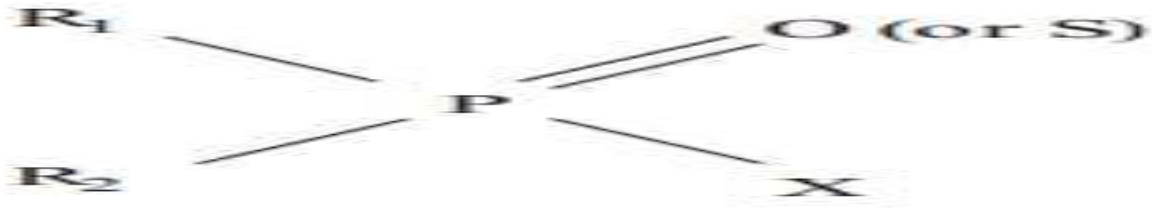
By: Esraa Hammadi Fahad

❖Background:

- ❖**Pesticides** can be defined as any substance or mixture of substances intended or preventing, destroying, repelling, or mitigating pests.
- ❖Pests can be insects, rodents, weeds, and a host of other unwanted organisms.
- ❖Pesticides may be more specifically identified as insecticides (insects), herbicides (weeds), fungicides (fungi and molds), rodenticides (rodents), acaricides (mites), molluscides (snails and other mollusks), miticides (mites), larvicides (larvae), and pediculocides(lice).
- ❖In addition, for regulatory purposes, plant growth regulators, repellants, and attractants (pheromones) often also all in this broad classification o chemicals.

❑ Classification of Pesticides :

❖ **1- Organophosphorus Insecticides**: the general structure o organophosphorus (OP) insecticides can be represented by:



-Where X is the so-called leaving group that is displaced when the OP phosphorylates acetylcholinesterase (AChE), and is the most sensitive to hydrolysis; R1 and R2 are commonly alkoxy groups (i.e., OCH3 or OC2H5) or other chemical substituents; either an oxygen or a sulfur (in this case the compound should be defined as a phosphorothioate) is also attached to the phosphorus with a double bond. Based on chemical differences, OPs can be divided into several subclasses, which include phosphates, phosphorothioates, phosphoramidates, phosphonates, and others.

❖ Biotransformation of OPs:

- **Biotransformation**—for all compounds that contain a sulfur bound to the phosphorus, a metabolic bioactivation is necessary for their biological activity to be manifest, as only compounds with a P= O moiety are effective inhibitors of AChE. Oxidative desulfuration (leads to the formation of an —oxon,‖ or oxygen analog of the parent insecticide) and thioether oxidation (formation o a sulfoxide, S= O, followed by the formation o a sulfone, O= S= O) are catalyzed **by cytochrome P450s**.
- Catalytic hydrolysis by phosphotriesterases, known as A-esterases (which are not inhibited by OPs), plays an important role in the detoxication of certain OPs. Non-catalytic hydrolysis of OPs also occurs when these compounds phosphorylate serine esterases classified as B-esterases.

❑ Signs and Symptoms of Toxicity and Mechanism of Action

- ❖Insecticides have high acute toxicity, with oral LD 50 values in rat often below 50 mg/kg. For several OPs, acute dermal toxicity is also high.
- ❖**Inhibition of AChE** by OPs causes accumulation of acetylcholine at cholinergic synapses, with overstimulation of muscarinic and nicotinic cholinergic receptors.

- As these receptors are localized in most organs of the body, a —**cholinergic syndrome**ll ensues, which includes increased sweating, salivation, bronchial secretion, bronchoconstriction, miosis, increased gastrointestinal motility, diarrhea, tremors, muscular twitching, and various central nervous system effects (table 22–4). **Whereas respiratory failure is a hallmark of severe OP poisoning, mild poisoning and/or early stages of an otherwise severe poisoning may display no clear-cut signs and symptoms**.

TABLE 22–3 Molecular targets of the major classes of insecticides.

Target	Insecticide	Effect
Acetylcholinesterase	Organophosphates Carbamates	Inhibition Inhibition
Sodium channels	Pyrethroids (types I and II) DDT Dihydropyrazoles	Activation Activation Inhibition
Nicotinic acetylcholine receptors	Nicotine Neonicotinoids	Activation Activation
GABA receptor–gated chloride channels	Cyclodienes Phenylpyrazoles Pyrethroids (type II)	Inhibition Inhibition Inhibition
Glutamate-gated chloride channels*	Avermectins	Activation
Octopamine receptors†	Formamidines	Activation
Mitochondrial complex I	Rotenoids	Inhibition
Ryanodine receptors	Diamides	Activation

- OPs with a P= O moiety phosphorylate a hydroxyl group on serine in the active (esteratic) site of the enzyme, impeding its action on the physiological substrate. Phosphorylated AChE is hydrolyzed by water slowly, and the rate of ―spontaneous reactivation‖ depends on the chemical nature of the R substituents. Reactivation of phosphorylated AChE does not occur once the enzyme-inhibitor complex has ―aged,‖ which occurs when there is loss by non-enzymatic hydrolysis of one of the two alkyl (R) groups.
- When phosphorylated AChE has aged, the enzyme is considered to be irreversibly inhibited, and the only means of replacing its activity is through synthesis of new enzyme, a process that may take days.

❑ Intermediate Syndrome:

- A second distinct manifestation of exposure to OPs is the so-called **intermediate syndrome**, which is seen in 20% to 50% of acute OP poisoning cases. The syndrome develops (**1 to several days) after the poisoning, during recovery from cholinergic manifestations, or in some cases, when patients have completely recovered from the initial cholinergic crisis.**

- Prominent features include a marked weakness of respiratory, neck, and proximal limb muscles. Mortality due to respiratory paralysis and complications ranges from 15% to 40%, and recovery in surviving patients takes up to 30 days.
- The intermediate syndrome is not an effect of AChE inhibition, and its precise underlying mechanisms are unknown. **The hypothesis that muscle weakness may result from nicotinic receptor desensitization due to prolonged cholinergic stimulation remains the most valid.**

❑ Organophosphate -induced Delayed Polyneuropathy (OPIDP)

- A new OPs may cause OPIDP. Signs and symptoms include **tingling** of the hands and feet, followed by sensory loss, progressive muscle weakness and flaccidity of the distal skeletal muscles of the lower and upper extremities, and ataxia. These may occur **2 to 3 weeks after a single exposure**, when signs of both the acute cholinergic and the intermediate syndromes have subsided. OPIDP can be classified as a **distal sensorimotor axonopathy**.

- Neuropathological studies in experimental OPIDP have evidenced that the primary lesion is a bilateral degenerative change in distal levels of axons and their terminals, primarily affecting larger/longer myelinated central and peripheral nerve fibers, leading to breakdown of neuritic segments and the myelin sheaths.
- Past studies suggested that aging of neuropathy target esterase (NTE) was involved in OPIDP, the exact mechanisms involved in phosphorylation and aging of NTE and axonal degeneration remain obscure.

❖ Carbamates Toxicity :

- Carbamate insecticides are derived from carbamic acid, and most are N-methylcarbamates. Acute oral toxicity ranges from moderate to low toxicity, such as carbaryl, to extremely high toxicity, such as aldicarb. Dermal skin penetration by carbamates is increased by organic solvents and emulsifiers present in most formulations.
- Carbamates are susceptible to a variety of enzyme-catalyzed biotransformation reactions, and the principal pathways involve oxidation and hydrolysis. The mechanism of toxicity of carbamates is by inhibition of AChE, **which is rapidly reversible.**

- The signs and symptoms of carbamate poisoning include miosis, urination, diarrhea, salivation, muscle fasciculation, and CNS effects **(table 22-4)**.
- **Acute intoxication by carbamates is generally resolved within a few hours.**
- The treatment of carbamate intoxication relies on the use **of atropine**. Carbamates can inhibit neuropathy target esterase (NTE), but because carbamylated NTE cannot age, they are thought to be unable to initiate OPIDP. Additionally, when given before a neuropathic organophosphate, carbamates offer protection against OPIDP, but when given after, they can promote OPIDP.

❑ Pyrethroids:

❖**Pyrethrins** decompose rapidly on exposure to light, the synthetic pyrethroid analogs were developed. Because of their high insecticidal potency, relatively low mammalian toxicity, lack of environmental persistence, and relatively low tendency to induce insect resistance, pyrethroids now account or 15% to 20% o the global insecticide market. The pyrethroids are used widely as insecticides both in the house and in agriculture, in medicine for the topical treatment of scabies and head lice, and in tropical countries in soaked bed nets to prevent mosquito bites.

- **Pyrethroids:** alter the normal function of insect nerves by modifying the kinetics of voltage-sensitive sodium channels, which mediate the transient increase in the sodium permeability of the nerve membrane that underlies the nerve action potential.

- On absorption, pyrethroids are very rapidly metabolized through two major biotransformation routes: hydrolysis of the ester linkage, which is catalyzed by hepatic and plasma **carboxylesterases**, and oxidation of the alcohol moiety by cytochrome P450s. These initial reactions are followed by further oxidations, hydrolysis, and conjugation with sulfate or glucuronide.

❑ Signs and Symptoms of Toxicity and Mechanism of Action of Pyrethroids

❖Toxic signs in rats, pyrethroids have been divided into two types (table 22-5). **Type I compounds** produce a syndrome consisting of marked behavioral arousal, aggressive sparring, increased startle response, and fine body tremor progressing to whole-body tremor and prostration (**type I or T syndrome**). Type II compounds produce profuse salivation, coarse tremor progressing to choreoathetosis, and **c**lonic **s**eizures (**type II or CS syndrome**).

- The pyrethroids **disrupt voltage-gated sodium channels in mammals and insects**. Pyrethroids bind to the α subunit of the sodium channel and slow the activation (opening), as well as the rate of inactivation (closing), of the sodium channel, leading to a stable hyperexcitable state.

- **Type II pyrethroids** bind to and inhibit GABAA-gated chloride channels at higher concentrations than those sufficient to affect sodium channels .This effect is believed to contribute to the seizures that accompany severe type II pyrethroid poisoning.

- On occupational exposure, the primary adverse effect resulting from dermal contact with pyrethroids **is paresthesia**. Symptoms include continuous **tingling or pricking** or, when more severe, burning. The condition reverses in **about 24 h**, and topical application of vitamin E has been shown to be an effective treatment. Paresthesia is presumably due to pyrethroid-induced abnormal repetitive activity in skin nerve terminals.
- Chronic studies with pyrethroids indicate that at high dose levels they cause **slight liver enlargement often accompanied by some histopathologic changes**. There is little evidence of teratogenicity and mutagenicity. An increased rate of lymphoma incidence in rodents has been reported for deltamethrin, but the effect was not dose-dependent.

TABLE 22–5 Classification of pyrethroid insecticides based on toxic signs in rats.

Syndrome	Signs and Symptoms	Examples
Type I (T syndrome)	Aggressive sparring Increased sensitivity to external stimuli Whole-body tremors Prostration	Allethrin Bioallethrin Resmethrin Phenothrin
Type II (CS syndrome)	Pawing and burrowing Profuse salivation Coarse tremor Choreoathetosis Clonic seizures	Deltamethrin Fenvalerate Cypermethrin Cyhalothrin

❑ Organo-chlorine Insecticides:

❖The organochlorine insecticides include the chlorinated ethane derivatives, such as DDT (dichlorodiphenyltrichloroethane) and its analogs; the cyclodienes, such as chlordane, aldrin, dieldrin, heptachlor, endrin, and toxaphene; the hexachlorocyclohexanes, such as lindane; and chlordecone. Their acute toxicity is moderate (less than that of organophosphates), but **chronic exposure may be associated with adverse health effects particularly in the liver and endocrine disruption of the reproductive system**.

- DDT and Its Analogs—is effective against a wide variety of agricultural pests, as well as against insects that transmit some of the world's most serious diseases, such as typhus, malaria, and yellow fever. DDT has a moderate oral acute toxicity and its dermal absorption is very limited.
- In humans, oral doses of 10 to 20 mg/kg produce illness, but doses as high as 285 mg/kg have been ingested accidentally without fatal results.
- Toxicity from dermal exposure in humans is also low, as evidenced by the lack of significant adverse health effects when thousands of people were liberally dusted with this compound. On absorption, DDT distributes in all tissues, and the highest concentrations are found in adipose tissue. It is excreted through the bile, urine, and milk.

- Acute exposure to high doses of DDT causes motor unrest, increased frequency o spontaneous movements, abnormal susceptibility to ear, and hypersusceptibility to external stimuli (light, touch, and sound). This is followed by the development of ne tremors, progressing to coarse tremors, and eventually tonic–clonic convulsions.
- **Death is typically due to respiratory failure**. In humans, the earliest symptom of poisoning by DDT is hyperesthesia of the mouth and lower part of the face, followed by paresthesia of the same area and of the tongue. Dizziness, tremor of the extremities, confusion, and vomiting follow; convulsions occur only in severe poisoning. Both in insects and in mammals, DDT interferes with the sodium channels in the axonal membrane by a mechanism similar to that of type I pyrethroids.

- An important target or chronic DDT exposure is **the liver**. DDT and its breakdown product DDE increase liver weight and cause hepatic cell hypertrophy and necrosis, and they are potent inducers of cytochrome P450s, particularly CYP2B and CYP3A. Both DDE and DDD, another breakdown product, **are carcinogenic in rodents, causing primarily an increase in hepatic tumors**.

❑ Other Old and New Insecticides:

❖**Retinoid**: the most abundant is rotenone, which is used as an agricultural insecticide particularly in organic farming. Toxicity of rotenone in target and non target species is due to its ability to inhibit, at nanomolar concentrations, mitochondrial respiration by blocking electron transport at NADH-ubiquinone reductase, the energy conserving enzyme complex commonly known as complex I. Poisoning symptoms include initial **increased respiratory and cardiac rates**, clonic and tonic spasms, and muscular depression, followed by respiratory depression. Rotenone may play a role in the etiology of Parkinson's disease.

Thanks for Listening

Any Question???