International Journal of Biological Research, 2 (2) (2014) 69-77

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International Journal of Biological Research

Journal home page: www.sciencepubco.com/index.php/IJBR
doi: 10.14419/ijbr.v2i2.2999
Research Paper



A review on organophosphorus toxicity in the farmers of solapur district from India

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Abstract

Organophosphorus compounds were first developed by scientist Schrader shortly before and during Second World War. They were first used as agricultural insecticides and later as potential chemical warfare agent. A great proportion of acute poisoning cases are caused by exposure to these pesticides. Pesticides can enter the body through the skin (dermal), mouth (oral), lungs (breathing), and eyes (ocular) and due to accidental ingestion. It is found that the Organophosphorus compound, dimethoate is more commonly used to attempt suicide as it is easily available and cheap. 54 % poisoning cases were observed only due to dimethoate. The poisoning due to warfarin, tick-20, chlorpyrifos, fenthion, thymate and lice powder is less common. Acute Organophosphorus poisoning leads to paralysis of skeletal muscles. Paralysis generally occurs in between 48 to 72 hours after poisoning and is associated with cranial and proximal limb muscle weakness. Inability to lift the neck, inability to sit up, opthalmoparesis, slow eye movements, facial weakness, difficulty in swallowing, limb weakness (proximal is more than distal), areflexia, respiratory failure etc. are clinical features of paralysis. These features together are called as intermediate syndrome. On other hand, organophosphorus poisoning is also associated with respiratory failure. Respiratory failure occurs due to many reasons, such as central respiratory depression, respiratory muscle weakness, bronchospasm, bronchorrhea, aspiration of gastric contents, anorexic brain damage etc. This togetherly is associated with Acute Respiratory Distress Syndrome (ARDS). Identification of poisoning is done on the basis of symptoms shown by patients while perfect diagnosis requires biochemical analysis. Symptoms such as hyper-salivation, convulsions, respiratory failure, ataxia, slurred speech, miosis, muscle cramping suggest about poisoning. To access Organophosphorus poisoning, it is necessary to analyze biological samples mostly blood and urine. Organophosphorus compounds can be detected in urine however, their degradation is rapid and hence their detection in urine is possible for short time. The detection of metabolites of Organophosphorus compounds is another way to detect Organophosphorus poisoning. Metabolites circulate for longer time and mostly excreted in urine. Detection of metabolites of Organophosphorus compounds is always better than detection of parent compound in blood or urine. This is because parent compound has short life time and its detection is not possible for more than hours after poisoning. For some Organophosphorus compounds (e.g. Parathion, Paraoxon), detection of P–nitrophenol in urine is an indicator of Organophosphorus poisoning. Recently, antibodies against Organophosphorus compounds in blood are also detected. Thus, blood and urine remains main source for biological and biochemical examination in Organophosphorus poisoning. Most commonly, detection of Organophosphorus poisoning is done by estimating activities of enzymes namely Acetyl Cholinesterase, Butyryl Cholinesterase and Acylpeptide Hydrolase from blood. All these enzymes contains serine residue at their catalytic sites. Organophosphorus compound binds with this serine residue and inactivates the enzymes. Such inactivation of above enzymes is only concerned with Organophosphorus poisoning and thus inhibition of Acetyl Cholinesterase, Butyryl cholinesterase and Acylpeptide Hydrolase is highly correlated with severity and duration of poisoning with Organophosphorus compounds.

Keywords: *Organophosphorus, Acetyl Cholinesterase, Butyryl Cholinesterase, Pest, ARDS Etc.*

1. Introduction

1.1. Definition of pesticides

Any substance or mixture of substance used to prevent, destroy and repel the pest such as insects, rodents, nematodes etc. is called as pesticide. (USACHPPM 2000, Ubale 2007) The term pesticides include insecticides, herbicides, fungicides, rodenticides and disinfectants. A pesticide may be a liquid (mist or spray), solid (dust, granule or bait) or gas (vapour) applied to control unwanted insects, ticks, mites, plants or animals in a given area (USACHPPM 2003).

1.2. Classification of pesticides

Classification of pesticides is done on the following ways,

i) According to nature of hydrocarbon chains

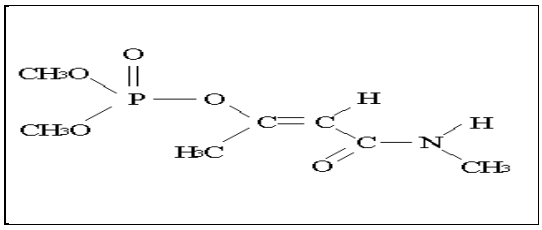
According to nature of hydrocarbon chain pesticides are of two types. (Ubale 2007).

Aliphatic Pesticides

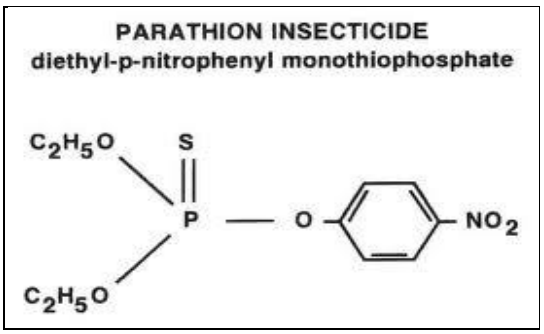
Hydrocarbon chain containing pesticide is aliphatic in nature. They may have single bond between two carbon atoms or may also have double bond between two carbon atoms.

E.g. Monocrotophos

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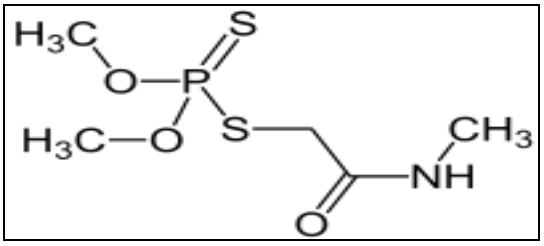


Aromatic Pesticides
Aromatic ring is present in hydrocarbon chain. E.g. Parathion

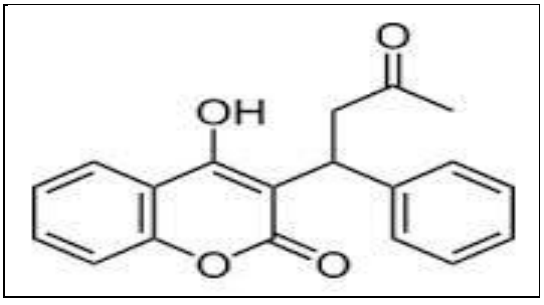


ii) According to pests against they are used
According to this type pesticides are classified in following ways. (Ford et.al. 2001 Barile 2003)

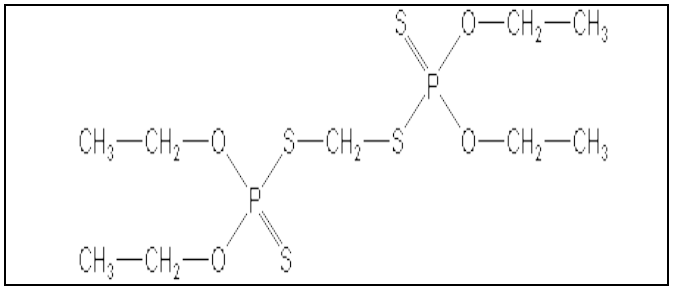
Insectides
These are pesticides used against insects. E.g. Dimethoate



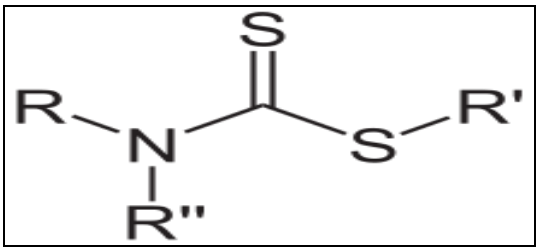
Rodenticides
These are the pesticides used against rodents such as mice, rat, squirrels etc. e.g. Warfarin.



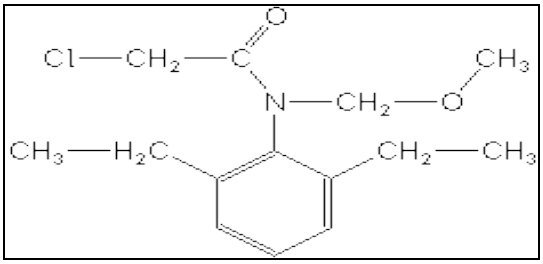
Miticides
These are also called as acaricides. These are pesticides which are used against mites. Mites are minute, transparent parasites. E.g. Ethion.



Fungicides
These are pesticides used against fungi. E.g. Dithiocarbamates.

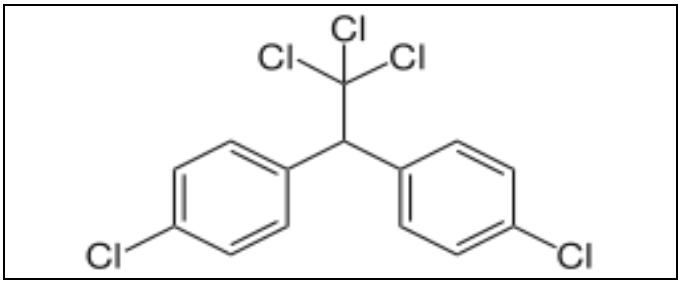


Herbicides
These are also called as weedicides, weeds are the unwanted plants. E.g. Alachlor

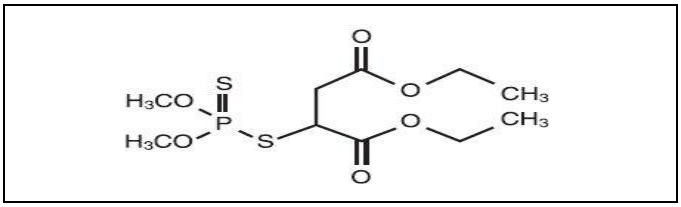


iii) According to mode of action
According to mode of action pesticides have following types, (Kuca et.al. 2005)

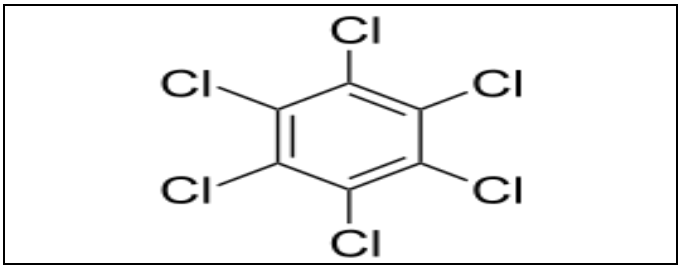
Stomach or internal pesticides
These are pesticides which kill the pest on its ingestion. E.g. DDT



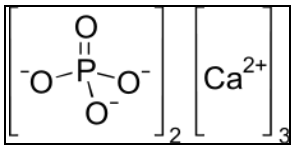
Contact or external pesticides
These are pesticides which kill the pests on its contact externally. E.g. Malathion



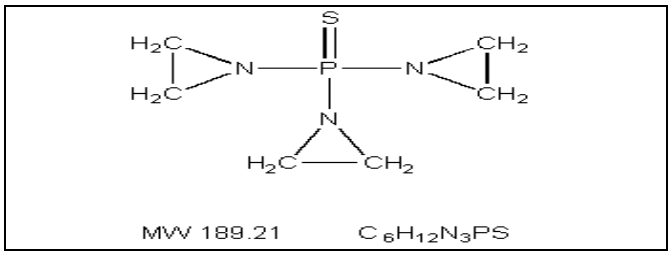
Fumigants
These are the pesticides which emit poisonous vapours and paralyze respiratory system of the pest. E.g. Benzene-hexachloride (BHC)



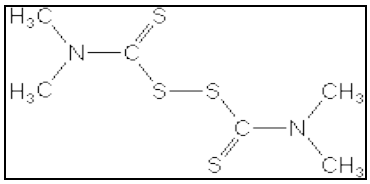
Dessicants
These are pesticides which kill pest by their dehydration. E.g. Calcium phosphate.



Chemosterilants
These are chemicals which affect reproductive system of pest and make them sterile. E.g. Thiotepa.

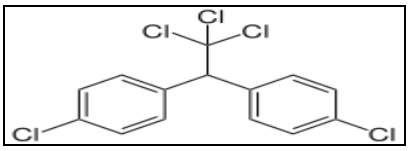


Repellents
These are chemicals which repel the pest and protect the plant.
E.g. Thiram.

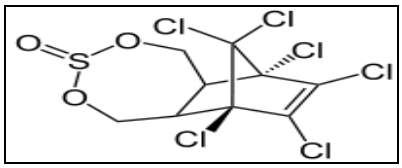


iv) According to functional group present in pesticide
According to this there are following types of pesticides.(Kuca et.al. 2005)

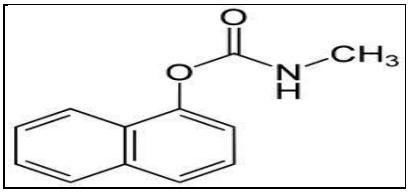
Organ chlorine pesticides
These pesticides contain C – Cl bond. E.g. DDT (Dichloro diphenyltrichloroethane).



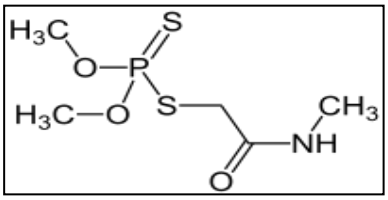
Organosulphur Pesticides
These pesticides contain C = S or – C – O – S bond. E.g. Endosulfan.



Carbamates
These pesticides contain – O – C = O bonding. E.g. Carbaryl (Sevin).

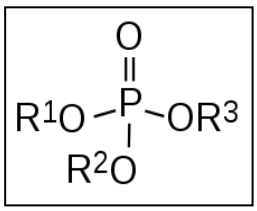


Organophosphorus Pesticides
These pesticides contain C O PO_3 bonding. (Reiner 2001)
E.g. Dimethoate.



1.3. Chemistry of organophosphorus pesticides

Organophosphorus compounds were first developed by scientist Schrader shortly before and during Second World War. They were first used as agricultural insecticides and later as potential chemical warfare agent. The general structure of organophosphorus compound is as follows.



In this case, R1 and R2 may be hydrogen, alkyl, aryl, alkylthio or amino groups. R3 is a dissociable group such as halogen, cyano, alkylthio or organic acid. (Bajgar 2005).

Organophosphates are traditionally used because of their effectiveness against a variety of pests and because the pests do not appear to develop resistance to this class of pesticides as they do to others. Pests are the animals or plants which are harmful to the interest of human beings. The term pest includes insects, rodents, nematodes, fungi, bacteria, weeds and various parasitic plants. Viruses and disease causing microorganisms not belongs to this category. (Sungur et.al. 2001)

Organophosphorus pesticides are most commonly used to control agricultural, household and structural pests. (Vidhyasagar et.al. 2004) Majority of pesticides belong to organophosphorus group.(James 2003) Organophosphates are largely used due to their effectiveness against variety of pests. Further, pests do not develop resistance to this class of pesticides as they do to others. Organophosphorus pesticides are generally less persistent than other chemical classes currently used. Organophosphorus compounds break down under the influence of sunlight, air, rainfall, soil moisture, bacteria, fungi etc. Organophosphorus compounds persist for a longer time when they are used indoors. Organophosphorus poisoning remains one of the major health issue in developed and especially in developing countries and its frequency is increasing over the years. A great proportion of acute poisoning cases are caused by exposure to these pesticides. Pesticides can enter the body through the skin (dermal), mouth (oral), lungs (breathing), and eyes (ocular) and due to accidental ingestion. (James 2003, Wessel et.al. 2003, Cherian et.al. 2005, DHSM 2005)

Poisoning occurs as a result of agricultural use, accidental exposure, suicidal and homicidal attempts.(Opavoye et.al. 1998, Sakrak et.al. 2007) Food including stored grains contaminated by a spray of these pesticides are also known to cause severe poisoning.(Sharma et.al.2009) There are several factors affecting the levels of exposure during agricultural application of pesticides. It is observed that maximum exposure occurs while mixing and handling of concentrated solutions. Wind is the single most important factor determining dermal exposure during spraying. Other factors are equipment used, the duration of exposure, the type of activity and individual protection. (Nauira et.al. 1994, Karki et.al. 2004)

1.4. Action of organophosphorus pesticides

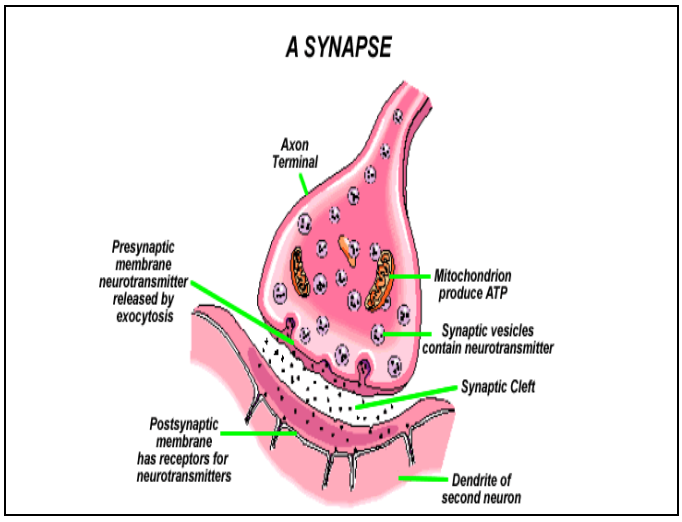
To understand how insecticides and rodenticides work (their mode of action), it is necessary to understand how the pests' targeted systems normally function. Insecticides used in structural pest control operations generally target the nervous system, growth and development, energy production, or water balance. Most rodenticides used in pest control interfere with blood clotting. A general description of these processes is presented in this leaflet, followed by a table listing the mode of action of pesticides (insecticides and rodenticides) used by structural pest control operators. (Sungur et.al. 2001)

Action on nervous system

The nervous system functions as a fast acting means of transmitting important information throughout the body. The nervous system has two components:

i) The peripheral nervous system to receive and transmit incoming signals (taste, smell, sight, sound, and touch) and to transmit outgoing signals to the muscles and other organs, effectively telling them how to respond.
ii) The central nervous system (CNS) that interprets the signals and coordinates the body's responses and movements.

A neuron is a single nerve cell. It connects with other neurons and with muscle fibers (the basic units of muscles) through gaps at the end of each neuron. The gap between neurons, or between a neuron and a muscle fiber, is 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 which then travels down the length of the neuron. When the electrical charge reaches the end of the neuron, it stimulates a chemical messenger called a neurotransmitter, to be released from the end of the neuron. This neurotransmitter crosses the synapse and binds to a receptor on the receiving end of the next neuron.



Binding to the receptor causes the signal to be converted back into an electrical charge in the second neuron, and the signal is transmitted along the length of that neuron. After transmitting its message across the synapse, the neurotransmitter is resorbed back into its originating neuron, and the nerve cell is then in a resting stage until the next signal is received. This process repeats over and over until the signal has reached the CNS (the brain and spinal cord in humans and a series of ganglia, or nerve bundles, in the insect) 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. Both humans and insects have many different neurotransmitters that work at different sites throughout the nervous system. Some neurotransmitters are excitatory (they result in the signal being sent on through the synapse to a connecting neuron), and some are inhibitory (they result in the reaction being blocked from traveling 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. Of the many neurotransmitters that both insects and humans have, acetylcholine (ACh) and gamma-aminobutyric 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 strictly 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. The most common mechanisms are explained below.(Patil et.al 2003, Mahdi et.al 2008)

Cholinesterase inhibitors

Organophosphate and carbamate insecticides are known as cholinesterase inhibitors. They bind to the enzyme that is normally responsible for breaking down ACh after it has carried its message across the synapse. When an insect has been poisoned by a cholinesterase inhibitor, the cholinesterase is not available to help break down the ACh, and the neurotransmitter continues to cause the neuron to "fire," or send its electrical charge. This causes overstimulation of the nervous system, and the insect dies. Like insects, humans also use ACh as a neurotransmitter and cholinesterase to break it down, and cholinesterase poisoning in humans can be very severe. Upon each exposure to an organophosphate or carbamate insecticide, more cholinesterase becomes bound and is unavailable to do its job. Although cholinesterase inhibition by carbamates is somewhat reversible, organophosphate poisoning is not reversible. 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. (Amy 2005)

Acetylcholine mimics

Imidacloprid, a nicotinoid insecticide, mimics the action of the neurotransmitter, acetylcholine (ACh). Although cholinesterase is not affected by this insecticide, the nerve is continually stimulated by imidacloprid itself, and the end result is similar to that caused by cholinesterase inhibitors – overstimulation of the nervous system leads to poisoning and death. Fortunately, imidacloprid is a closer mimic for the insect's ACh than for human ACh, giving this insecticide more specificity for insects and less ability to poison humans.

Chloride channel modulators

Avermectins are derived from a soil microorganism and belong to a group called the macrolactones. Fipronil is a member of the class of insecticides known as phenylpyrazoles. Avermectins and fipronil both bind to the GABA-gated chloride channel. This channel normally blocks reactions in some nerves, preventing excessive stimulation of the central nervous system (CNS). Avermectins activate the chloride channel, causing an inhibitory effect, which, when excessive, results in the insect's death. Fipronil has the opposite effect on the chloride channel, blocking it from performing its normal inhibitory action Thus, when fipronil binds to the channel, the nerve is overstimulated, and death eventually occurs.

Sodium channel modulators

Pyrethrins are naturally occurring compounds derived from members of the chrysanthemum family. While they have a quick knock-down effect against insects, they are unstable in the environment, so may not last long enough to kill the pest. Pyrethroids are synthetic versions of pyrethrins, specifically designed to be more stable in the environment (although still asting only days or weeks), and thus provide longer-lasting control. Pyrethrins and pyrethroids act on tiny channels through which sodium is pumped to cause excitation of neurons. They prevent the sodium channels from closing, resulting in continual nerve impulse transmission, tremors, and eventually, death. Pyrethrins and pyrethroids are wellknown irritants of humans' respiratory

systems as well as of the skin and eyes. Applicators that have an allergic reaction to these insecticides must either increase the amount of personal protective equipment worn during handling, or stop working with this class of insecticides.

Growth and Development

Unlike humans, insects must shed their skin in order to grow and to develop into their next life stage. Insects' skin is a hard exoskeleton, also called the cuticle, which provides both protection and structure. Molting is necessary not only for the insect to grow, but also for the insect to reach the adult stage so that it can reproduce. Some insecticides target the insect's growth and development processes.

Chitin synthesis inhibitors (CSIS)

One important component of the cuticle is chitin. Some insecticides, called chitin synthesis inhibitors, block the production of chitin. An insect poisoned with a CSI cannot make chitin and so cannot molt. Because molting must take place for the insect to reach the adult stage, a CSI poisoned insect also cannot reproduce. Eventually, the insect dies. Because humans do not make chitin, CSIs are not considered toxic to humans. However, CSIs are very toxic to any organism that has an exoskeleton, such as crustaceans (shellfish), and should be used with great care, if at all, in areas where they could contaminate the environment.

Insect growth regulators (IGRs)

Insects produce a special protein, juvenile hormone, which is circulated throughout the insect's body and "tells" the insect to stay in its current stage. When it is time to metamorphose into its next life stage the insect stops producing juvenile hormone. Some insecticides, called insect growth regulators (IGRs), mimic juvenile hormone. Insects poisoned with IGRs act as if they have not stopped making juvenile hormone. They cannot molt or reproduce, and eventually they die. Humans do not make or use juvenile hormone. IGRs are considered to have little human toxicity. (Opawoy et.al. 1998, James et.al. 2003, Sharma et.al. 2009)

1.5. Action on metabolism and energy production Interference with water balance

Insects have a thin covering of wax on their bodies that helps prevent water loss. Silica aerogels and diatomaceous earth are tiny, sharp particles that scratch through this protective layer and absorb the protective oils, leaving the insect's body vulnerable to water loss. Boric acid also disrupts water balance in insects, but its mode of action is not completely understood. It appears to disrupt digestion, causing the insect to starve to death. Boric acid is toxic to humans and can harm the stomach, intestines, blood, and brain, and can irritate the respiratory tract and skin.

Interference with energy production

All organisms must generate energy from the food they take in. Several classes of insecticides inhibit or disrupt energy production. Exactly how they work differs, but the end result is the same. Initially, the insect can mobilize enough stored energy to continue its basic functions. While it can eat and digest food in the initial stages after being poisoned, it cannot produce energy from the food. Eventually, the insect "runs out of steam," stops eating and even moving, and dies. Hydramethylnon, sulfuryl fluoride, chlorfenapyr, and sulfluramid are all in different classes of insecticides, and work through different mechanisms, but all disrupt energy production. Chlorfenapyr and sulfluramid must be converted to an active orm before they can cause this effect. Fortunately, humans do not seem to be as able to produce the activated form as insects, so are less affected by chlorfenapyr and sulfluramid.

Interference with micronutrient balance

Micronutrients are substances that the body needs in order to function properly, but excessive amounts can be toxic. Vitamins and elements such as phosphorus, potassium, selenium, calcium, and other inorganic compounds are examples of micronutrients. Cholecalciferol is the activated form of vitamin D, and this substance has a use as a rodenticide. Cholecalciferol mobilizes calcium and phosphorus from the bones into the blood stream. Too much calcium causes calcification (hardening) of soft tissues. Eventually, death occurs, usually from heart failure. (Nauira et.al. 1994)

1.6. Effect on circulatory system

Anticoagulants

Several rodenticides interfere with the production of vitamin K, which is necessary for blood clotting. The anticoagulants also increase the permeability of the capillaries, allowing blood to seep out of the vessels and into the organs and surrounding body cavity. When poisoned with an anticoagulant, the rodents bleed internally and, since the blood will not clot, the animal eventually bleeds to death. There are two classes of anticoagulants – coumarins and inandiones. Coumarins are usually effective in only a single dose, while inandiones must be eaten in several doses to cause death. The anticoagulants are considered to have low toxicity to humans. (Patil et.al. 2003).

1.7. Incidence of poisoning

Organophosphorus poisoning remains one of the major health issue in developed and especially in developing countries and its frequency is increasing over the years. A great proportion of acute poisoning cases are caused by exposure to these pesticides. Pesticides can enter the body through the skin (dermal), mouth (oral), lungs (breathing), and eyes (ocular) and due to accidental ingestion. Poisoning occurs as a result of agricultural use, accidental exposure, suicidal and homicidal attempts. Food including stored grains contaminated by a spray of these pesticides is also known to cause severe poisoning. There are several factors affecting the levels of exposure during agricultural application of pesticides. It is observed that maximum exposure occurs while mixing and handling of concentrated solutions. Wind is the single most important factor determining dermal exposure during spraying. Other factors are equipment used, the duration of exposure, the type of activity and individual protection. (Dandapani et.al. 2003)

1.8. Effects of organophosphorus poisoning on human body

Effects on skeletal muscles

Acute Organophosphorus poisoning leads to paralysis of skeletal muscles in between 48 to 72 hours after poisoning and is associated with cranial and proximal limb muscle weakness. Inability to lift the neck, inability to sit up, opthalmoparesis, slow eye movements, facial weakness, difficulty in swallowing, limb weakness (proximal is more than distal), areflexia, respiratory failure etc. are clinical features of paralysis. These features together are called as intermediate syndrome. The generation of free radicals is also responsible for muscle damage and intermediate syndrome. Organophosphorus poisoning induces muscle overactivity by hyperstimulation of acetylcholine receptors. This overactivity of muscles causes free radical production by lipid peroxidation. This is associated with injury to muscle cells causing their damage and hence paralysis. (Rahiman et.al. 2008). According to De Bleecker et.al. slow release of organophosphorus compounds from deep tissue and longtime inhibition of Acetyl Cholinesterase causes intermediate syndrome. Avasthi and Singh et.al. Showed that desensitization of Acetylcholine receptors are responsible for intermediate syndrome. According to Yang et.al. intermediate syndrome occurs due to disruption in energy metabolism and calcium homeostasis. Mathew et.al. depicted that the magnitude of muscle damage in intermediate syndrome occurs is proportional to severity of intermediate syndrome.(Hussain et.al. 2003).

Effects on respiratory system (Lungs)

Organophosphorus poisoning is associated with respiratory failure. In organophosphorus poisoning patients respiratory failure occurs due to many reasons, such as central respiratory depression,

respiratory muscle weakness, bronchospasm, bronchorrhea, aspiration of gastric contents, anorexic brain damage etc. This togetherly is associated with Acute Respiratory Distress Syndrome (ARDS). The increase in respiratory rate from 22 ± 6 breaths/min to 38 ± 8 breaths/min suggest about respiratory failure. There are two forms of respiratory failure. In one form called as early form, patients showing respiratory failure are unconscious. This case is observed suddenly after acute Organophosphorus poisoning and shows severe symptoms. In another form called as delayed form, patients showing respiratory failure are conscious. This case is observed from several hours to 5 days after Organophosphorus poisoning without any severe symptoms. Thus, fatalities from acute Organophosphorus poisoning generally occurs due to the respiratory failure. (Eyer et.al. 2006)

Effects on cardiac system (heart)

Organophosphorus compound produces direct toxic effect on the heart. These toxic effects may be serious and are often fatal. The cardiac toxicity associated with Organophosphorus poisoning is caused by more than one mechanism. Possible mechanisms include sympathetic and parasympathetic over activity, hypoxemia, acidosis, electrolyte de-rangement and a direct toxic effect of the compounds on myocardium. Hypertension and sinus tachycardia which are seen in Organophosphorus poisoning are nicotinic effects. On other hand, hypotension and sinus bradycardia are cholinergic manifestations. Most of cardiac complications occur during first few hours after exposure. (Teague et.al. 1999)

Effects on liver

Acute toxicity of Organophosphorus poisoning induces severe hepatic damage. This leads to increased levels of Aspartate transminase (AST), Alanine transminase (ALT) and γ-glutamyl transpeptidase (GGT) which represents marked hepatic tissue injury. The ratio of lactate/ pyruvate is increased in the liver which is referred to as an enhancement of anaerobic glycolysis. The increased level of the serum lactate is observed which leads to tissue hypoxia. According to TOS-Luty et.al. an organophosphorus compound Malathion induces damages in the intercellular structure of the liver. Slizova et.al. Further stated that Organophosphorus poisoning causes changes in the microvascularization of liver. Further, serum total protein level is decreased due to lowered synthesis of albumin in liver in Organophosphorus poisoning. Serum globulins (mostly α-globulin) rise due to prolonged exposures to Organophosphorus compounds. (Murat et.al. 2007)

Effects on pancreas

Acute pancreatitis is a rare complication found in organophosphorus poisoning. The frequency of acute pancreatitis related to organophosphorus poisoning is 12.7%. Acute pancreatitis occurs due to excessive release of acetylcholine from pancreatic nerves which hyperstimulate pancreatic acinar cells. Hyper-stimulation of these pancreatic acinar cells is thought to be mechanisms of acute pancreatitis after poisoning by organophosphorus insecticides. (Krupesh et.al. 2002).

Effects on kidney

The kidney, the major detoxification organ for many xenobiotics is frequently susceptible to nephrotoxic effects of organophosphorus compounds. Acute renal failure is observed following poisoning with Organophosphorus compounds and is indicated by increased blood urea nitrogen and serum creatinine level. Parenchymatous degeneration of cells of renal tubules and infiltration between the proximal tubules were observed in high doses of Fenthion – an Organophosphorus compound. Organophosphorus poisoning induced cholinergic crisis causes tubular cell necrosis by hypo-volemic shock and rhabdomyolysis.(Haded 1985).

Effects on nervous system

According to Shih et.al. Organophosphorus poisoning induced convulsions are associated with post exposure brain pathology. Other effects such as headache, tremors, restlessness, ataxia, confusions, slurred speech, seizures and coma are observed in organophosphorus poisoning due to effects on central nervous system. (Hadded 1985).

Effects on reproductive system

Acute Organophosphorus poisoning does not produce severe effects on reproductive system. But, chronic and longer time exposure of Organophosphorus compounds is associated with reproductive disorders such as infertility, birth defects, adverse pregnancy outcomes, prenatal mortality etc. Larsen et.al. Concluded that use of Organophosphorus pesticides for longer time affect the semen quality and reproductive hormones. The reproductive function is suspected due to inhibition of brain Acetyl Cholinesterase activity and also due to adverse effects of pesticides on gonads. (Recio et.al. 2005).

Effects on endocrine system

Organophosphorus compounds inhibit brain Acetyl Cholinesterase which in turn increases levels of acetylcholine, γ-amino butyric acid (GABA), epinephrine, nor-epinephrine, dopamine, and 5- hydroxytryptamines in serum. Altered levels of these neurotransmitters disturb hormonal level in the serum. Some pesticides are endocrine disruptors as they activate or block hormone receptors. Inhibition of brain Acetyl Cholinesterase activity is associated with reduction in serum levels of luteinizing hormone and progesterone. Further, excess stimulation by acetylcholine leads to increased secretion of hypothalamic Corticotrophin – releasing hormone which in turn stimulates Adrenocorticotropic hormone secretion. In general organophosphorus poisoning is associated with increased serum level of hormones such as luteinizing hormone, Follicle stimulating hormone, adreno corticotropic hormone etc. whereas, testosterone level is found to be decreased. Guven et.al. Showed that acute Organophosphorus poisoning is associated with higher serum levels of prolactin, cortisol and adrenocorticotropic hormone. According to Straube et.al. Serum estradiol and testosterone levels were found to be decreased while those of luteinizing hormone found to be increased in organophosphorus poisoning. Padungtod et.al. Also found increased serum luteinizing hormone level and follicle stimulating hormone level while decreased testosterone level can be detected by measuring p – nitro phenol level in urine. (Recio et.al. 2005).

1.9. Stages of organophosphorus poisoning

On the basis of severity of clinical symptoms, organophosphorus poisoned patients are divided into three stages as mildly poisoned, moderately poisoned and severely poisoned.

Mild poisoning stage

It is initial stage of organophosphorus poisoning and is acute cholinergic crisis. This stage is associated with number of poisoning symptoms such as muscle twitching, headache, dizziness, tremor, restlessness, anxiety, confusion, convulsions and coma. Patients can also develop pancreatitis, hypo or hyperglycemia and acute renal failure during this phase. This is also called as type I paralysis and it generally occurs in the first 48 hours of poisoning.

Moderate poisoning stage

It is the stage associated with intermediate syndrome. It is type II paralysis. It occurs between 48 to 72 hours after poisoning. Symptoms observed in this stage include weakness of neck flexors, muscles of respiration and proximal limb muscles. Intermediate syndrome is a state of muscle paralysis that occurs after recovery from cholinergic crisis but before the expected onset of the delayed polyneuropathy and probably results from post-synaptic neuromuscular junction dysfunction. According to De Bleecker et.al. The slow release of Organophosphorus compounds from deep tissue persistent inhibition of Acetyl Cholinesterase is responsible for development of intermediate syndrome. According to Mathew et.al. ntermediate syndrome is due to severe muscle damage in Organophosphorus poisoning patients and the magnitude of muscle damage that occurs during cholinergic crisis determines the severity of intermediate syndrome. Intermediate syndrome requires prolonged mechanical ventilation and chances of mortality increases in this stage.

Severe poisoning stage
It is the severe stage associated with delayed polyneuropathy. It is type III paralysis. It occurs 15 to 30 days after exposure to the organophosphorus poisoning. Delayed polyneuropathy occurs due to inhibition of Neuropathy Target Esterase (NTE) an enzyme present in nervous tissue. Clinical manifestations of this stage are distal weakness, parasthesia, ataxia, and diminished and absent reflexes. Mortality rate is very high in this stage. (Reiner 2001, Paudyal et.al. 2008).

1.10. Diagnosis of organophosphorus poisoning

Identification of poisoning is done on the basis of symptoms shown by patients while perfect diagnosis requires biochemical analysis. Symptoms such as hyper-salivation, convulsions, respiratory failure, ataxia, slurred speech, miosis, muscle cramping suggest about poisoning. To access organophosphorus poisoning, it is necessary to analyze biological samples mostly blood and urine. Organophosphorus compounds can be detected in urine however, their degradation is rapid and hence their detection in urine is possible for short time. The detection of metabolites of Organophosphorus compounds is another way to detect organophosphorus poisoning. Metabolites circulate for longer time and mostly excreted in urine. Detection of metabolites of organophosphorus compounds is always better than detection of parent compound in blood or urine. This is because parent compound has short life time and its detection is not possible for more than hours after poisoning. For some Organophosphorus compounds (e.g. Parathion, Paraoxon), detection of p–nitrophenol in urine is an indicator of Organophosphorus poisoning. Recently, antibodies against Organophosphorus compounds in blood are also detected. Thus, blood and urine remains main source for biological and biochemical examination in Organophosphorus poisoning. Most commonly, detection of Organophosphorus poisoning is done by estimating activities of enzymes namely Acetyl Cholinesterase, Butyryl Cholinesterase and Acylpeptide Hydrolase from blood. All these enzymes contains serine residue at their catalytic sites. Organophosphorus compound binds with this serine residue and inactivates the enzymes. Such inactivation of above enzymes is only concerned with Organophosphorus poisoning and thus inhibition of Acetyl Cholinesterase, Butyryl cholinesterase and Acylpeptide Hydrolase is highly correlated with severity and duration of poisoning with Organophosphorus compounds. (Robenshtok et.al 2002, Vidyasagar et.al. 2004, Quistad et.al. 2005).

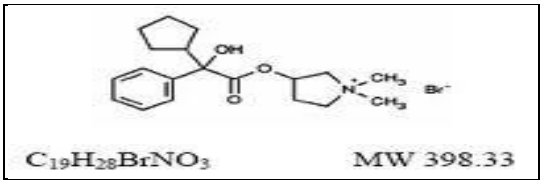
1.11. Treatment of organophosphorus poisoning

Two therapeutic principles are used to treat organophosphorus poisoning. The main drugs are anticholinergic that opposes the effects of accumulated acetylcholine at the cholinergic synapses and are called as symptomatic antidotes. On other hand, cholinesterase reactivators i.e. oximes are used to reactivate inhibited enzymes especially Acetyl Cholinesterase and Butyryl Cholinesterase and are called as casual antidotes. Their effects are synergistic. Atropine is considered as the drug of choice for organophosphorus poisoning since 1940s. It is the competitive inhibitor of the muscarinic acetylcholine receptor. It blocks the effect of excess acetylcholine and protects the receptor from further stimulation. It has minimal effects at nicotinic receptor site. Though Atropine is the drug of choice for organophosphorus poisoning treatment, it has some adverse effect. There are two types of adverse effects of atropine as,

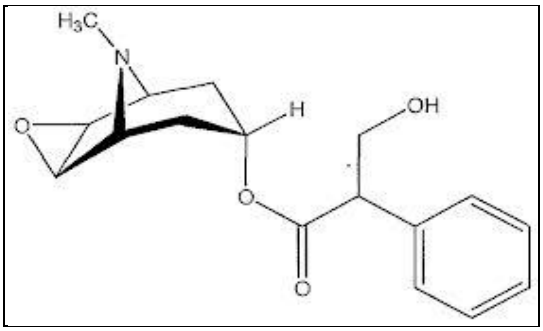
Toxic effects
Atropine when injected in large doses shows toxicity such as conjuctival injection, dry and red skin, tachycardia, tachypnea, elevated body temperature and CNS stimulation marked by restlessness, confusion, psychotic reactions, delirium and occasionally seizures. A rash may appear on the face or upper trunk. In severe intoxication, central stimulation may cause circulatory and respiratory failure and ultimately death.

Allergic effects
The allergic effects of atropine include dermatitis over the eyelids with erythema, itching and local edema. Reports of anaphylaxis due to atropine are extremely rare. Though allergic reactions are mild, it has increased risk for severe toxic effects in patients in future. Thus, in such patients other antimuscarinic drugs should be used. (Leibsan et.al. 2008)
The two main drugs that are used as a replacement for atropine are scopolamine and glycopyrrolate.

Glycopyrrolate
Glycopyrrolate is a synthetic quaternary amine with no central effects.



Because of marked difference in chemical structure of glycopyrrolate from atropine it does not produce that allergic reaction which is produced by atropine. Further, glycopyrrolate is twice potent as compared atropine. It is used to reduce salivary, tracheo-bronchial and pharyngeal secretions. It is also used to reduce acidity of gastric secretions and also prevent bradycardia.
Scopolamine:-Scopolamine (hyostine methonitrate) is an anti-muscarinic agent with central and peripheral action. It is specially used for the treatment of seizures caused by nerve gas agents because it has ability to cross bloodbrain barrier and possess the central anti-muscarinic activity.



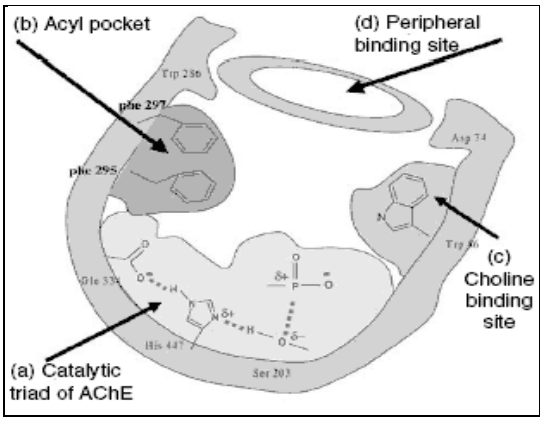
Scopolamine stops such seizures within first 5 to 10 minutes of epileptic activity. In general use of a combination therapy of atropine and glycopyrrolate provides adequate control of secretions and heart rate and avoids the central toxic effects that can occur when only large dose of atropine is used. In some organophosphorus poisoning and nerve agent intoxication, a combination therapy of atropine and scopolamine is always beneficial. Central nervous anti-depressants such as benzodiazepines are used to treat organophosphorus induced convulsions. These benzodiazepines are most effective against organophosphorus induced seizures with strong synergistic effects when combined with anticholinergic drugs. Cholinesterase reactivators are used to reactivate Acetyl Cholinesterase and Butyryl Cholinesterase. These reactivators include different types of oximes (mono and bisquaternary pyridinium oximes) such as pralidoxime, obidoxime, trimedoxime and HI – 6. Oximes reactivates cholinesterase by removing phosphate group from phosphorylated enzymes with formation of oxime – phosphonate Oximes reactivates cholinesterase by removing phosphate group from phosphorylated enzymes with formation of oxime – phosphonate.(Leibsan et.al. 2008)

2. Result and discussion

Organophosphorus poisoning is globally major clinical problem with thousands of deaths occurring every year. Most of the

organophosphorus pesticide poisoning and subsequent deaths occur in developing countries. From age and sexwise distribution of poisoned patients, it is concluded that maximum poisoning cases (92 %) belong to age group between 16-45 years. Poisoning occurs as a result of agricultural use, accidental exposure, suicidal and homicidal attempts. Sometimes, food including stored grains contaminated by a spray of these pesticides is also known to cause severe poisoning. It is found that the organophosphorus compound, dimethoate is more commonly used to attempt suicide as it is easily available and cheap. 54 % poisoning cases were observed only due to dimethoate. The poisoning due to warfarin, tick-20, chlorpyrifos, fenthion, thymate and lice powder is less common.

There are two main types of Cholinesterases occur in the body. They are Acetyl Cholinesterase and Butyryl Cholinesterase. These are serine esterases which hydrolyzes acetyl choline. Organophosphorus compound bind to hydroxyl group of serine residue present at active site of enzyme i.e. phosphorylation of enzyme take place. This reaction occurs via an intermediate Michaelis – type complex between the enzyme and organophosphorus compound. This phosphorylated enzyme is catalytically inactive. (Wessel et.al. 2003) For some organophosphorus compound this Michaelis type complex is less stable and it breaks down to restore original enzyme. But, for many Organophosphorus compound, the inhibited enzyme is dealkylated and a new complex is formed which is non-reactivable. This new complex is nonreactivable enzyme formed with alcohol as side product. This reaction is called as aging or de-alkylation. (Sakrak et.al. 2007) Thus, when serine residue of enzyme present at enzymes catalytic site is phosphorylated, it is not available to catalyze the substrate, thus, the enzyme gets inhibited.



Earlier findings support our results. It has shown that, there is weak interaction between Acetyl choline and Butyryl Cholinesterase. Thus, Acetyl Cholinesterase is predominant enzyme which hydrolyzes acetyl choline at synapses. The inhibition of Acetyl Cholinesterase activity leads to the accumulation of acetylcholine at synapses causing overstimulation of acetyl choline receptors in both central and peripheral nervous system. This will interfere with synaptic transmission at receptors. This is associated with symptoms seen in organophosphorus poisoning such as vomiting, meiosis, hyper-salivation, respiratory distress, abdominal pain, depressed level of consciousness and muscle fasciculation. From the study, it can be concluded that activity of Acetyl Cholinesterase inhibition and severity of poisoning symptoms in humans increases with increased pesticide dose and exposure time. Further, Acetyl Cholinesterase is equally sensitive to all Organophosphorus compounds. Thus, a progressive decline in Acetyl Cholinesterase activity is proportional to increase in severity of poisoning and it reflects proportionate amount of pesticide consumed and absorbed. (Quistad et.al. 2005) Organophosphorus poisoning is identified on the basis of definite clinical symptoms and the extent of poisoning can be judged by estimating activity of Acetyl Cholinesterase and Butyryl Cholinesterase.

3. Conclusion

The present study was carried out to know nature of pesticides, use of pesticides, benefits of pesticides and incidence of poisoning with pesticides. The pesticides are helpful in killing or repelling the pest and thus it prevent damage to the property like crops, furnitures, wooden material etc. However, as they are potentially toxic careful handling must be necessary. Poisoning occurs as a result of agricultural use, accidental exposure, suicidal and homicidal attempts. Sometimes, food including stored grains contaminated by a spray of these pesticides is also known to cause severe poisoning. It is found that the organophosphorus compound, dimethoate is more commonly used to attempt suicide as it is easily available and cheap. Half of poisoning cases were observed only due to dimethoate. The poisoning due to warfarin, tick-20, chlorpyrifos, fenthion, thymate and lice powder is less common. The activities of Acetyl Cholinesterase are inhibited by the Organophosphorus compounds. Organophosphorus compound binds to hydroxyl group of serine residue present at active site of enzyme. This reaction is called as phosphorylation of enzyme. This phosphorylated enzyme is catalytically inactive. A progressive decrease in Acetyl Cholinesterase activity is proportional to increase in severity of poisoning and it reflects proportionate amount of Organophosphorus compound consumed and absorbed. Thus, Acetyl Cholinesterase can be used as sensitive and specific biomarker of Organophosphorus poisoning.

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