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Review Article

Neurotoxic Effect of Insecticides on Human Nervous System

Vikash[1], Anil Kumar Verma[2], A.K. Jaiswal[3], Sudeep Mishra[4]

Authors Affiliation: [1]Department of Forensic Science, Galgotias University, Greater Noida, Uttar Pradesh 201310, India. [2,4]Institute of Pesticide Formulation Technology, Sec-20, Udyog Vihar, Gurugram, Haryana 122016, India. [3]Department of Forensic Medicine and Toxicology, AIIMS, New Delhi, Delhi 110029, India.

Reprints Requests: Vikash, Department of Forensic Science, Galgotias University, Greater Noida, Uttar Pradesh 201310, India.

E-mail: vikashratawjia.pmt@gmail.com

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Abstract

Prologue- Pesticides is a generic term for a variety of agents that may be classified more specifically on the basis of pattern of use and organism killed such as insects, weeds, fungi, and rodents. A number of pesticides can cause neurotoxicity. It is not surprising that these agents also have neurotoxic effects on large mammals including humans. Despites man's persistent efforts to develop mechanism of actions in selectivity and specificity of these agents towards certain species while reducing toxicity to other forms of life, all pesticides possess an inherent degree of toxicity to human being.

This family of chemicals such as the organophosphates, the carbamates, the pyrethroids, the organochlorines, and other compounds directly target nervous system to show their mechanism of toxicity. Insecticides interfere with chemical neurotransmitter or ion channels in nerve cell, and usually cause reversible neurotoxic effects, that could nevertheless be lethal. The effects of pesticides on the nervous system is as neurotoxins, or may contribute to chronic neurodegenerative disorder, one of the most common notably is Parkinson's and Alzhemier Disease. This brief review summarizes some of the main neurotoxic insecticides, their effects and mode of action.

Keywords: Neurotoxicity; Neurotransmitter; Organophosphates; Carbamates; Organochlorines; Pyrethroids.

Introduction

The term "agricultural chemicals" has largely been replaced by the term "pesticides," defined as economic poisons, regulated by federal and state laws that are used to control, kill, or repel pests [1]. It 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 [2]. 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 fact, however, most pesticides are not highly selective, but are generally toxic to many non target species, including humans.

Thus, the use of pesticides must minimize the possibility of exposure of non target organisms to injurious quantities of these chemicals [3]. As there are dozens of drugs with different therapeutically indications and different mechanisms of action, several different classes of pesticides exist, with different uses, mechanisms and hence, toxic effects in non target 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).

In addition, for regulatory purposes, plant growth regulators, repellents, and attractants (pheromones) often also fall in this broad classification of chemicals. Furthermore, within each class, several subclasses exist, with substantially different chemical and toxicological characteristics. For example, among

insecticides, one can find organophosphorus compounds, carbamates, organochlorines, pyrethroids, and many other chemicals.

Depending on what a compound is designed to do, pesticides have been sub classified (as shown in Table 1) into a number of categories [4].

- Generally, a new pesticide takes some five to seven years to bring it to market once its pesticidal properties have been verified. Many tests must be conducted to determine such things as the compound's synthesis, its chemical and physical properties, and its efficacy and there are numerous toxicity tests are undertaken including those for acute toxicity and chronic effects such as reproductive anomalies, carcinogenesis, and neurological effects and those for environmental effects.
- In the United States, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) was passed in 1962 (amended in 1974, 1978, and 1988.This act divides all pesticides in four broad classes depending on their toxicity.

The label of each pesticide has to contain a signal word depending on its toxicity. The criteria established by the FIFRA are given in (Table 2) [5].

Table 1: Classification of Pesticides, with Examples

Class	Principal Chemical Type	Example, Common Name
Fungicide	Dicarboximide	Captan
	Chlorinated aromatic	Pentachlorophenol
	Dithiocarbamate	Maneb
	Mercury	Phenyl mercuric acetate
Herbicide	Amides, acetamides	Propanil
	Bipyridyl	Paraquat
	Carbamates, thiocarbamates	Barban
	Phenoxy	2,4-D
	Dinitrophenol	DNOC
	Dinitroaniline	Trifluralin
	Substitute urea	Monuron
	Triazine	Atrazine
Insecticide	**Chlorinated hydrocarbons**	
	DDT analogous	DDT, DDD
	Chlorinated alicyclic	BHC
	Cyclodiene	Aldrin
	Chlorinated terpenes	Toxaphene
	Organophosphorus	Chlorpyrifos
	Carbamate	Carbaryl
	Thiocyanate	Lethane
	Botanicals	
	Nicotinoids	Nicotine
	Rotenoids	Rotenone
	Pyrethroids	Pyrethrin
	Synthetic pyrethroids	Fenvalerate
	Synthetic nicotinoids	Imidacloprid
	Fiproles	Fipronil
	Juvenile hormone analogs	Methroprene
	Growth regulators	Dimilin
	Inorganic	
	Arsenicals	Lead arsenate
	Fluorides	Sodium fluoride
	Microbial	Thuricide, avermectin
Rodenticides	Anticoagulants	Warfarin
	Botanicals	
	Alkaloids	Strychine sulphate
	Glycosides	Scillaren A and B
	Fluorides	Fluoroacetate
	Inorganics	Thallium sulphate

What's the LD_{50}???

It's the Lethal Dose of a chemical compound, measured as milligrams of chemical per kilogram of body weight (mg/kg), which would theoretically kill 50% of an exposed population.

Table 2: Criteria of Pesticide Toxicity, Established by the Federal Insecticide, Fungicide and Rodenticide Act of 1962 [5]

S. No.	Category	Toxicity	Acute Oral LD50	Inhalation LD50
1	Danger& poison	High	0-50 mg/kg	Up to 0.2mg/L
2	Warning	Moderate	50-500mg/kg	0.2-2 mg/L
3	Caution	Low	500-5000mg/kg	2-20 mg/L
4	Caution	Relative safe	more than 5000 Mg/kg	more than 20 mg/L

- In India, a predominantly agricultural country, handling of insecticides is governed by *The Insecticides Act 1968 and The Insecticides Rules, 1971 (amended in 1993). Section 19 of The Insecticide Rules, 1971* classifies insecticides on a similar basis. Section 19 also insists on affixing a label to the insecticide container in such a manner that it cannot be ordinarily removed. Among other things, it must contain a square, occupying not less than one sixteenth of the total area of the face of the label, set at an angle of 45° ***(diamond shape).*** This square is to be divided into two equal triangles, the upper portion of which shall contain the "signal word" and the lower portion the specified colour. The classification of insecticides, signal words to be used, and the colour of the "identification band" on the label according to The Insecticide Rules, 1971 of India are given below: (see figure 1).

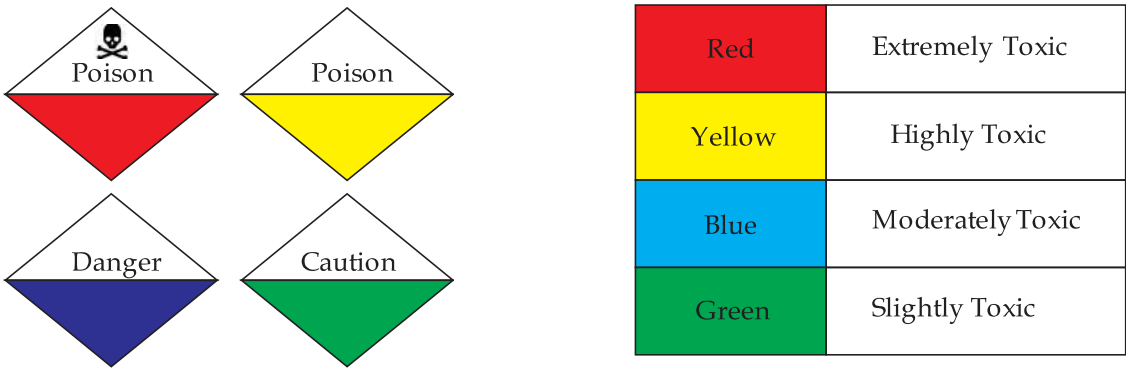

Fig. 1: Toxicity classification of pesticides using signal word and identification band color

Human Poisoning

Fig. 2: Exclusive news of mass poisoning through pesticides in India

Agrochemical poisoning remains one of the major causes of morbidity and mortality around the world today [6]. Peoples are exposed to low levels of pesticides every day. You can be exposed to pesticides in a variety of places including your home, at school, or at work. Pesticides can get inside your body from eating, drinking, breathing, them in, and by skin contact. Different pesticides affect human health in different ways. For example, some pesticides may affect the nervous system, while other may show their affect on skin and eyes. Yet, from a global perspective, the major problem with pesticides remains that of acute human poisoning.

- The ***World Health Organization (WHO)*** estimated that there are around three million hospital admissions for pesticide poisoning each year, that result in around 220,000 deaths (WHO, 1990). The 2002 annual report of the *American Association of Poison Control Centres (AAPCC)* Toxic Exposure Surveillance System listed a total of 2,380,028 human exposures to poisons occurring in the United States during the year 2002 alone. Most occur in developing countries, particularly in Southeast Asia, and a large percentage is due to intentional ingestion for suicide purposes [7].

Insecticide

An insecticide is a substance used to kill insects. They include ovicides and larvicides used against insect eggs and larvae. Insecticides are used in agriculture, medicine, industry and by consumers. Insecticides are claimed to be a major factor behind the increase in agricultural 20th century's productivity. Nearly all insecticides have the potential to significantly alter ecosystems; many are toxic to humans; some concentrate along the food chain [8]. All of the chemical insecticides in use today are neurotoxicants, and act by poisoning the nervous systems with specific molecular target of insecticide in organisms with their different mode of action (Table 3,4). The central nervous system of insects is highly developed and not unlike that of mammals, and the peripheral nervous system, though less complex, also presents striking similarities. Thus, insecticides are mostly not species-selective with regard to targets of toxicity, and mammals, including humans, are highly sensitive to their toxicity [9].

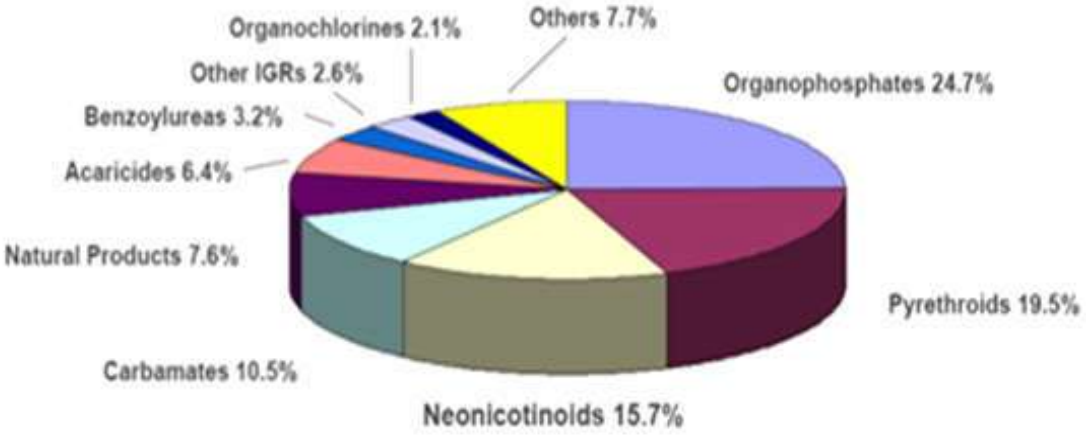

Fig. 4: Global Insecticide Sales in 2003

Table 3: Molecular Targets of the Major Classes of Insecticides

Toxicity Target	Insecticide	Effect
Acetyl cholinesterase	Organophosphates	Inhibition
	Carbamates	Inhibition
Sodium channels	Pyrethroids (Type I and II)	Activation
	DDT (Organochlorine)	Activation
Nicotinic acetylcholine	Nicotine	Activation
Receptors	Neonicotenoids	Activation
GABA receptors-gated	Organochlorine (Cyclodiene type)	Inhibition
Chloride channels	Pyrethroid (Type II)	Inhibition

Toxicological Effects of Insecticides on Nervous System

Human Nervous System???

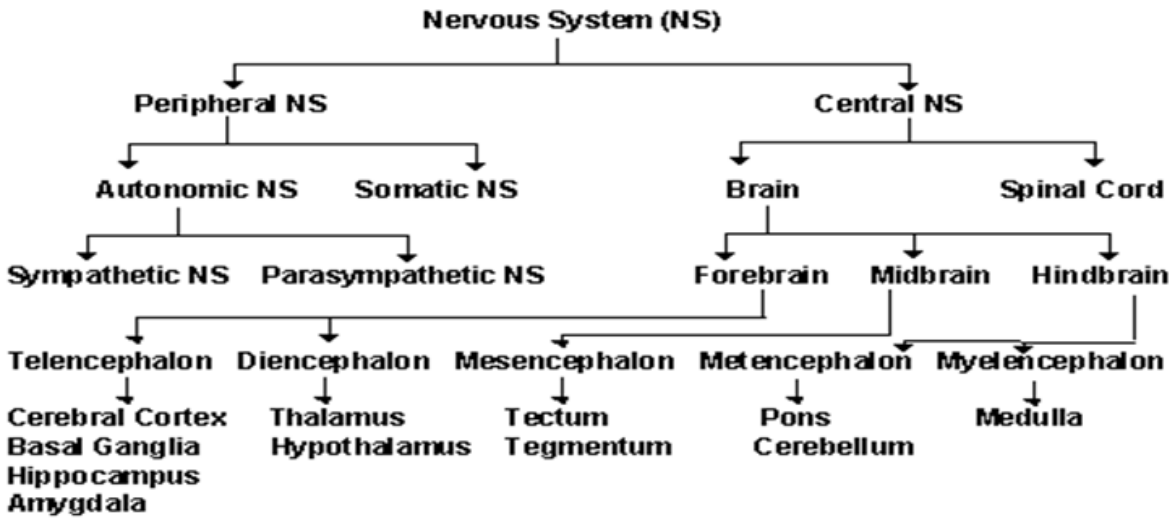

Fig. 5: Typical view of arrangement of Physiological System of Nervous System

The nervous system functions as a fast-acting means of transmitting important information throughout the body. The nervous system has two components :(shown in figure 5)

1. The *peripheral nervous system* receives and transmits incoming signals (taste, smell, sight, sound, and touch) to the central nervous system, and transmits outgoing signals to the muscles and other organs, effectively telling them how to respond.
2. The *central nervous system (CNS)* interprets the signals and coordinates the body's responses and movements. The CNS is composed of the brain and spinal cord in humans and a series of ganglia, or nerve bundles, in insects.
3. A *neuron* is a single nerve cell. It connects with other neurons and with muscle fibers (the basic units of muscles). These connecting neurons (or connecting neuron and muscle fiber) do not touch, however, and instead have a slight gap between them called a *synapse*.

Incoming signals (the pain from a sharp object, the sight of a predator, or the odor of food, etc.) are transformed by the neuron into an *electrical charge* that travels down the length of the neuron. The charged particles (called ions) that deliver the charge move through *channels* in the membrane of the neurons.

There are four main types of channels to allow different ions to move along the neuron: *sodium channels, potassium channels, calcium channels*, and *chloride channels*. Many of the channels have gates that open or close in response to a certain stimulus, which is an important mechanism through which some pesticides work. This process repeats over and over until the signal has reached the CNS to be interpreted. Impulses from the CNS to the peripheral nervous system continue in the same way until the signal reaches the appropriate muscles or organs. (Please see the figure 6 to understand the mechanism of signal transfer in neuron)

Humans have many different neurotransmitters that work at different sites throughout the nervous system. Some neurotransmitters are:

The first neurotransmitter is acetylcholine discovered by Otto Loewi got Nobel Prize. Many functions of body are associated with this. It is also present in sensory neurons of nervous sys

Inhibitory: they result in the signal being blocked from travelling to a connecting neuron. In this way, the body ensures that the signal has the desired effect in each muscle or organ, since many different reactions are involved in even a simple movement. e.g.: GABA , Dopamine, Serotonin, Endorphin).

Excitatory: they result in the signal being sent on through the synapse to a connecting neuron. It is not necessary that they are always exciting but they also stimulate the brain. (Epinephrine or Adrenaline, Norepinephrin, Acetylcholine, Glutamate,) [10].

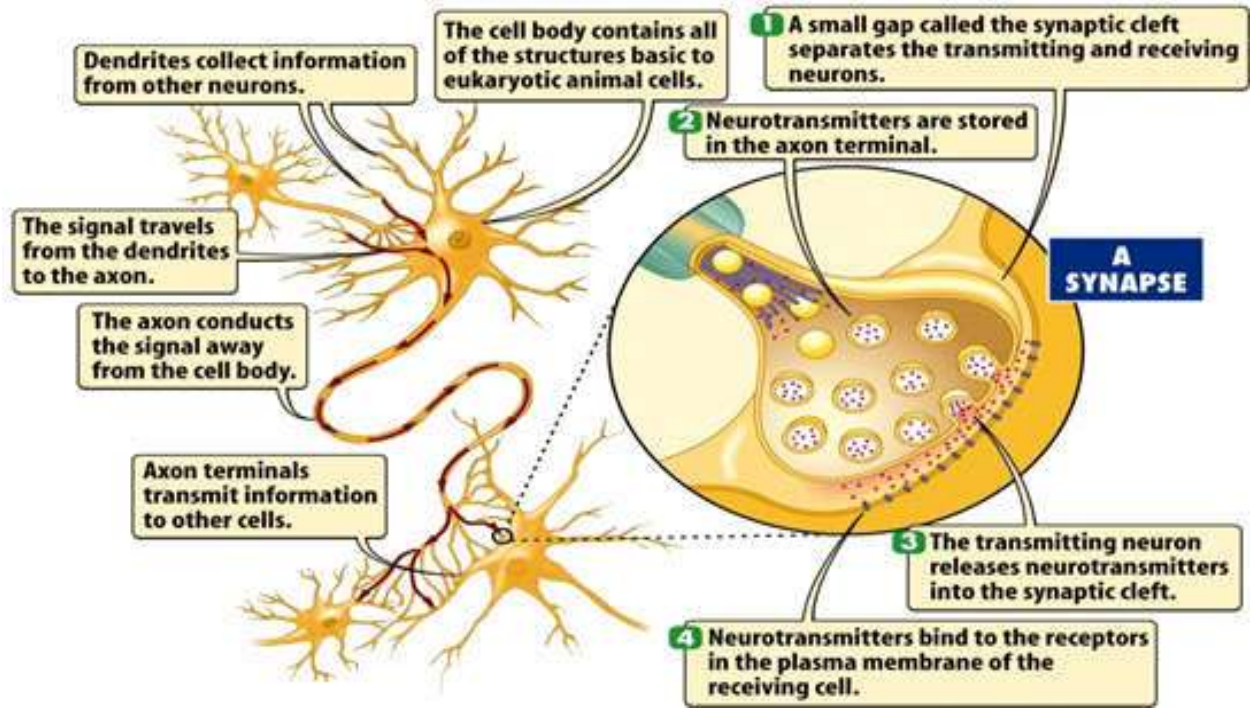

Fig. 6: Mechanism of signal transfer in human nerve cells (Neuron)

Definition of Neurotoxicity

Neurotoxicity is the damage to the brain or the peripheral nervous system by exposure to natural or man-made toxic substances or chemicals**.** This can eventually disrupt or even kill neurons, key cells that transmit and process signals in the brain and other parts of the nervous system.

Mechanism Action of Neurotoxic Effect of Insecticides

The mechanism of action of individual neurotoxin compounds have begun with the identification of the cellular target. In the nervous system, this has most often been one of four targets: the neuron, the axon, the myelinating cell, or the neurotransmitter system. As a result, neurotoxic compounds may be identified which cause neuronopathies, axonopathies, myelinopathies, or neurotransmitter-associated toxicity [11]. Many of the neurotransmitters that humans have, *acetylcholine (ACh)* and *gamma-amino butyric acid (GABA*) are important targets of some insecticides. ACh can either excite or inhibit its target neurons. Depending on the particular neuron and the specific receptors at the site, ACh can cause particular neurons to "fire," continuing the nerve impulse transmission, or it can cause the nerve impulse to stop at that particular site. In contrast, GABA is an inhibitory neurotransmitter. When GABA is the neurotransmitter activated at a synapse, the nerve impulse stops. Some insecticides interfere with the normal action of these neurotransmitters. Other insecticides attacking the nervous system work by other means.

This means the insecticide does not release the bound cholinesterase. Fortunately, the body continually produces cholinesterase, although it may take several weeks to again reach the desirable circulating level. Applicators using cholinesterase-inhibiting pesticides regularly should consider having their cholinesterase level monitored [12].

Organophosphorus Insecticides

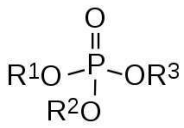

Fig. 7: General Chemical Structure of Organophosphorus Compound

General Review

Organophosphorus pesticides (OPs) are phosphoric acid esters or thiophosphoric acid esters and are among the most widely used pesticides for insect control. During the 1930s and 1940s Gerhard Schrader and co-workers began investigating OP compounds. They realized that the insecticidal

Table 4: Insecticides Modes of Action

Common name (examples of trade names)	Chemical Family (GROUP)	Targeted system/process	Mode of action
Chlorpyrifos (Lorsban) Acephate (Orthene) Chlorpyrifos methyl (Reldan) Diazinon Dimethoate (Rebelate) Disulfoton (Di-Syston) Ethyl parathion (Parathion) Fenitrothion (Sumithion) Fenthion (Baycid, Baytex) Isofenphos (Oftanol, Pryfon) Malathion Methamidophos (Monitor) Methidathion (Supracide) Mevinphos (Phosdrin) Monocrotophos (Azodrin) Naled (Dibrom) Phorate (Thimet) Phosmet (Imidan)	Organophosphates	Nervous system	Cholinesterase inhibitor
Aldicarb(Temik) Aldoxycarb(Standaz) Bendiocarb (Garvox) Carbaryl (Sevin) Carbofuran (Furadan) Carbosulfan(Advantage) Methiocarb (Mesurol) Methomyl (Lannate) Promecarb (Carbamult) Propathrin (Danitol) Propoxur (Baygon)	Carbamates	Nervous system	Cholinesterase inhibitor
Bifenthrin (Brigade, Capture, Empower, Talstar) Cyfluthrin (Baythroid, Countdown, Cylense, Laser, Tempo) Cypermethrin (Ammo, Barricade, Cymbush, Cynoff, Ripcord) Deltamethrin (Decis, DeltaDust, DeltaGard, Flythrin, Suspend) Esfenvalerate (Asana, Hallmark) Fenpropathrin (Danitol) Fenpropathrin (Danitol) Fluvalinate (Mavrik) Gamma-cyhalothrin (Proaxis) Lambda-cyhalothrin (Demand, Karate, Matador, Scimitar, Warrior) Permethrin (Ambush, Astro, Coopex, Outflank, Pounce, Pramex, Talcord) Tau-fluvalinate (Mavrik) Tefluthrin (Evict, Fireban, Force, Raze) Tralomethrin (Scout X-TRA, Tralex)	Pyrethroid	Nervous system	Sodium-channel modulator
Acetamiprid (Assail, Chipco, Pristine) Clothiamidin (Poncho) Imidacloprid (Admire, Advantage, Confidor, Gaucho, Marathon, Merit, Premier, Provado)	Neonicotinoid	Nervous system	Nicotinic Acetylcholine receptor stimulant Agonists/Antagonist
Endosulfan (Thiodan, Thoinex) Methoxychlor Eldrin Dieldrin Endrin Isobenzan Chlordane Chlorinated terpenes (Toxaphene) DDT and its analogs	Organochlorine insecticides of Cyclodiene types(Alicyclics)	Nervous system	Affected the chloride channel by inhibiting the GABA-receptor
Lindane (BHC)	Organochlorine Insecticide Gamma-HCH (Hexachlorocyclohexane)	Nervous system Nervous system	Sodium-channel modulator Affected the chloride channel by inhibiting the GABA-receptor

properties of these compounds and by the end of the World War II had made many of the insecticidal OPs in use today, such as ethyl parathion [*O*,*O*-diethyl *O*-(4 nitro phenyl) phosphorothioate]. Chlorpyrifos [*O*, *O*-diethyl *O*-(3, 5, 6-trichloro-2-pyridinyl) phosphorothioate] (as shown in fig: 8) became one of the largest selling insecticides in the world and had both agricultural and urban uses [13]. Other examples in this category are Acephate, Malathion, Methamidophos etc.

Chemically, organophosphates are derived from phosphoric acid (H3PO4) and two chemical groups are available [14]:

i. *Alkyl phosphates* -e.g. tetraethyl pyrophosphate (TEPP), hexaethyl tetraphosphate (HETP), octamethyl pyrophosphoramide (OMPA), dimefox, isopestox, sulfotepp, demeton, malathion (Kill bug; Bugsoline), etc. and

ii. *Aryl phosphates*- e.g. parathion (Follidol; Kill phos; Ekato), paraoxon, methyl parathion (Metacide), chlorthion, diazinon (Diazion; Tik 20).

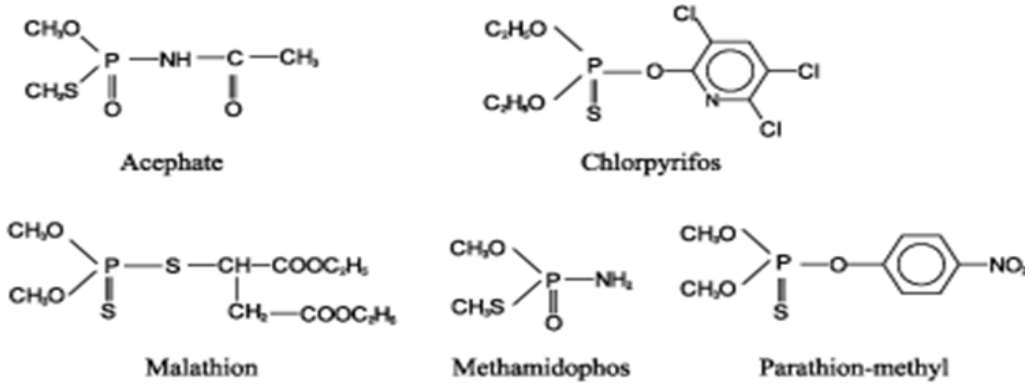

Fig. 8: Chemical Structure of Organophosphorus Insecticides

Neurotoxic Mode of Action of Ops Insecticides

OPs are toxic because of their inhibition of the enzyme acetyl cholinesterase. Acetylcholine is a neurotransmitter that affects the preganglionic and postganglionic parasympathetic synapses (muscarinic actions), sympathetic preganglionic synapses including the adrenal medulla (nicotinic actions) and the neuromuscular junctions (nicotinic actions). It is also a transmitter in the central nervous system. *At the synapses, it is hydrolysed by the enzyme, acetyl cholinesterase, thus producing acetate and choline*. The toxic effects of organophosphates are due to the inhibition of acetyl cholinesterase (that is why they are called as cholinesterase inhibitors) (Figure 10) resulting in the excessive accumulation of acetylcholine at the synapse [15].

- Normally the cholinesterase rapidly hydrolyze the neurotransmitter acetylcholine (Figure 9) into inactive fragments of choline and acetic acid after the completion of neurochemical transmission. The neurotransmitter acetylcholine is present in the terminal endings of all postganglionic parasympathetic nerves, at myoneural junctions, and at both parasympathetic and sympathetic ganglia. The major toxicity of organophosphate compounds is the covalent binding of phosphate radicals to the active sites of the cholinesterase, transforming them into enzymatically inert protein.

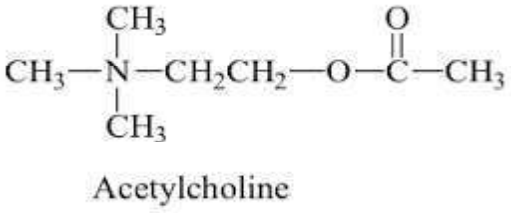

Fig. 9: Chemical structure of Acetylcholine

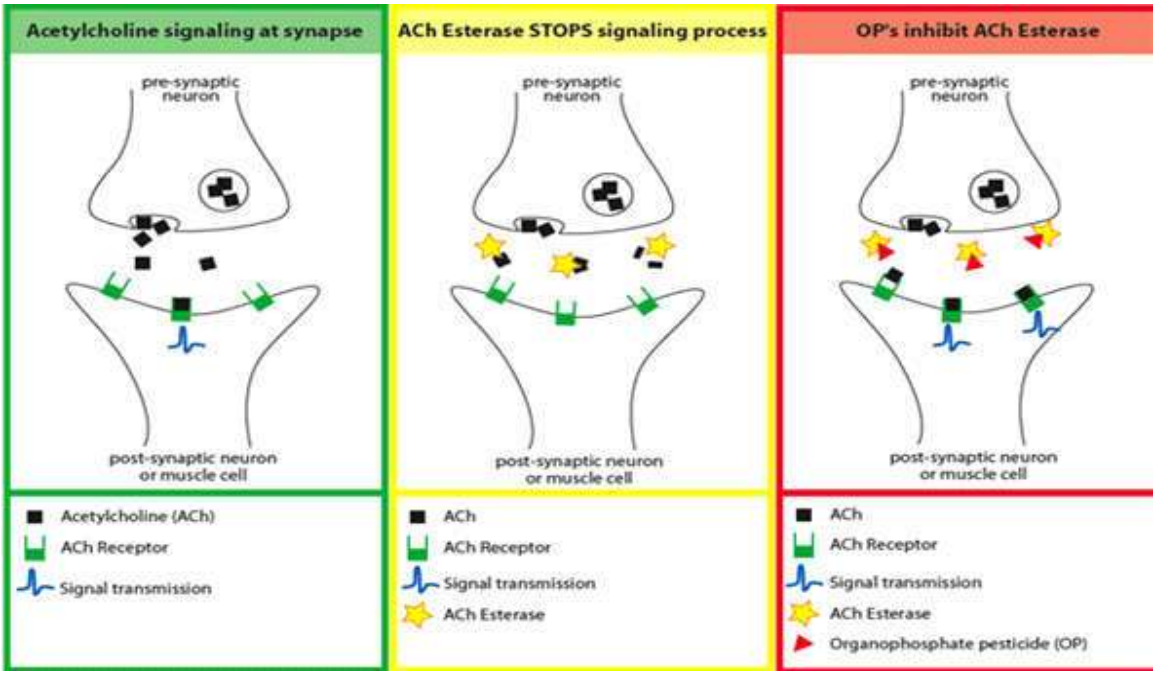

Fig. 10: Schematic Diagram of mode of action of OPs Poisoning

Carbamates Insecticides

Fig. 11: General Chemical Structure of Carbamates Compound

General Review

The carbamate insecticides are esters of *N*-methyl (or occasionally *N*,*N*-dimethyl) carbamic acid *(*H2NCOOH*)*. The first recognized anti-ChE was in fact a carbamate, physostigmine (also called eserine), obtained in pure form in 1864 by Jobst and Hesse from the Calabar bean Like organophosphates, carbamates are inhibitors of AChE, but instead of phosphorylating, they carbamoylate the serine moiety at the active site (Figure 12). This is a reversible type of binding, and therefore, their toxicity is less severe and of lesser duration. Because they do not penetrate the CNS to any great extent, the CNS toxicity of carbamates is relatively low [16]. One of the most widely used carbamate insecticides is carbaryl (1- napthyl methylcarbamate), a broad spectrum insecticide. Carbaryl is not considered to be a persistent compound, because it is readily hydrolyzed. It is used widely in agriculture, including home gardens where it generally is applied as a dust or solution, such as aldicarb (Temik), aminocarb (Matacil), approcarb (Baygon), carbaryl (Sevin), carbofuran (Furaxdan) as shown in(see Figure 13). Absorption occurs through all routes [17].

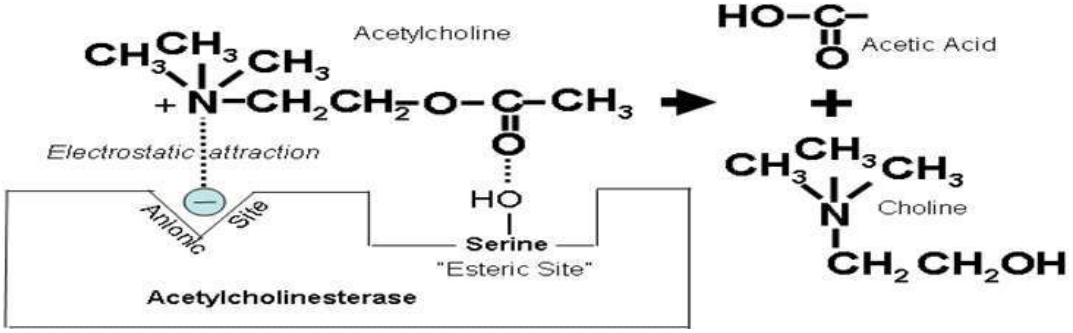

Fig. 12: Breakage of Acetylcholine into Acetic Acid and Choline (by cholinesterase enzyme)

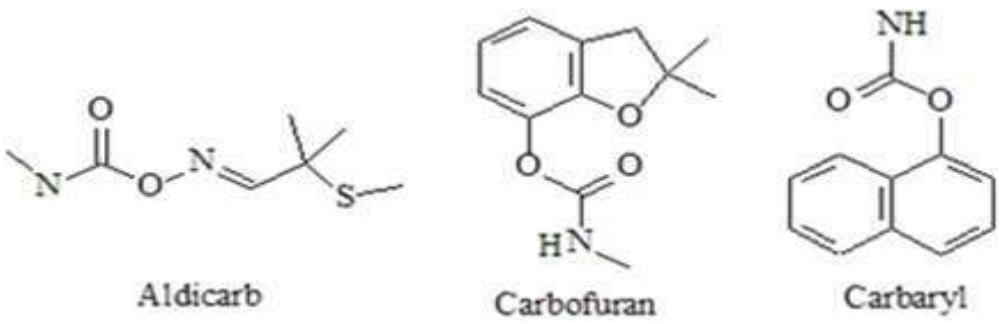

Fig. 13: Chemical structure of Carbamates Insecticides

Neurotoxic Mode of Action of Carbamate Insecticides

Like the OP insecticides, the mode of action of the carbamates is acetyl cholinesterase inhibition, but carbamylate the serine moiety at the active site instead of phosphorylation with the important difference that this is reversible type of binding (Figure 12). The inhibition is more rapidly reversed than with OP compounds. Because there is rapid reactivation of the carbamylated enzyme in the presence of water and hence symptoms are less severe and of shorter duration. Also, as carbamates do not penetrate the CNS effectively toxic features related to CNS are not much prominent in the event of poisoning [18].

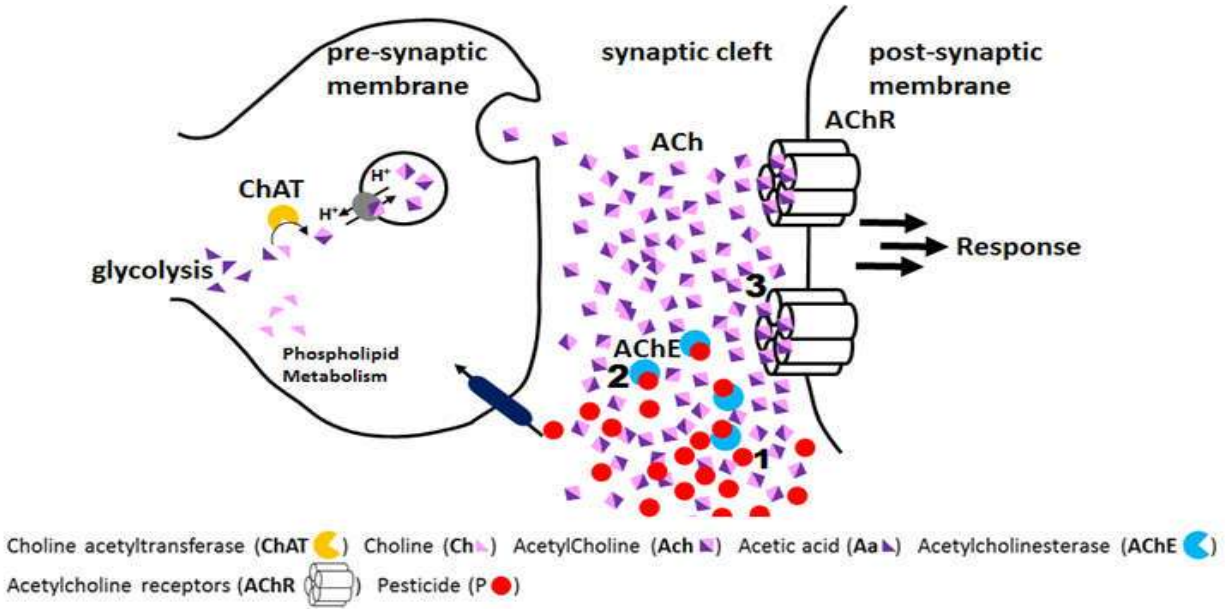

Fig. 14: Schematic Diagram of mode of action of Carbamates Poisoning

Pyrethroid Insecticides

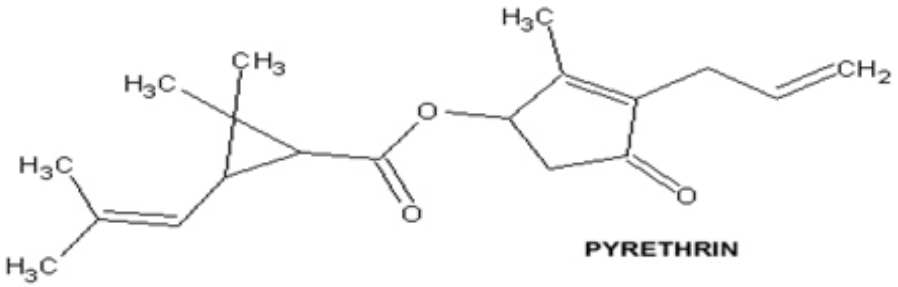

Fig. 15: Chemical structure of Pyrethrin

General Review

Pyrethrins were first developed as insecticides from extracts of the flower heads of *Chrysanthemum cinerariaefolium*, whose insecticidal potential was appreciated in ancient China and Persia. However, because pyrethrins were decomposed rapidly by light, synthetic analogs, the pyrethroids were developed. Pyrethroids are used widely as insecticides both in the house and in agriculture. 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 [28]. There are two broad classes of pyrethroids depending on whether the structure contains a cyclopropane ring [e.g., cypermethrin {(±)-α-cyano-3-phenoxybenzyl (±)-*cis*,*trans*-3-(2,2-dichlorovinyl 2,2-dimethyl cyclopropanecarboxylate)}] or whether this ring is absent in the molecule [e.g., fenvalerate{(*RS*)-α-cyano-3-phenoxybenzyl(*RS*)-2-(4-chlorophenyl)-3-methylbutyrate}] [19].

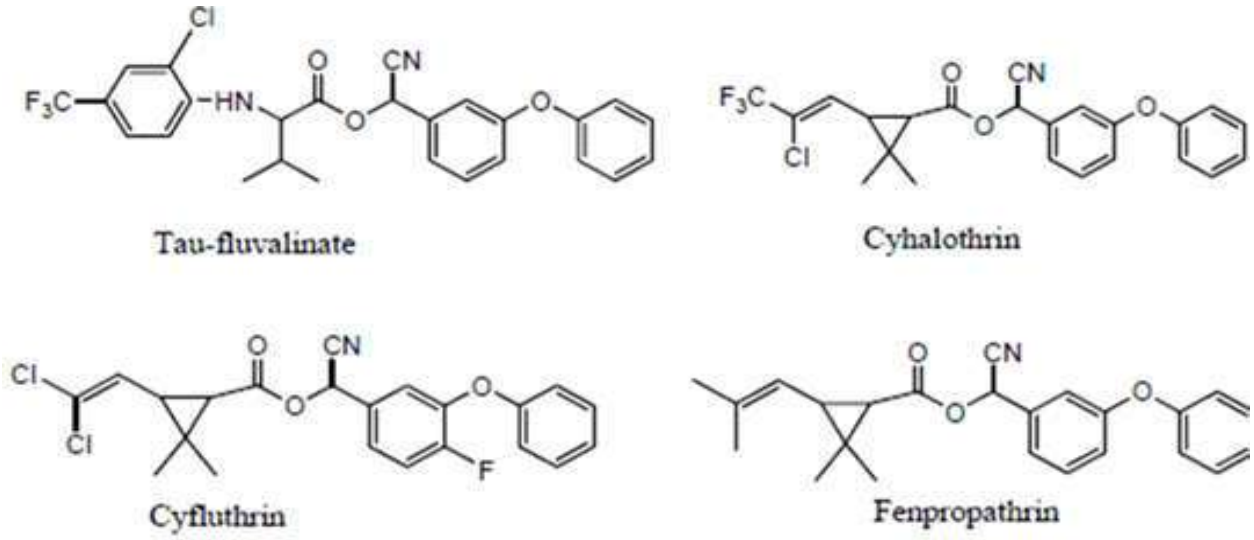

Fig. 16: Chemical Structure of Pyrethroid Insecticides

Neurotoxic Mode of Action of Pyrethroid Insecticides

Based on its sign and mechanism action Pyrethroid has been divided into two types:

- Type I (T) and Type II (CS) Syndrome (Figure 17)

A key structural difference between type I and type II pyrethroids is the presence only in the latter of a cyano group at the carbon of the alcohol moiety of the compound [20].

The mode of action of pyrethroids in mammals is the disruption of the voltage-gated sodium channels that maintains the electrical charge of nerve cell membrane [21]. Pyrethroids bind to the á 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. Sodium channels then open at more hyperpolarized potentials, and are held open longer, allowing more sodium ions to cross and depolarize the neuronal membrane [22](Figure 18).

- Type I compounds prolong channel opening only long enough to cause repetitive firing of action potential (repetitive discharge).
- Type II compounds hold the channels open for such long periods that the membrane potential ultimately becomes depolarized to the point at which generation of action potential is not possible (depolarization-dependent block). Type II pyrethroids also bind to, and inhibit GABA-gated chloride channels.

These differences in the time of opening of sodium channels are believed to be at the basis of the differences observed between the T and CS syndromes [23].

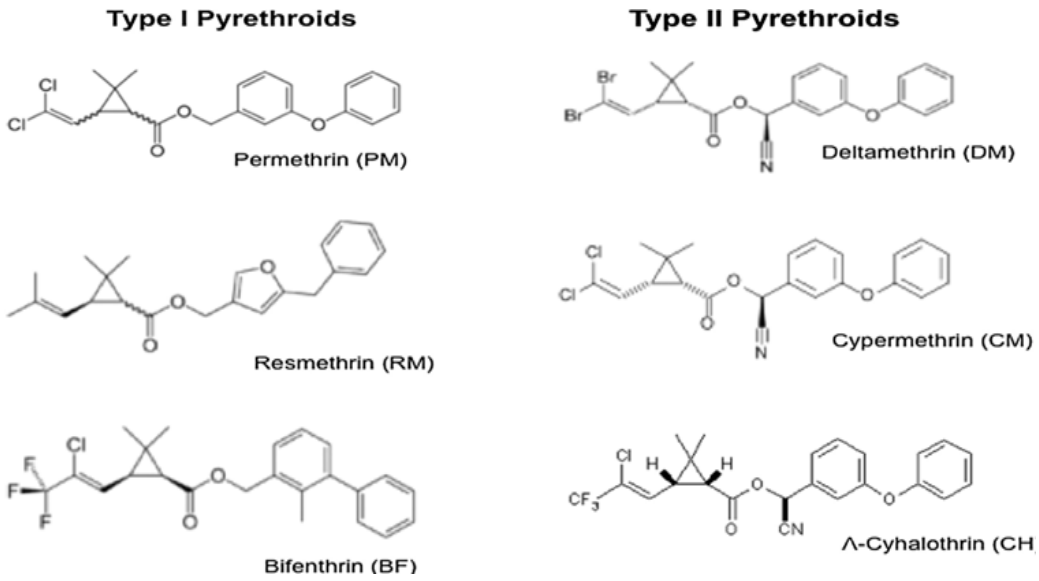

Fig. 17: Chemical Structure of Type I and Type II Pyrethroid Insecticides

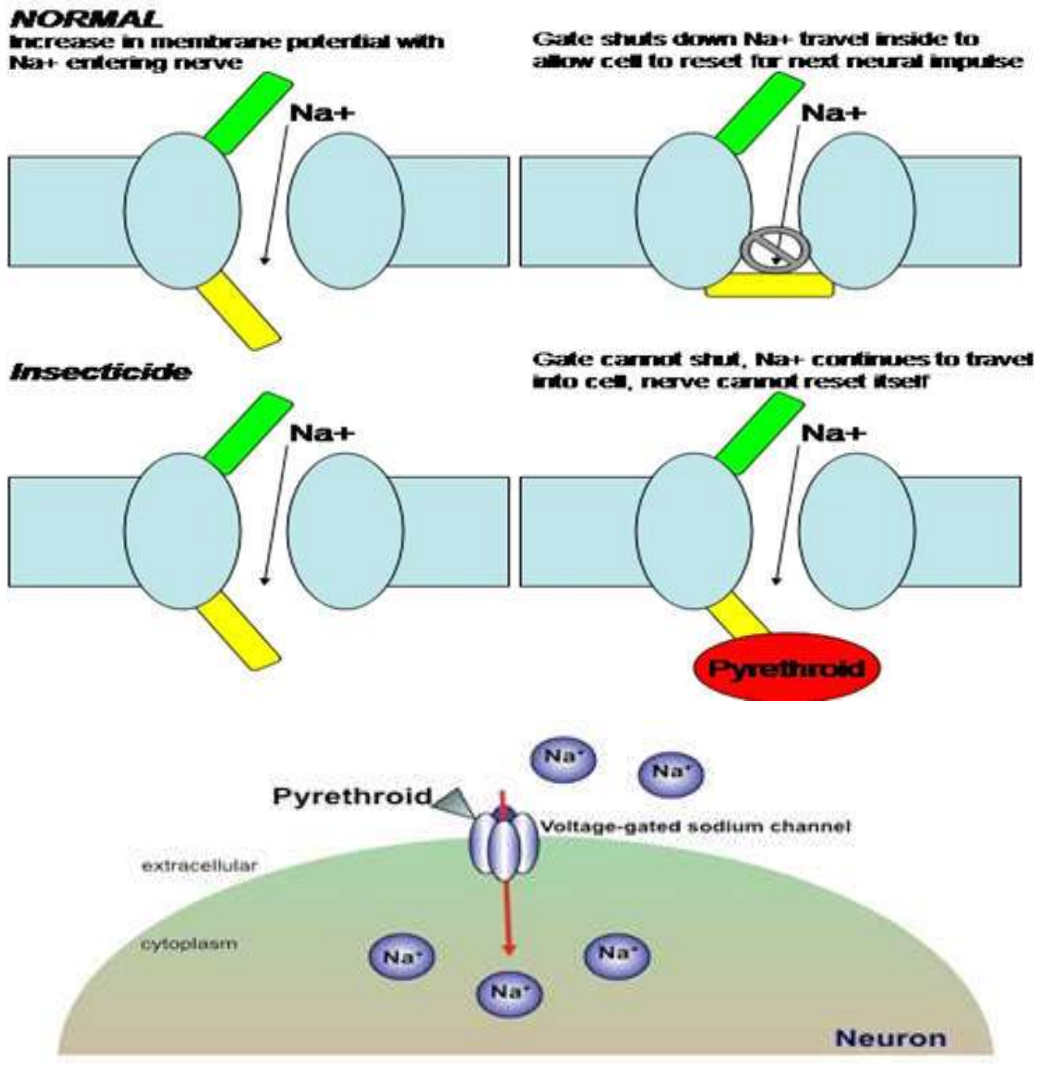

Fig. 18: Schematic diagram of mode of action of Pyrethroid Poisoning.

Organochlorine Insecticides

General Review

The organochlorine insecticides include the chlorinated ethane derivatives, such as DDT and its analogues; the cyclodienes, such as chlordane, aldrin, dieldrin, heptachlor, endrin, and toxaphene; the hexachlorocyclohexanes (HCH), such as lindane; and the caged structures mirex and chlordecone (Figure 19). From the 1940s to the 1970s and 1980s, the organochlorine insecticides enjoyed wide use in agriculture, structure insect control, and malaria control programs. Their acute toxicity is moderate (less than that of organophosphates) [24]. *DDT* was synthesized by the German chemist Othmar Zeidler in *1874*, but he failed to realize its value as an insecticide. It was the Swiss Paul Hermann Muller (1899–1965) who recognized its potential as an effective insecticide (Nobel Prize in Medicine in 1948). It is ironic that just 24 years later, in 1972, DDT was banned in the United States [25].

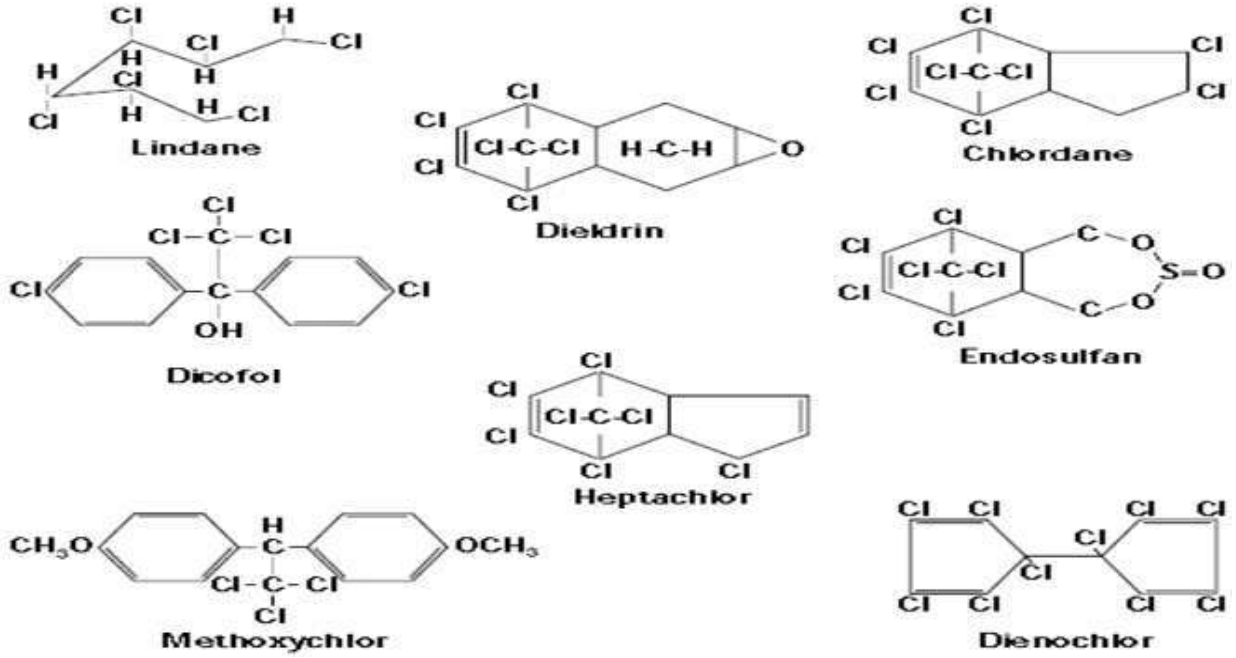

Fig. 19: Chemical Structure of Organochlorine Cyclodiene type Insecticides

Neurotoxic Mode of Action of Organochlorine Insecticides

The two main groups of organochlorine insecticides are the DDT-type compounds and the

Chlorinated cyclodienes (alicyclics). Their mechanism of action differs slightly:

The DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (Figure 20) like compounds acts on the central nervous system by interfering with the movement of ions through axon neuronal membranes. DDT both delays the closing of the sodium ion channel and prevents the full opening of the potassium gates [36]. DDT has been shown to target a specific neuronal adenosine triphosphatase (ATPase) thought to be involved in the control of the rate of sodium, potassium, and calcium fluxes through the nerve membrane [26] (Figure 21). This leakage causes repeated discharges in the neuron either spontaneously or after a single stimulus.

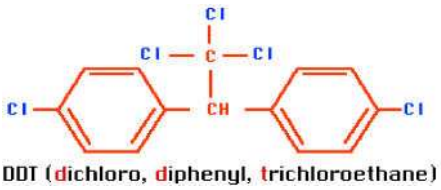

Fig. 20: Chemical structure of DDT

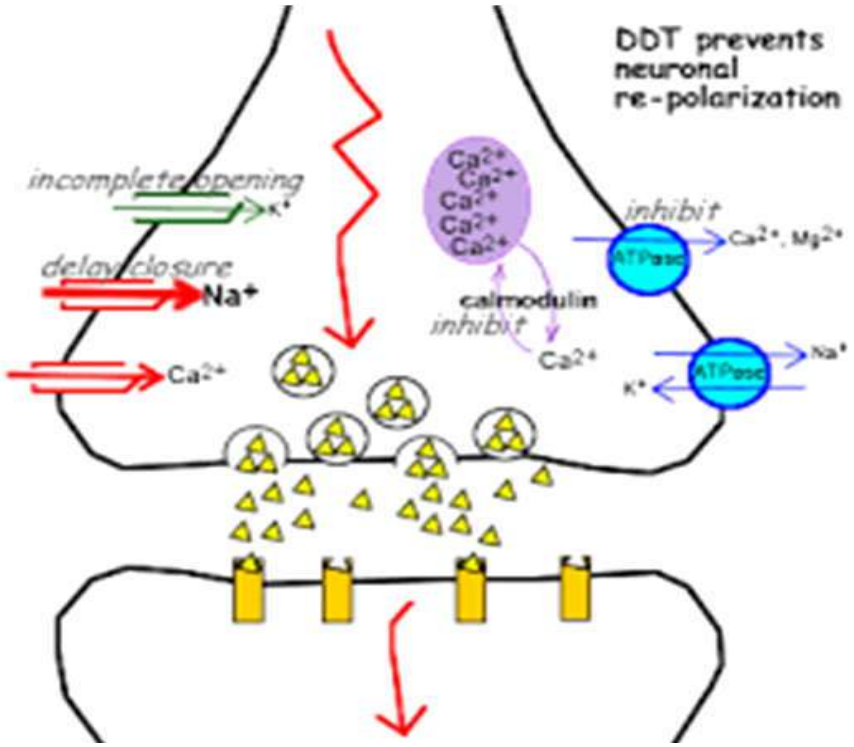

Fig. 21: Schematic diagram of mode of action of DDT Poisoning

Chlorinated Cyclodienes

After 2- to 8-hour exposure leads to depressed central nervous system (CNS) activity, followed by hyperexcitability, tremors, and then seizures. The mechanism action of these compounds to interfere with γ-amino butyric acid (GABA)–mediated neurotransmission. GABA is an important neurotransmitter in the mammalian CNS and in the neuromuscular junction. GABA receptors are members of the super family of ligand-gated ion channels that contain a chloride ionophore; by binding to these receptors, endogenous GABA causes the opening of chloride channels resulting in hyper polarization of the membrane. Lindane and cyclodienes bind to a specific site (the picrotoxin site) on the chloride channel, thereby blocking its opening and thus antagonizing the "inhibitory" action of GABA [27,28,29]. Additional reported neurochemical effects of organochlorine insecticides include inhibition of Na+- K+, Ca2+, and Mg2+ -ATPases, and changes in neurotransmitter levels.

Neonicotinoid Insecticides

General Review

The neonicotinoids is one of the newest categories of insecticides. The neonicotinoid family includes acetamiprid, cloth ianidin, imidacloprid, nitenpyram, nithiazine, thiacloprid and thiamethoxam. (Figure 22). The nicotinoids similar to and modelled after the natural nicotine. Imidacloprid is the most widely used insecticide in the world. Imidacloprid was the first in this chemical category to obtain registration in internationally. Compared to organophosphate and carbamate insecticides neonicotinoids cause less toxicity in human.

Neurotoxic Mode of Action of Neonicotinoid Insecticides

Neonicotinoids, like nicotine bind or fill up the nicotinic- acetylcholine receptors and blocking neural transmission (Figure 23). In mammals, nicotinic acetylcholine receptors are located in cells of both the central nervous system and peripheral nervous systems. Nicotinic acetylcholine receptors are activated by the neurotransmitter acetylcholine. While low to moderate activation of these receptors causes nervous stimulation or high level over stimulates and block the AchR receptors causing paralysis and death. Acetyl cholinesterase breaks down acetylcholine to terminate signals from these receptors. However, acetyl cholinesterase cannot

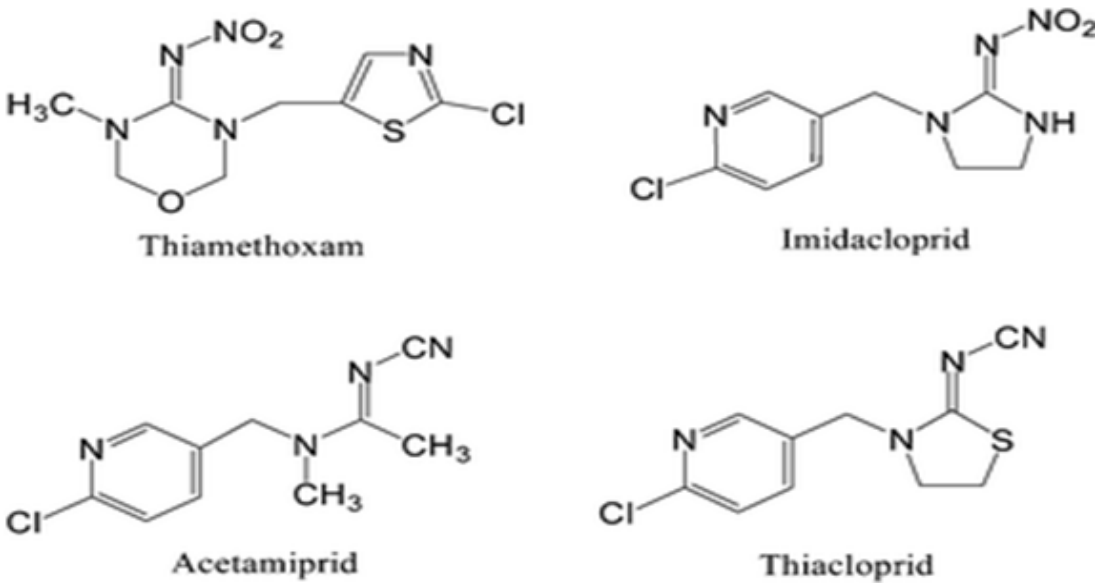

Fig. 22: Chemical structure of Neonicotinoid Insecticides

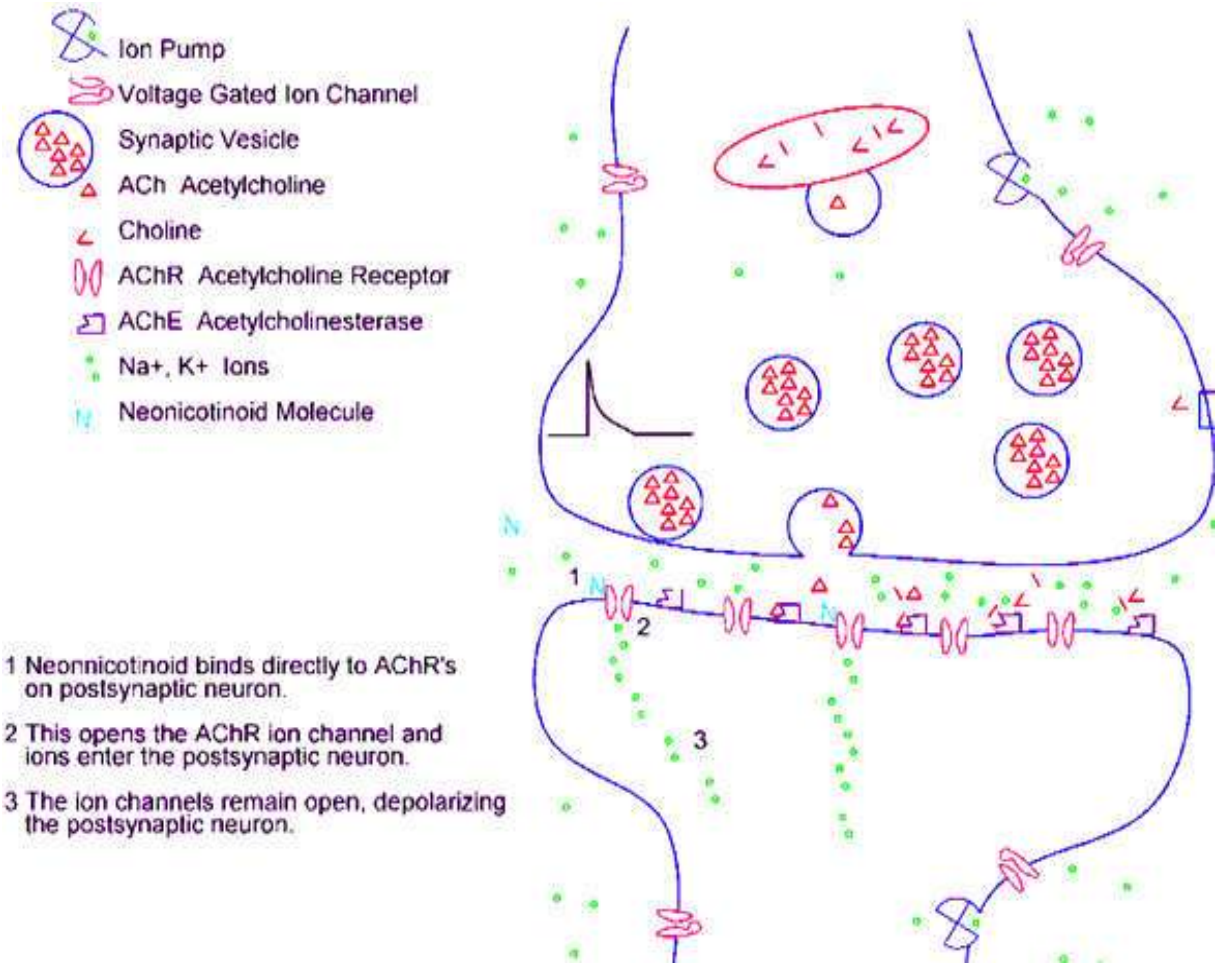

Fig. 23: Schematic diagram of Mode of Action of Neonicotinoid Poisoning

break down neonicotinoids and their binding is irreversible [30].

Conclusion

This section has covered only a few of the pesticides available today on the United States and world markets. An understanding of the basic chemical processes affected by pesticides has led to the discovery and production of new families of chemicals. Today's modern pesticide is generally safe to use if the directions on the label are followed. Many pesticides, particularly insecticides, are specifically designed to target the nervous systems of pests. For this reason, these substances can also be neurotoxic to non-target animals, including (in some cases) humans and other mammals. Understanding the underlying mechanisms in the inter-play between such environmental and genetic components is an important area of future research. There is, therefore an urgent need to reduce and, wherever possible, avoid human exposures to hazardous chemicals. In the case of agrochemicals, this will require us to fundamentally rethink and change our farming systems to eliminate our exposure to synthetic pesticides and protect the health not only of particularly highly exposed and/or vulnerable groups, such as agricultural workers and children, but also the general population and wild ecosystems.

Most studies of moderate pesticide exposure have found increased prevalence of neurologic symptoms and changes in neurobehavioral performance, reflecting cognitive and psychomotor dysfunction. Also the most studies have focused on organophosphate insecticides, but some found neurotoxic effects from other pesticides, including fungicides, fumigants, and organochlorine and carbamate insecticides. Future studies will need to improve assessment of pesticide exposure in individuals and consider the role of genetic susceptibility. Advances in instrumentation and an understanding of how adverse health effects are produced have resulted in the production of many environmentally friendly but effective pesticides.

- Organochlorine insecticides, pyrethoids as well as the new fiproles disrupt the sodium/potassium/chloride channel systems that maintain the electrical charge of nerve cell membranes. When this is disrupted, nerves cannot properly transmit the electrical impulse. (*Neural Membrane Disruption* or *Ion Transport Disruption*).
- Organophosphate and carbamate insecticides block the acetylcholine-esterase enzyme which causes the receiving nerve to keep firing. This causes the affected animals to virtually twitch to death. (Neural Synapse Disruption or Enzyme Activity Disruption).
- Neonicotinoids fill up the acetylcholine receptors, actually the nicotinic-acetylcholine receptors (which insects have), thereby blocking neural transmission. Affected insects simply stop activity especially feeding, grooming and protective behaviors. (Neural Post-synapse Disruption or Blockage the Receptors).

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