Toxic Effects of Pesticides Lec:7

INTRODUCTION

Pesticides can be defined as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating pests. Pests can be insects, rodents, weeds, and a host of other unwanted organisms. The four major classes (and their target pests) are those of insecticides (insects), herbicides (weeds), fungicides (fungi, molds), and rodenticides (rodents), but there are also acaricides (mites), molluscides (snails, other mollusks), miticides (mites), larvicides (larvae), and pediculicides (lice).

ECONOMICS AND PUBLIC HEALTH

The use of pesticides must take into consideration the balance of the benefits that may be expected versus the possible risks of injury to human health or degradation of environmental quality. Pesticides play a major role in the control of vector-borne diseases, which represent a major threat to the health of large human populations. Pesticides of various types are used in the control of insects, rodents, and other pests that are involved in the life cycle of vector-borne diseases such as malaria, filariasis, yellow fever, viral encephalitis, typhus, and many others.

When introduced in 1942, DDT appeared to hold immense promise of benefit to agricultural economics and protection of public health against vector-borne diseases. However, because of its bioaccumulation in the environment and its effects on bird reproduction, DDT was eventually banned in most countries by the mid1970s. In South Africa, DDT was only banned in 1996, and at the time <10,000 cases of malaria were registered in that country. By the year 2000, cases of malaria had increased to 62,000, but with the reintroduction of DDT at the end of that year, cases were down to 12,500.

Excessive loss of food crops to insects or other pests may contribute to possible starvation, in developed countries, pesticides allow production of abundant, inexpensive, and attractive fruits and vegetables, as well as grains. Along with insecticides, herbicides and fungicides play a major role in this endeavor.

Use of Pesticides

Pesticides are often, if not always, used as multiagent formulations, in which the active ingredient is present together with other ingredients to allow mixing, dilution, application, and stability. These other ingredients are lumped under the term “inert” or “other”. Although they do not have pesticidal action, such inert ingredients may not always be devoid of toxicity; thus, an ongoing task of manufactures and regulatory agencies is to assure that inert ingredients do not pose any unreasonable risk of adverse health effects.

Exposure

Exposure to pesticides can occur via the oral or dermal routes or by inhalation. High oral doses, leading to severe poisoning and death, are achieved as a result of pesticide ingestion for suicidal intents, or of accidental ingestion, commonly due to storage of pesticides in improper containers. Chronic low doses, on the other hand, are consumed by the general population as pesticide residues in food, or as contaminants in drinking water. Regulations exist to ensure that pesticide residues are maintained at levels below those that would cause any adverse effect. Workers involved in the production, transport, mixing and loading, and application of pesticides, as well as in harvesting of pesticide-sprayed crops, are at highest risk for pesticide exposure.

In the occupational setting, dermal exposure during normal handling or application of pesticides, or in case of accidental spillings, occurs in body areas not covered by protective clothing, such as the face or the hands. Furthermore, deposition of pesticides on clothing may lead to slow penetration through the tissue and/ or to potential exposure of others, if clothes are not changed and washed on termination of exposure.

Human Poisoning

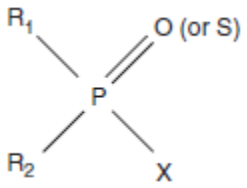
Pesticides are not always selective for their intended target species, and adverse health effects can occur in nontarget species, including humans. In the general population and in occupationally exposed workers, recurring concerns relate to a possible association between pesticide exposure and increased risk of cancer. The WHO has recommended a classification of pesticides by hazard, where acute oral or dermal toxicities in rats were considered.

INSECTICIDES

Insecticides play a most relevant role in the control of insect pests, particularly in developing countries. All of the chemical insecticides in use today are neurotoxicants, and act by poisoning the nervous systems of the target organisms. The central nervous system of insects is highly developed and not unlike that of mammals. As a class, insecticides have higher acute toxicity toward nontarget species compared with other pesticides. Some of them, most notably the organophosphates, are involved in a great number of human poisonings and deaths each year.

1. Organophosphorus Compounds

The general structure of OP insecticides can be represented as follows:



where X is the so-called leaving group, which is displaced when the OP phosphorylates AChE, and is the most sensitive to hydrolysis; R1 and R 2 are most commonly alkoxy groups (OCH 3 or OC 2 H 5), although other chemical substitutes are also possible; 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- 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. This bioactivation consists of an oxidative desulfuration, mediated, mostly but not exclusively in the liver, by cytochrome P450 enzymes (CYPs), and leading to the formation of an “oxon,” or oxygen analog of the parent insecticide. Catalytic hydrolysis by phosphotriesterases, known as A-esterases (which are not inhibited by OPs), also plays an important role in the detoxication of certain Ops. Noncatalytic hydrolysis of OPs also occurs when these compounds phosphorylate serine esterases classified as B-esterases.

Signs and Symptoms of Toxicity and Mechanism of Action

OP 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 cholinergic receptors of the muscarinic and nicotinic type. As these receptors are localized in most organs of the body, a "cholinergic syndrome" ensues, which includes increased sweating and salivation, profound bronchial secretion, bronchoconstriction, miosis, increased gastrointestinal motility, diarrhea, tremors, muscular twitching, and various central nervous system effects. While 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.

Treatment of Poisoning

Procedures aimed at decontamination and/or at minimizing absorption depend on the route of exposure. In case of dermal exposure, contaminated clothing should be removed, and the skin washed with alkaline soap. In case of ingestion, procedures to reduce absorption from the gastrointestinal tract do not appear to be very effective. Atropine represents the cornerstone of the treatment for OP poisoning; it is a muscarinic receptor antagonist, and thus prevents the action of accumulating acetylcholine on these receptors.

Atropine is preferably given intravenously, although the intramuscular route is also effective. Oximes, such as pralidoxime (2-PAM), are also used in the therapy of OP poisoning. 2-PAM contains a positively charged atom capable of attaching to the anionic site of AChE, and facilitates dephosphorylation of the enzyme, thus restoring the catalytic site of AChE to its function.

2. Carbamates

Carbamate insecticides are derived from carbamic acid, and most are *N*-methylcarbamates. They present different degrees of acute oral toxicity, ranging from moderate to low toxicity such as carbaryl, to extremely high toxicity, such as aldicarb. Dermal toxicity is lower, but skin penetration 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 analogous to that of OPs, in that they inhibit AChE. However, inhibition is transient and rapidly reversible.

Organochlorine Compounds

The organochlorine insecticides include the chlorinated ethane derivatives, such as DDT and its analogs. 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 the reproductive system.

DDT and Its Analogs

1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane (DDT) was 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 acute toxicity when given by the oral route 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.

Acute exposure to high doses of DDT causes motor unrest, increased frequency of spontaneous movements, abnormal susceptibility to fear, and hypersusceptibility to external stimuli (light, touch, sound). This is followed by the development of fine tremors, progressing to coarse tremors, and eventually tonic–clonic convulsions.

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. Both in insects and in mammals, DDT interferes with the sodium channels in the axonal membrane by block physiologic inactivation in the sodium channels of nerve membranes and cause uncontrolled firing of action potentials.

Chronic exposure has been, and still is, a primary concern. In this regard, an important target for DDT is the liver. DDT and DDE increase liver weight and cause hepatic cell hypertrophy and necrosis, and are potent inducers of cytochromes P450, particularly CYP2B and CYP3A. Both DDE and DDD were also shown to be carcinogenic, causing primarily an increase in liver tumors.

Other Old and New Insecticides

Rotenone- is used as an agricultural insecticide/ acaricide, particularly in organic farming. Toxicity of rotenone in target and nontarget species is due to its ability to inhibit, at nanomolar concentrations, the mitochondrial respiratory chain, 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. Most recently, however, an association between use of rotenone and increased risk of Parkinson disease has been reported.

Nicotine-Nicotine is an alkaloid extracted from the leaves of tobacco plants and is used as a free base or as the sulfate salt. Nicotine is a minor insecticide. Signs and symptoms of poisoning include nausea, vomiting, muscle weakness, respiratory effects, headache, lethargy, and tachycardia. Most cases of poisoning with nicotine occur after exposure to tobacco products, or gum or patches. Workers who cultivate, harvest, or handle tobacco may experience green tobacco sickness, caused by dermal absorption of nicotine.

Pyrethrum—The most common toxic effect of this mixture of plant alkaloids is contact dermatitis. Ingestion or inhalation of large quantities may cause CNS excitation (including seizures) and peripheral neurotoxicity.

HERBICIDES

Herbicides are chemicals that are capable of either killing or severely injuring plants.

Chlorophenoxy Compounds

Chlorophenoxy herbicides are chemical analogs of auxin, a plant growth hormone, and produce uncontrolled and lethal growth in target plants. Because the auxin hormone is critical to the growth of many broad-leaf plants, but is not used by grasses, chlorophenoxy compounds can suppress the growth of weeds. The most commonly used compound of this class is 2,4-dichlorophenoxyacetic acid (2,4-D).

Ingestion of 2,4-D has caused several cases of acute poisoning in humans, usually at doses above 300 mg/kg, although lower doses have been reported to elicit symptoms. Vomiting, burning of the mouth, abdominal pain, hypotension, myotonia, and CNS involvement including coma are among the clinical signs observed.

Bipyridyl Compounds

Paraquat was introduced as a herbicide in 1962, and is formulated as an aqueous solution or as a granular formulation. It is a very effective, fast-acting, nonselective contact herbicide, used to control broad-leaved weeds and grasses in plantations and fruit orchards, and for general weed control. Paraquat has one of the highest acute toxicities among herbicides.

On absorption, independently of the route of exposure, paraquat accumulates in the lung and the kidney, and these two organs are the most susceptible to paraquat induced injury. Only a small fraction of paraquat is metabolized, and the greater part is excreted unchanged in the urine. Paraquat has minimal to no genotoxic activity, is not carcinogenic in rodents, has no effect on fertility, is not teratogenic, and only produces fetotoxicity at maternally toxic doses. Thus, the major toxicological concerns for paraquat are related to its acute systemic effects, particularly in the lung, and, secondarily, the kidney.

Paraquat can be reduced to form a free radical, which, in the presence of oxygen, rapidly reoxidizes to the cation, with a concomitant production of superoxide anion ($O2^{-}$•). Thus, once paraquat enters a cell, it undergoes alternate reduction followed by reoxidation, a process known as redox cycling. Intracellular redox cycling of paraquat would also result in the oxidation of NADPH, leading to its cellular depletion, which is augmented by the detoxification of hydrogen peroxide formed in the glutathione peroxidase/reductase enzyme system to regenerate GSH.

Damage to alveolar epithelial cells is seen within 24 hours after exposure. Damage progresses in the following two to four days with large areas of the alveolar epithelium completely lost. This is followed by alveolar edema, extensive infiltration of inflammatory cells into the alveolar interstitium, and finally death due to severe anoxia. On chronic exposure, target organs for toxicity are the gastrointestinal tract, the kidney, and particularly the eye.