General Toxicology

Toxic Effects of Pesticides

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- 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.

- Thus, pesticides occupy a rather unique position among the many chemicals that we encounter daily, in that they are deliberately added to the environment for the purpose of killing or injuring some form of life.

- Ideally, their injurious action would be highly specific for undesirable targets; in reality, however, many pesticides are not highly selective, and are often toxic to many nontarget species, including humans.

- Thus, the use of pesticides must minimize the possibility of exposure of nontarget organisms to injurious quantities of these chemicals.

- several different classes of pesticides exist, with different uses, mechanisms, and, hence, toxic effects in nontarget organisms. The most common classification of pesticides relies on the target species they act on.

- The four major classes (and their target pests) are those of insecticides (insects), herbicides (weeds), fungicides (fungi, molds), and rodenticides (rodents), and there are also acaricides (mites), molluscicides (snails, other mollusks), miticides (mites), larvicides (larvae), and pediculicides (lice).

- In addition, for regulatory purposes, plant growth regulators, repellents, and attractants (pheromones) often also fall in this broad classification of chemicals.

- subclasses exist, with substantially different chemical and toxico logical characteristics. For example, among insecticides, one can f ind organophosphorus compounds, carbamates, organochlorines, pyrethroids, neonicotinoids, and many other chemicals.

- Even within each of these subclasses, significant differences can exist, as is the case, for example, of organochlorine compounds such as DDT, aldrin, or chlordecone.

- Thus, detailed knowledge of the toxicological characteristics of each chemical is needed to properly evaluate their potential risks for nontarget species.

Exposure

- Exposure to pesticides can occur via the oral or dermal routes, or by inhalation.

- From a quantitative perspective, oral exposure lies on the extremes of a hypothetical dose–response curve.

- 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. In contrast, chronic low doses are consumed by the general population as pesticide residues in food, or as contaminants in drinking water.

- 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.

- The dermal route is believed in this case to offer the greatest potential for exposure, with a minor contribution of the respiratory route when aerosols or aerial spraying are used.

- 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 upon termination of exposure.

- Several methodologies exist to assess exposure by passive dosimetry, such as the use of absorbent cloth.

Human Poisoning

- Pesticides are not always selective for their intended target species, and adverse health effects can occur in nontarget species, including humans.

Basic Toxicology Testing Requirements for Pesticide Registration

TEST	ANIMAL SPECIES*
Acute lethality (oral, dermal, inhalation)	Rat, mouse, guinea pig, rabbit
Dermal irritation	Rabbit, rat, guinea pig
Dermal sensitization	Guinea pig
Eye irritation	Rabbit
Acute delayed neurotoxicity	Hen
Genotoxicity studies (in vitro, in vivo)	Bacteria, mammalian cells, mouse, rat, *Drosophila*
Teratogenicity	Rabbit, rodent (mouse, rat, hamster)
Two-four week toxicity study (oral, dermal, inhalation)	Rat, mouse
90-Day toxicity study (oral)	Rat
Chronic toxicity study (oral; 6 months to 2 years)	Rat, dog
Oncogenicity study	Rat, mouse
Reproductive/fertility study	Rat
Developmental neurotoxicity study	Rat

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 (CNS) of insects is highly developed and not unlike that of mammals, and the peripheral nervous system, though less complex, also presents striking similarities.

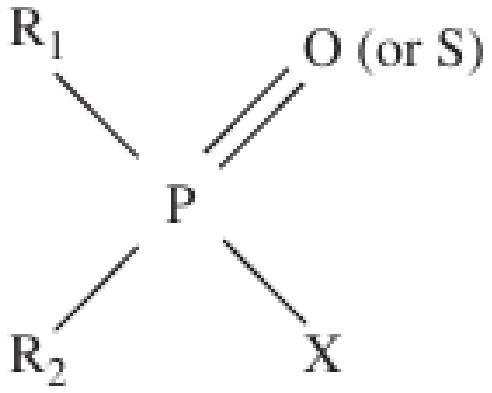
- As a class, insecticides have higher acute toxicity toward nontarget species compared to other pesticides.

Molecular Targets of the Major Classes of Insecticides

TARGET	INSECTICIDE	EFFECT
Acetylcholinesterase	Organophosphates Carbamates	Inhibition Inhibition
Sodium channels	Pyrethroids (Type I and II) DDT Dihydropyrazoles	Activation Activation Inhibition
Nicotinic acetylcholine receptors	Nicotine Neonicotinoids	Activation Activation
GABA receptors–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

Organophosphorus Compounds

- The chemistry of OPs has been thoroughly investigated. The general structure of OP insecticides can be represented by



- where X is the so-called “leaving group,” which is removed when the OP phosphorylates acetylcholinesterase (AChE), and is the most sensitive to hydrolysis; R1 and R2 are most commonly alkoxy.

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.

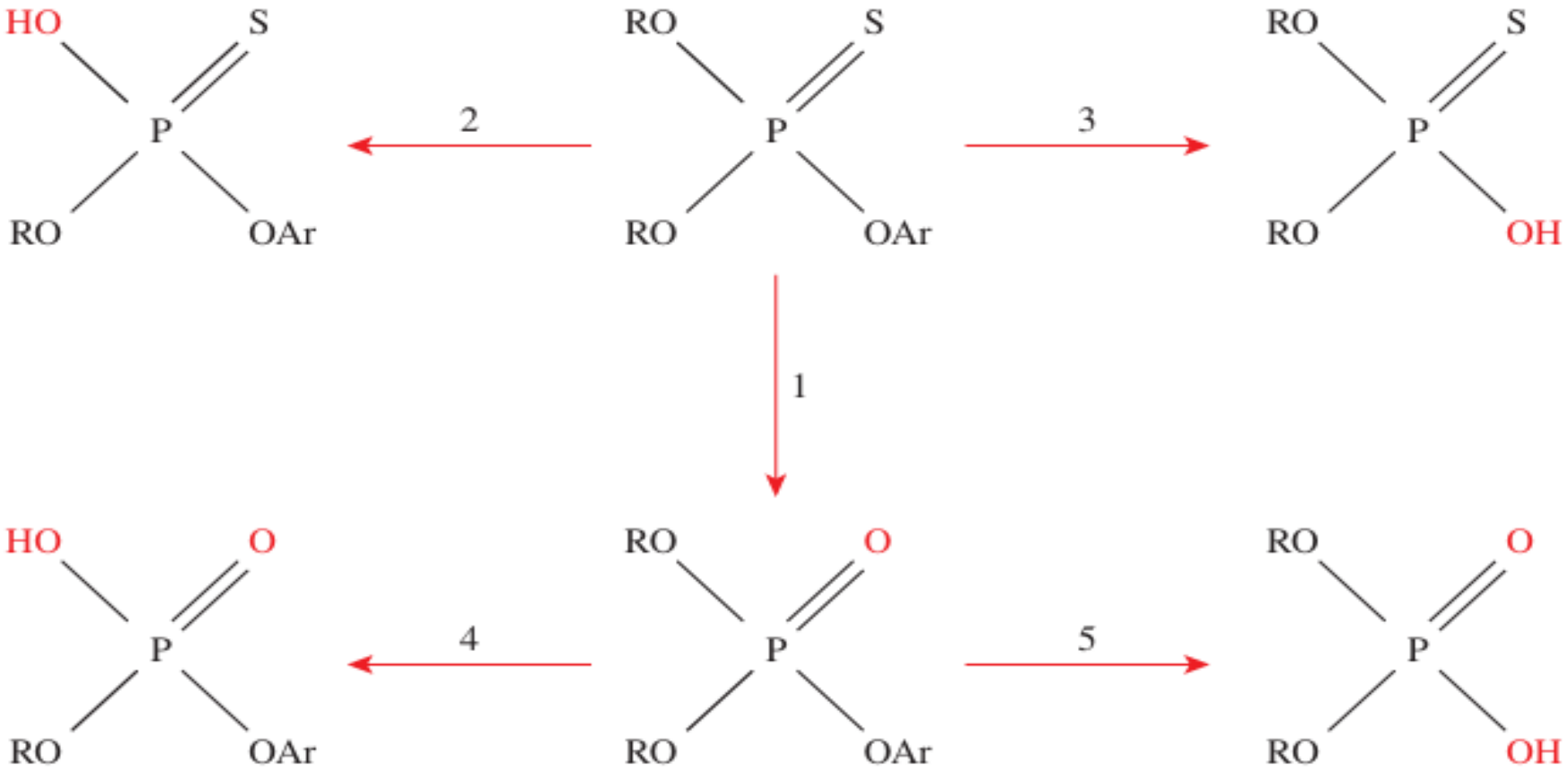
- This bioactivation, which consists in an oxidative desulfuration mediated by cytochrome P450 enzymes (CYPs), and occurring mostly but not exclusively in the liver, leads to the formation of an “oxon,” or oxygen analog of the parent insecticide.

- Multiple CYPs have been shown to activate organophosphorothioates to their oxons, with different substrate specificities;

- for example, diazinon is activated by human hepatic CYP2C19, while parathion is activated primarily by CYP3A4/5 and CYP2C8, and chlorpyrifos by CYP2B6.

- Other reactions can also activate OPs; a relevant one is thioether oxidation (formation of a sulfoxide, S=O, followed by the formation of a sulfone, O=S=O) which occurs in the leaving group moiety, and is also catalyzed by CYPs.

- In the case of the OP disulfoton, the sulfoxide and the sulfone are more potent inhibitors of AChE than the parent compound.



General scheme of biotransformation of dialkyl, aryl phosphorothioate insecticides. Reaction 1 is the bioactivation by oxidative desulfuration of the parent compound to the active metabolite, the oxon. The other reactions are enzymatic detoxication reactions that yield products that do not inhibit acetyl cholinesterase. Reactions 2 and 4 are dealkylation reactions, while reaction 3 is a dearylation. All are mediated by various cytochromes P450. Reaction 5 is a hydrolytic reaction, catalyzed by paraoxonase (PON1). Note that not all reactions occur with every organophosphorus insecticide.

Signs and Symptoms of Toxicity, Mechanism of Action, and Treatment of Poisoning

- OP insecticides have high acute toxicity, with oral LD50 values in rat often below 50 mg/kg, though for some widely used compounds (e.g., chlorpyrifos and diazinon) toxicity is somewhat lower due to effective detoxication.
- One exception is malathion, which has an oral LD50 in rat of more than 1 g/kg, due to rapid detoxication by CarE.

- For several OPs, acute dermal toxicity is also high, with some exceptions being azinphosmethyl and malathion.

- The primary target for OPs is AChE, a B-esterase whose physiological role is that of hydrolyzing acetylcholine, a major neurotransmitter in the central and peripheral (autonomic and motor-somatic) nervous systems.

- Acetylcholine released from cholinergic nerve terminals is disposed of solely through hydrolysis by AChE.

- In fact, in contrast to other neurotransmitters (e.g., norepinephrine or dopamine), it is choline, the product of acetylcholine hydrolysis by AChE, that is taken up by the presynaptic terminal.

- Hence, inhibition of AChE by OPs causes accumulation of acetylcholine at cholinergic synapses, with over stimulation 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 CNS effects.

- When death occurs, this is believed to be due to respiratory failure as a result of inhibition of respiratory centers in the brainstem, bronchoconstriction, and increased bronchial secretion, and flaccid paralysis of respiratory muscles

Signs and Symptoms of Acute Poisoning with Anticholinesterase Compounds

SITE AND RECEPTOR AFFECTED	MANIFESTATIONS
Exocrine glands (M)	Increased salivation, lacrimation, perspiration
Eyes (M)	Miosis, blurred vision
Gastrointestinal tract (M)	Abdominal cramps, vomiting, diarrhea
Respiratory tract (M)	Increased bronchial secretion, bronchoconstriction
Bladder (M)	Urinary frequency, incontinence
Cardiovascular system (M)	Bradycardia, hypotension
Cardiovascular system (N)	Tachycardia, transient hypertension
Skeletal muscles (N)	Muscle fasciculations, twitching, cramps, generalized weakness, flaccid paralysis
Central nervous system (M, N)	Dizziness, lethargy, fatigue, headache, mental confusion, depression of respiratory centers, convulsions, coma

Abbreviations: M, muscarinic receptors; N, nicotinic receptors.

- The first signs to appear are usually muscarinic, which may or may not be in combination with nicotinic signs.

- 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.

- Therefore, diagnosis is made through symptom recognition; miosis is observed most often, followed by gastrointestinal symptoms (nausea, vomiting, abdominal pain, vomiting) and hypersalivation.

- The interaction of OPs with AChE has been studied in much detail.

- OPs with a P=O moiety phosphorylate a hydroxyl group on serine in the active (esteratic) site of the enzyme, thus impeding its action on the physiological substrate.

- The first reaction leads to the formation of a Michaelis complex, while a subsequent reaction leads to phosphorylated AChE.

- Rates of these two reactions, which are usually very rapid, indicate the affinity of the enzyme for a given OP.

- The bond between the phosphorus atom and the esteratic site of the enzyme is much more stable than the bond between the carbonyl carbon of acetate (in acetylcholine) at the same enzyme site.

- While breaking of the carbon–enzyme bond is complete in a few microseconds, breaking of the phosphorus enzyme bond can take from a few hours to several days, depending on the chemical structure of the OP.

- Phosphorylated AChE is hydrolyzed by water at a very slow rate, and the rate of “spontaneous reactivation” depends on the chemical nature of the R substituents.

- Reactivation decreases in the order demethoxy, diethoxy, and diisopropoxy.

- While water is a weak nucleophilic compound, certain hydroxylamine derivatives, known as oximes, can facilitate dephosphorylation of AChE, and are utilized in the therapy of OP poisoning.

- Reactivation of phosphorylated AChE does not occur once the enzyme–inhibi tor complex has “aged”.

- Aging consists of the loss (by nonenzymatic hydrolysis) of one of the two alkyl (R) groups, and the rate of aging depends on the nature of the alkyl group.

- When phosphorylated AChE has aged, the enzyme can be considered to be irreversibly inhibited, and the only means of replacing its activity is through synthesis of a new enzyme, a process that may take days.

- Upon OP poisoning, prompt treatment is essential. 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.

- The muscarinic receptor antagonist atropine represents the cornerstone of the treatment for OP poisoning, as it prevents the action of accumulating acetylcholine on these receptors.

- Atropine is preferably given intravenously, though the intramuscular route is also effective.

- The best clinical approach is to administer doses of atropine large enough to achieve evidence of atropinization, that is, flushing, dry mouth, changes in pupil size, bronchodilation, and increased heart rate, which should be maintained for at least 48 hours.

- 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.

- However, this chemical reaction occurs only when the phosphorylated AChE has not undergone aging.

- In addition to atropine and oximes, diazepam, to relieve anxiety in mild cases and to reduce muscle fasciculations and antagonize convulsions in the more severe cases, or magnesium sulfate, to reduce acetylcholine release, can also be used in the treatment of acute OP poisoning.

Biochemical Measurements

- In addition to synapses, AChE is also present in red blood cells (RBCs).

- Additionally, BuChE, also known as pseudo-cholinesterase, is found in plasma.

- Though the physiological functions of these enzymes in blood are yet to be dis covered, activity of both enzymes is usually inhibited upon exposure to OPs, hence their measurements are widely used as an indication of exposure and/or biological effect of OPs.

- The specificity and use fulness of measurements of RBC AChE and of plasma BuChE, in the case of OP exposure, have been debated for some time.

The Intermediate Syndrome

- A second distinct manifestation of exposure to OPs is the so-called intermediate syndrome.

- The intermediate syndrome is seen in a small subset (20% to 30%) of acute OP poisoning cases, and has been observed following expo sure to a large variety of Ops.

- The syndrome develops one to several days after the poisoning, during recovery from cholinergic manifestations, or in some cases, when patients are completely recovered from the initial cholinergic crisis.

- Prominent features of the intermediate syndrome are a marked weakness of respiratory, neck, and proximal limb muscles.

- Extrapyramidal symptoms may also be present.

- Mortality due to respiratory paralysis and complications ranges from 15% to 40%, and recovery in surviving patients usually takes up to 30 days.

- The intermediate syndrome is not a direct effect of AChE inhibition, and its precise underlying mechanisms are still unknown.

- The hypothesis that muscle weakness may result from nicotinic receptor desensitization due to prolonged cholinergic stimulation remains the most valid.

- There is no specific treatment for the intermediate syndrome and intervention is exclusively supportive.

Organophosphate-Induced Delayed Polyneuropathy

- A few OPs may also cause another type of toxicity, known as organophosphate-induced delayed polyneuropathy (OPIDP).

- Signs and symptoms of this delayed neurotoxicity include tingling of the hands and feet, followed by sensory loss, progressive muscle weak ness 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.

Long-Term Toxicity

- While the effects of acute exposure to OPs have been clearly identified and characterized by thousands of animal studies and cases of human poisonings.

- Acute exposure to high doses of OPs may result, in some cases, in long lasting adverse health effects (particularly CNS sequelae) as shown in animals, as well as in humans.

- An increased risk of dementia may also be associated with acute OP poisoning.

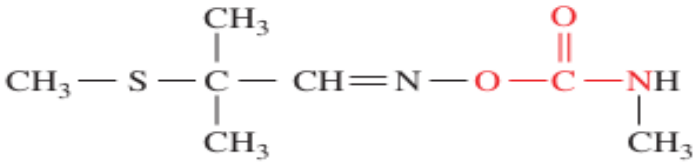
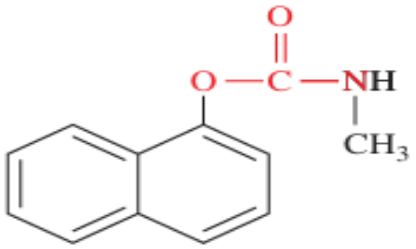
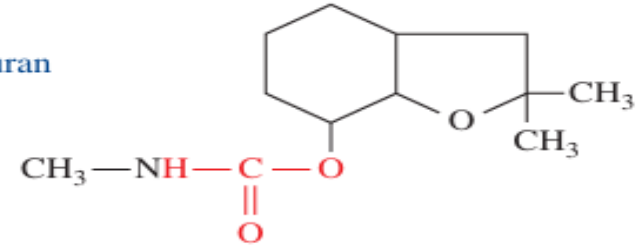
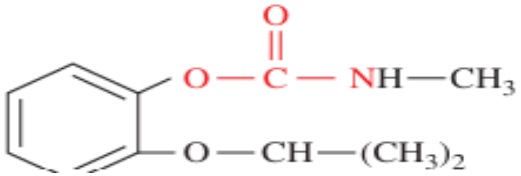
Carbamates

- Carbamate insecticides have a variety of chemical structures, but all derive from carbamic acid, the majority being 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 bio transformation reactions, and the principal pathways involve oxidation and hydrolysis.

		LD_{50} in rats (mg/kg)		Water solubility (g/L)
		Oral	Dermal	
Aldicarb		0.8	3.2	6.0
Carbaryl		400	>5000	0.7
Carbofuran		10	>1000	0.7
Propoxur		85	~1500	2.0

Structures of some carbamate insecticides, with indication of acute oral and dermal toxicity in the rat, and of water solubility. Note that carbo furan has been banned in recent years in several countries.

- They do not require metabolic bioactivation, and the metabolites are for the most part devoid of biological activity, though this is not always the case.

- For example, two metabolites of aldicarb, the sulfoxide and the sulfone, are more potent anticholinesterases than the parent compound.

- The mechanism of toxicity of carbamates is analogous to that of OPs, in that they inhibit AChE.

- However, inhibition is transient and rapidly reversible, because there is rapid reactivation of the carbamylated enzyme in the presence of water.

- Additionally, carbamylated AChE does not undergo the aging reaction.

- The sign and symptoms of carbamate poisoning are the same observed following intoxication with OPs, and include miosis, urination, diarrhea, salivation, muscle fasciculation, and CNS effects.

- However, differently from OPs, acute intoxication by carbamates is generally resolved within a few hours.

- Experimental data on AChE inhibition by propoxur in mice; maximal inhibition is achieved very rapidly, as carbamates are direct AChE inhibitors and do not require metabolic bioactivation, and enzyme activity returns to control levels within 2 hours.

- Carbamates also inhibit BuChE; the degree of such inhibition varies depending on the specific compound, but is generally modest after moderate exposure (when, however, inhibition of red blood cells and nervous tissue AChE can be substantial) and equivalent to that of AChE after severe exposure.

- The treatment of carbamate intoxication relies on the use of the muscarinic antagonist atropine. Use of oximes is generally not recommended, as 2-PAM has been shown to aggravate the toxicity of carbaryl.

Pyrethroids

- Pyrethrum extracts contain six insec ticidal esters, referred to as pyrethrins.

- However, because pyrethrins were decomposed rapidly by light, synthetic analogs—the pyrethroids— were developed.

- Due to their high insecticidal potency, generally low mammalian toxicity, and lack of environmental persistence, pyrethroids have encountered much success in the past 40 years and now account for about 15% to 20% of the global insecticide market.

- Pyrethroids are used widely as insecticides both in the house and in agriculture, in medicine for the topical treatment of scabies and headlice, and in tropical countries for malaria control, in soaked bed nets to prevent mosquito bites, as well as in indoor residual spraying.

- Pyrethroids are known to 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.

- The acute oral mammalian toxicity of pyrethroids is generally low.

- Values of LD50 range, for example, from 100 mg/kg (deltamethrin) to 10,000 mg/ kg (phenothrin).

- Upon absorption, pyrethroids are very rapidly metabolized through two major biotransformation routes: hydrolysis of the ester linkage, which is catalyzed by hepatic and plasma CarEs and oxidation of the alcohol moiety by CYPs.

- These initial reactions are followed by further oxidations, hydrolysis, and conjugation with sulfate or glucuronide.

Signs and Symptoms of Toxicity and Mechanisms of Action

- these compounds have been divided into two classes.

- Type I compounds produce a syndrome consisting in marked behavioral arousal, aggressive sparring, increased startle response, and fine body tremor progressing to whole-body tremor and prostration (type I or T [tremor] syndrome).

- Type II compounds produce profuse salivation, coarse tremor progressing to choreoathetosis, and clonic seizures (type II or CS [choreoath etosis with salivation] syndrome)

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 2 (CS syndrome)	Pawing and burrowing Profuse salivation Coarse tremor Choreoathetosis Clonic seizures	Deltamethrin Fenvalerate Cypermethrin Cyhalothrin

- The principal mode of action of pyrethroids in mammals is the same as in insects, that is, disruption of the voltage-gated sodium channels, though secondary targets have also been identified.

- 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.

- In general, type II compounds delay the inactivation of sodium channels substantially longer (more than 10 milliseconds) than do type I compounds (less than 10 milliseconds).

- Type I compounds prolong channel opening only long enough to cause repetitive firing of the action potential (repetitive discharge), analogously to DDT.

- Upon 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 hours, and topical application of vitamin E has been shown to be an effective treatment.

- Paresthesia is presumably due to abnormal pyrethroid-induced repetitive activity in skin nerve terminals.

Organochlorine Compounds

- The organochlorine insecticides include the chlorinated ethane derivatives, such as DDT and its analogs; the cyclodienes, such as chlordane, aldrin, dieldrin, heptachlor, endrin, and toxaphene; the hexachlorocyclohexanes, such as lindane; and the caged structures mirex and chlordecone.

- The organochlorine insecticides enjoyed wide use in agriculture, structure insect control, and malaria control pro grams.

- Their acute toxicity is moderate (less than that of OPs), but chronic exposure may be associated with adverse health effects particularly in the liver and the reproductive system.

- Primarily because of ecological considerations, these compounds have been banned in most countries in the past 30 to 40 years.

- Yet, because of their environmental persistence and high lipophilicity, exposure to these compounds continues, most notably through the diet.

- Furthermore, some, such as DDT, are being reintroduced in part of the world for malaria control; hence, a discussion of their toxicity has more than historical value.

DDT and Its Analogs

- DDT (1,1,1-trichloro-2, 2-bis(4-chloro phenyl)ethane).

- Early experiments showed that 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, with an LD50 of about 250 mg/kg; p,p′-DDT is at least 10-fold more toxic than o,p′-DDT.

- Dermal absorption of DDT is very limited, resulting in dermal LD50 values of more than 1000 mg/kg.

- In humans, oral doses of 10 to 20 mg/kg produce ill ness, 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.

- Upon absorption, DDT distributes in all tissues, and the highest concentrations are found in adipose tissue.
- DDT is also extensively but slowly metabolized, with DDE, DDD, and DDA (in each case both the p,p′ and the o,p′ isomers) being the primary metabolites in humans.

- DDE is also stored in adipose tissue.
- Excretion is through the bile, urine, and the milk.
- Acute exposure to high doses of DDT causes motor unrest, increased frequency of spontaneous movements, abnormal susceptibility to fear, and hypersusceptibility to external stimuli.
- This is followed by the development of fine tremors, progressing to coarse tremors, and eventually tonic–clonic convulsions.
- Symptoms usually appear several hours after exposure, and death, usually due to respiratory failure, may follow after 24 to 72 hours

- Signs and symptoms of acute poisoning clearly point at the nervous system as the primary target for DDT toxicity.

- 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.

- the principal effect of DDT is to slow down the closing of sodium channels once they have opened, while having little or no effect on closed gates.

- In addition to this effect on sodium channels, DDT also affects ATPases. Though DDT inhibits Na+, K+-ATPase, this action would not contribute to its neurotoxic effect.

- Rather, inhibition of a Ca2+-ATPase (an ecto-ATPase, located on the outside of the cell membrane) may be involved in the effects of DDT.

- As the function of this Ca2+-ATPase is considered to be that of maintaining high external calcium concentrations, its inhibition would lower external calcium and contribute to membrane instability and repetitive firing.

- Several neurochemical studies have also shown that DDT exposure alters the levels of some neurotransmitters such as acetylcholine, norepinephrine, and serotonin, as well as of cyclic GMP, but these effects appear to be the results, rather than the cause, of DDT-induced neurotoxicity.

- Treatment for DDT poisoning focuses on the nervous system.

- In laboratory animals, phenytoin and calcium gluconate have been found to reduce DDT-induced tremors and mortality, respectively.

- In humans, in addition to decontamination and supportive treatment, diazepam or phenobarbital may be beneficial to control convulsions, if present.

- While acute exposure to DDT is a rare event, 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 CYPs, particularly CYP2B and CYP3A.

- DDT, as well as DDE and DDD, have been shown to be carcinogenic in rodents, causing primarily an increase in liver tumors.

- DDT is not genotoxic in in vitro and in vivo tests. Associations between cancer and DDT have been studied in several.

- Given the endocrine-disrupting actions of DDT and DDE, particular attention has been devoted to possible associations between exposure to these compounds and hormonally sensitive cancers, and positive associations were found for some (e.g., testicular cancer) but not for others (e.g., breast cancer).

- DDT is classified as a probable human carcinogen.

Environmental Ubiquity and Persistence

- The properties (low volatility, chemical stability, lipid solubility, slow rate of biotransformation, and degradation) that made organochlorine compounds such effective insecticides also brought about their demise because of their persistence in the environment, bioconcentration, and biomagnification in food chains, and the acquisition of biologically active body burdens at higher trophic levels.