



Organophosphates Toxicity: Pathophysiology, Diagnosis, and Treatment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Pesticides are composed of chemicals that can be employed to kill pests or minimize their negative effects. Pesticides and other organophosphate containing compounds have been beneficial in agriculture, forestry, industries, and in households (as personal insect repellents). Chemical compounds known as organophosphates (OP) are produced when phosphoric acid and alcohol undergo esterification. Although pesticides are beneficial, they pose dangers to both humans and the environment and include the following are types of pesticides: herbicide, insecticides (which may include regulators for insect growth, termiticides), nematicide, molluscicide, piscicide, avicide, rodenticide, bactericide, insect repellent, animal repellent, antimicrobial, and fungicide. Organophosphate insecticides primarily work by inhibiting carboxyl ester hydrolases, especially acetylcholinesterase (AChE). Acetylcholine (ACh) is a neurotransmitter that is broken down by the enzyme AChE into acetic acid and choline. Non-specific nature and improper application of pesticides has led to toxicities such as eye stinging, blisters, rashes, blindness, nausea, lightheadedness, diarrhea, and even death. Long-term consequences include malignancies, birth defects, reproductive harm, immunotoxicity, neurological, renal toxicity, hepatotoxicity, and endocrine system disruption. Organophosphate poisoning can be diagnosed in the laboratory through serum cholinesterase, urine alkylphosphate, and liver function test, while treatment can be done by administering antioxidants and emetics. This study is tailored towards highlighting organophosphates toxicity: pathophysiology, diagnosis, and treatment.

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1. INTRODUCTION

Pesticides and other organophosphate containing compounds have been beneficial in agriculture (fungicides and insecticides are used to prevent plant diseases and crop damage, respectively), in forestry, and industries (in paints or metalworking fluids for material preservatives), and in households (as personal insect repellents). Pesticides are composed of chemicals that can be employed to kill pests or minimize their negative effects. Although pesticides are beneficial, they pose dangers to both humans and the environment [1]. Due to the ability of some pesticides to persist in the environment, they can remain there for years. The general public may be exposed to pesticide residues by environmental pollution or occupational use, including through physical and biological breakdown products found in the air, water, and food [2]. Pesticides, according to the United States Environmental Protection Agency (2018), are compounds employed in pest management. According to Buchel [3], the following are types of pesticides: herbicide, insecticides (which may include regulators for insect growth, termiticides), nematocide, molluscicide, piscicide, avicide, rodenticide, bactericide, insect repellent, animal repellent, antimicrobial, and fungicide [3].

Chemical compounds known as organophosphates (OP) are produced when phosphoric acid and alcohol undergo esterification. They can hydrolyze when alcohol is released from the esteric link. These chemicals are the main ingredients of herbicides, insecticides and pesticides [4]. OPs can be classified as: insecticides, nerve gases, ophthalmic agents, antihelmintics, herbicides, industrial chemical (plasticizer). Organophosphates present in different environments such as the air, dust, water, sediment, soil and biota samples at higher frequency and concentration [5]. Their toxicity may come from exposure at home or at work, military or terrorist activity, or an iatrogenic accident [6,7]. According to certain research, farm laborers who are exposed to organophosphate insecticides on a regular basis may experience cognitive problems. Executive function, psychomotor speed, language, memory, attention, processing speed, visual-spatial functioning, and coordination issues have been among them [8].

Pesticides are the broad term for herbicides and insecticides. The majority of pesticides are used as herbicides, which make up around 80% of total pesticide use. They significantly improve food production efficiency and lower food-borne and vector-borne illnesses, which benefits public health. Most pesticides are meant to be used as crop protection products, or plant protection products [9], which generally, offer protection to plants from weeds, fungi, and insects. However, depending on the agent and the exposure, pesticides pose to be hazardous to humans and animals. Pesticides and other substances containing organophosphates can be consumed, breathed, injected, or absorbed cutaneously (via the skin). The onset and severity of symptoms are influenced by the individual molecule, dosage, exposure route, and rate of metabolic breakdown, despite the fact that most patients experience symptoms quickly [10].

Given that exposure to organophosphate pesticides (OPP) can elicit cholinergic symptoms as well as toxicity, they are particularly important [11]. Pesticides and organophosphate containing compounds toxicity may result to acute and chronic effects. They are highly toxic and exposures to high levels of these substances can cause death. According to Moen [12], persistent pesticide exposure can harm the reproductive system, the liver, the brain, and other organs in addition to causing chronic disorders like cancer. The report went on to cite that several pesticides, such as lindane, mankozeb, and pentachlorophenol, are classified as carcinogenic and may result in cancer. A number of the pesticides fall under the category of being hazardous to reproduction [13], either by inducing spontaneous abortions or undesirable impacts on the developing child. Both humans and the ecosystem are harmed by pesticides and organophosphates. The harm to human and environmental health from pesticides and organophosphates may be reduced and prevented with effective management [14].

2. PESTICIDES

Pesticides are substances (like carbamate) or biological agents (such bacteria, viruses, or fungus) that prevent, inhibit, or eliminate pests. Insects, plant pathogens, weeds, mollusks, birds, mammals, fish, nematodes (roundworms), and microorganisms can all be considered target pests if they cause property damage, cause

annoyance, transmit disease, or are disease vectors. In addition to these economic importance, pesticides can potentially be harmful to people and other animals. Pesticides are defined by the US Environmental Protection Agency (2018) as compounds used to manage pests. This is among its components: insecticides and herbicides (which may include insect growth regulators, termiticides, etc.) Nematicides, piscicides, molluscicides, avicides, rodenticides, bactericides, repellents for insects and animals, antimicrobials, and fungicides [1]. The most common of them all are the herbicides which account for approximately 80% of all pesticide use.

2.1 Classifications of Pesticides Based on their Target Pest Specie

The Table 1 represents the classification of pesticides on the basis of the corresponding pest target.

2.2 Pesticides Classification Based on Composition

All insecticides, herbicides, fungicides, rodenticides, wood preservatives, garden chemicals, and household disinfectants that may be used to kill some pests are together referred to as "pesticides." Based on their chemical makeup and the nature of their active ingredients, pesticides are categorized in the most popular and practical way possible. Such classification provides information about the effectiveness, physical characteristics, and chemical makeup of the various pesticides. In deciding on the manner of application, the precautions to be taken during application, and the application rates, knowledge of the chemical and physical properties of pesticides is highly helpful. Pesticides are divided into four main classes according to their chemical makeup: organochlorines, organophosphorus, carbamates, pyrethrin, and pyrethroids [3,7].

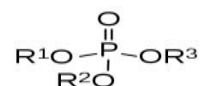
2.3 Organophosphate Containing Pesticides

Parathion, malathion, diaznon, and glyphosate are a few examples of the commonly used organophosphate pesticides. The chemical process of esterification between phosphoric acid and alcohol results in the formation of organophosphates (OP). Organophosphates can

hydrolyze when alcohol is released from the ester link. These substances are the primary ingredients in pesticides, insecticides, and herbicides. Additionally, OPs make up the majority of nerve gas. Organophosphate exposure, whether acute or ongoing, can cause different levels of toxicity in people, animals, plants, and insects [13,14]. Organophosphates also are widely used in plastics and solvents production. OPs are interesting from a clinical standpoint because of the toxicity that results from their exposure. Due to the cholinergic symptoms caused by exposure, nerve gas and organophosphate pesticides (OPP) are particularly significant from a clinical standpoint [4].

2.3.1 Structure of organophosphates

Organophosphates are a type of organophosphorus compounds with the typical formula $O=P(OR)_3$, a core phosphate molecule with alkyl or aromatic substituents [15]. They could be thought of as phosphoric acid esters. Organophosphates are found in a wide variety of forms, like most functional groups. Important examples include vital biomolecules like DNA, RNA, and ATP, as well as several insecticides, herbicides, nerve agents, and flame retardants [16].



2.3.2 Organophosphates mode of action

Organophosphate insecticides primarily work by inhibiting carboxyl ester hydrolases, especially acetylcholinesterase (AChE). Acetylcholine (ACh) is a neurotransmitter that is broken down by the enzyme AChE into acetic acid and choline. The central and peripheral neurological systems, neuromuscular junctions, and red blood cells all contain ACh (RBCs) [17]. By phosphorylating the serine hydroxyl group that is present at AChE's active site, organophosphates render AChE inactive. Aging is the result of phosphorylation, which is then followed by the loss of an organophosphate leaving group and the irreversible formation of the bond with AChE [7]. Following inactivation of AChE, ACh builds up in the nervous system, overstimulating muscarinic and nicotinic receptors. Clinical effects appear as a result of skeletal muscle nicotinic receptors, the autonomic and central nervous systems, and other mechanisms. AChE can go through one of the following processes once an organophosphate bind to it:

- Endogenous hydrolysis of the phosphorylated enzyme by esterases or paraxonases.
- Reactivation by a strong nucleophile such as pralidoxime (2-PAM).
- Permanent inactivation of enzyme (aging) and irreversible binding [18].

Organophosphates can be injected, swallowed, inhaled, or absorbed via the skin. The onset and severity of symptoms are influenced by the individual molecule, dosage, exposure route, and rate of metabolic breakdown, despite the fact that most patients experience symptoms quickly [19].

2.4 Health Benefits of Pesticides Containing Organophosphates

By reducing the spread of vector-borne diseases, pesticides have raised human health standards, yet their extensive and indiscriminate usage has had detrimental consequences on human health. Due to the non-specific nature and improper application of pesticides, humans, especially infants and children, are extremely susceptible to their harmful effects [20]. Approximately 3,000,000 cases of pesticide poisoning and 220,000 fatalities are reported in developing nations each year, according to the World Health Organization (WHO) [10,21]. Instances of immediate health consequences include eye stinging, blisters, rashes, blindness, nausea, lightheadedness, diarrhea, and even death. Examples of recognized long-term consequences include malignancies, birth defects, reproductive harm, immunotoxicity, neurological, renal toxicity, hepatotoxicity, and endocrine system disruption.

2.4.1 Neurologic effects

Pesticides have a variety of negative consequences on human health, but the effect they have on the nervous system is the most prevalent and usual one. Insecticides in particular tend to behave in this way, and some of these are detailed in more depth here. Numerous of these are referred to as nerve gases, and in addition to being utilized in agriculture, they are also used as chemical weapons in conflict. This reveals how detrimental these chemicals are to health [22].

Dichlorodiphenyltrichloroethane (DDT) is one of the kinds of pesticide that has an adverse effect on the neurological system. This substance has

been extensively employed, not only in agriculture but also in the fight against typhoid fever and malaria. This chemical is a severe neurotoxic, meaning it has a negative impact on the nervous system. DDT exposure at high levels can result in tremor, seizures, and even death. After exposure to lesser doses of the chemical for a longer period of time, this toxin may also have long-lasting, chronic effects. Affected workers may develop an ataxic gait and tremor. Animals and people can consume DDT in plants that have been sprayed with DDT. DDT exposure rises due to human ingestion of DDT-contaminated animals [23]. DDT can therefore have negative consequences for a long time because it builds up in the environment. When the spraying is carried out over sizable agricultural areas, it can be challenging to avoid this exposure for both humans and animals. DDT has been prohibited in many nations due to the fact that both humans and animals' bodies store it in their fat tissue for years before they are expelled [24].

2.4.2 Cancer

Studies on cancer examined the dangers of consuming particular goods that have organophosphate pesticide residues. Among these food items are: fish and water [11,21] seafood [13] and milk or other dairy products [25]. Generally, these studies found no relationship between cancer risks and other organophosphates, but do identify a tiny but statistically significant association between cancer risks and select specific pesticide residues, such as Malathion and Chopyrifos. Particularly, consumers are at greater danger from echothiophate [26]. Since the 1970s, the public has been concerned about the threat that pesticides pose to human health. When the costs and advantages of pesticide use were compared, research on monetizing the benefits and costs of pesticide use was done. The International Agency for Research on Cancer also classifies pesticides when there is sufficient proof of their ability to cause cancer in people (IARC) [27].

2.4.3 Reproductive disorders

2.4.3.1 Effects on male reproductive system

A major problem for the livestock sector is the dysfunction of the male reproductive system. Key factors in insecticide-induced male infertility include impaired spermatogenesis, anti-androgenic effects, changes in reproductive

enzyme pathways, lower sperm quality, and decreased sperm motility [28]. By directly influencing reproductive organs like the testes, sertoli cells, and leydig cells, as well as germ cells, insecticides have a harmful effect on the male reproductive system. They can also disrupt the hormonal balance in the secondary endocrine system [29]. Carbamates have been shown to have harmful effects on the male reproductive system in laboratory animals. Numerous investigations have found anomalies in the morphology and weight of the male accessory glands, the seminiferous tubules, the epididymis, spermatogenesis, the number and motility of sperm, the levels of blood hormones and total proteins, and the expression of estrogen receptors [29]. However, specific chemical pathways for how carbamate poisoning affects the male reproductive system are still unknown [30,24,10]. Organophosphates may have harmful effects on the HPG axis and may change the chromatin structure, DNA, acrosome, and motility of spermatozoa. Organophosphate exposure resulted in lower testosterone levels measured as a result of inhibiting testosterone synthesis, which may happen as a result of lower expression levels of steroidogenic enzymes [31,32]. Organophosphates cause atrophy and induce the death of germ cells in the testis and seminiferous tubules, negatively affecting their shape in a dose-dependent manner [18]. Furthermore, sialic acid levels and glycogen alkaline phosphatase activity are lowered and raised, respectively, by organophosphate exposure, whereas total protein, cholesterol, and acid phosphatase levels are elevated. Organophosphate insecticides cause DNA damage in the sperm chromatin, which changes the spermatogenesis process and renders male animals infertile [33].

2.4.3.2 Effects on female reproductive system

Numerous studies have demonstrated the harmful effects of insecticides on the female reproductive system, and it has been determined that these chemicals alter the female endocrine system and affect the reproductive organs and germ cells [34]. Insecticides impair the physiology of the ovary. It is a two-way street because alterations in hormone secretion brought on by altered organ functions mostly affect the female reproductive system and lead to dysfunctions via the HPG axis. An oxidative imbalance in the cells is linked to altered hormone synthesis, changed follicular maturation, disturbed ovarian cycle, prolonged

pregnancy, stillbirth, and infertility, which ultimately result in DNA damage, inflammation, and induction of apoptosis [35].

It has been hypothesized that organophosphate pesticides play a significant impact in the reproductive abnormalities of slaughtered buffaloes. This may be related to characteristics of the follicular membrane that allow xenobiotics to enter the system. Stronger insecticides, such as Paraquat, Malanthion, endosulphan, and chlopyrifos, were found in the ovary than in the serum. This might allow for changes to the follicular wall and increased pesticide entry into the cellular system. In addition, pesticides may harm developing germ cells, resulting in adult-stage infertility [36].

2.4.4 Effects on the liver

The liver, the body's primary metabolic organ, is thought to be a strong barrier against xenobiotics in the environment and metabolic poisons [37]. Through the use of serum ALT and AST, two biochemical indicators, its integrity was evaluated in the current study. The findings showed that ALT significantly increased among agricultural pesticide users whereas AST did not change. Since ALT is a cytosolic enzyme that is primarily expressed by hepatocytes, its elevated activity in serum samples from farmers suggests that the agrochemicals are having a cytotoxic effect on the liver by lysing the liver cells and leaking the enzyme into the blood [12]. Since AST is also present in other organs like the heart and skeletal muscle, while ALT is primarily produced in the hepatocyte and has low concentrations in the kidney and skeletal muscle, it is more indicative of liver alteration when there is an increase in ALT without a significant change in AST [38]. Farmers' usage of the organophosphate active principles metalaxyl and copper oxide was also linked to increased ALT activity, which supports earlier studies showing that these compounds are hazardous to rodents' livers [39,40]. Despite not being linked to increased ALT in the current study, other pesticide active ingredients used by farmers, such as malathion and cypermethrin, have been proven to cause hepatotoxicity in test animals [41,3].

2.4.5 Effects on the kidney

Kidney impairment may be brought on by severe organophosphate poisoning. Despite the fact that the effects do not appear to be correlated with

the degree of acetylcholinesterase inhibition, this type of harm is more common in cases of severe poisoning. Acute tubular necrosis, proteinuria, and oliguric and non-oliguric acute renal failure have all been reported. The paucity of experimental evidence makes the pathogenesis unknown. Multiple mechanisms have been proposed to explain the increase in low-osmolarity urinary flow in laboratory animals, which suggests a direct impact on tubular function. These mechanisms include direct injury to the distal convoluted tubule, an increase in oxidative stress, rhabdomyolysis, and hypovolaemia from dehydration [42].

A diagnosis can be made by measuring serum acetylcholinesterase activity, however the agent and prognosis cannot be identified. Since substitute renal treatments have been ineffective and don't seem to improve survival, kidney failure may be lethal. This may be a result of the drugs' unique toxokinetics, which include a high distribution volume, low blood level, tissue accumulation, and gradual release. However, hemofiltration has been reported to be a successful treatment [42]. Additionally, a rise in the levels of the waste products urea and creatinine suggested kidney disease. These abnormalities were noted in various cases of OPs poisoning in rats, including those caused by dimethoate, fenthion, and chlorfenvinfos [43,44].

2.5 Laboratory Investigation of Organophosphate Toxicity

2.5.1 Serum cholinesterase test

The cholinesterase level in red blood cells (RBCs) is a sensitive indication, but it is difficult to estimate and frequently unavailable. After OP poisoning, the amount of serum cholinesterase, which is frequently estimated locally, is decreased. The predictive value of serum cholinesterase levels in acute organophosphate poisoning is zero. Therefore, a grading system based on this parameter to identify high-risk individuals is probably unreliable [45].

2.5.2 Urine alkylphosphate

The kinetics of chlorpyrifos, propetamphos, diazinon, and malathion have been studied in human volunteer studies and non-occupational

exposure studies. 95% of urine alkyl phosphates in those who are not occupationally exposed do not surpass 72 $\mu\text{mol/mol}$ creatinine. The 95th percentile of total urine alkyl phosphates in individuals exposed to their jobs is 122 $\mu\text{mol/mol}$ creatinine. The mean peak levels were 160, 750, and 404 $\mu\text{mol/mol}$ creatinine, respectively, in volunteer experiments with 1 mg oral doses of chlorpyrifos, diazinon, and propetamphos. None of these values were connected to any decrease in blood cholinesterase activity [46]. OP metabolite concentrations in the urine of employees who may have been exposed to OPs are typically low and unlikely to significantly reduce blood cholinesterase activity [47].

2.5.3 Liver function test

The various enzymes are linked to each other and when exposed to organophosphates, ALT rises significantly above AST [1].

2.6 Preventive Measures of Pesticides and Organophosphates

The following are some of the key general preventive measures that should be followed in other to minimize the exposure of organophosphates. All highly toxic organophosphates should be banned or regulated. Also, using personal protective equipment properly, cleaning hands and exposed skin both before and after work, changing into different clothes between shifts, and providing workers with first aid instruction and practices are all recommended [47]. Workers should be encouraged to have their baths at the end of each day's work before handling food or drinks. They should also be trained on identifying OP containing products. All OP containing products and substances should be properly stored and kept out of reach from unauthorized persons. Additionally, they should be labelled also for easy recognition. Stay indoors with the windows closed if spraying occurs nearby. All fruits and vegetables should be properly washed before consumption. There should also be a reduction or elimination of home use of organophosphate pesticides, especially if pregnant women or young children are in the home. Highly toxic pesticides should not be stored, especially agricultural pesticides at homes. Don't Re-entry of areas of application should be avoided until after the interval specified on label or instructed [48,49,50].

2.7 Treatment of Organophosphate Pesticide Toxicity

2.7.1 Antioxidants

Atropine antidotal therapy aims to counteract the effects of high acetylcholine concentrations at muscarinic receptor-containing end organs. The cholinesterase enzyme is not activated by atropine, and organophosphate disposal is not accelerated. If tissue organophosphate concentrations are still high after atropine wears off, re-intoxication may occur, necessitating additional doses [51,52]. Atropine is useful against muscarinic symptoms but ineffective against nicotinic ones, such as respiratory

depression and muscular twitching and weakening. Despite these drawbacks, atropine frequently saves lives in cases of organophosphate poisoning. A positive reaction to a test dose of atropine can assist distinguish between other diseases and anticholinesterase agent overdose [53,54].

Test Dosage of Atropine: Adults: 1 mg and children under 12 years: 0.01 mg/kg [55].

2.7.2 Emetics

Emetics can be used by inducing vomiting to enable the gastric system clear out the poison e.g., copper sulphate, Ipecac syrup [56].



Fig. 1. Different pesticides [2]

Table 1. Pesticides classification based on corresponding pest target

Pesticides	Pest target
Insecticides	These act especially on insects
Herbicides	Controls or kills weeds
Rodenticides	Kills or prevents rodents i.e. rats or mice
Bactericides	Acts against bacteria
Fungicides	Acts against fungi
Nematicides	They tend to kill nematodes that act as parasites of plants
Larvicides	Inhibits growth of larvae
Avicides	These are used to kill birds
Molluscicides	They inhibit or kill mollusc's i.e snail's usually disturbing growth of plants or crops

Source: Robb & Baker, Lushchak et al. and Lah [4,6,10]

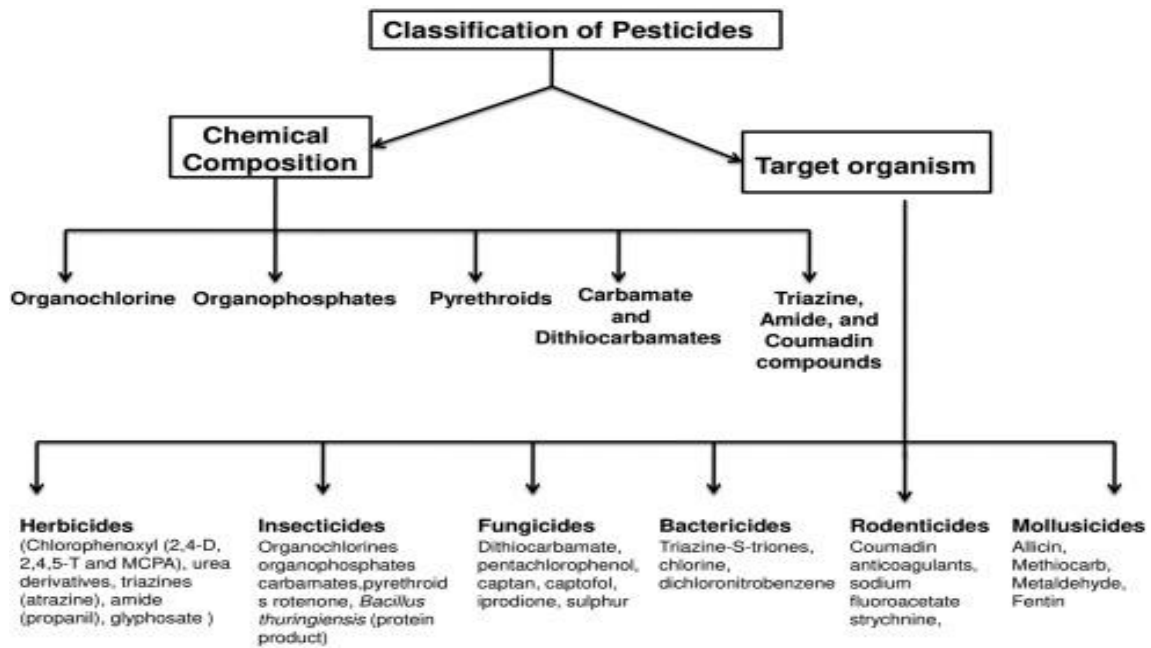


Fig. 2. Classification of pesticides [9]

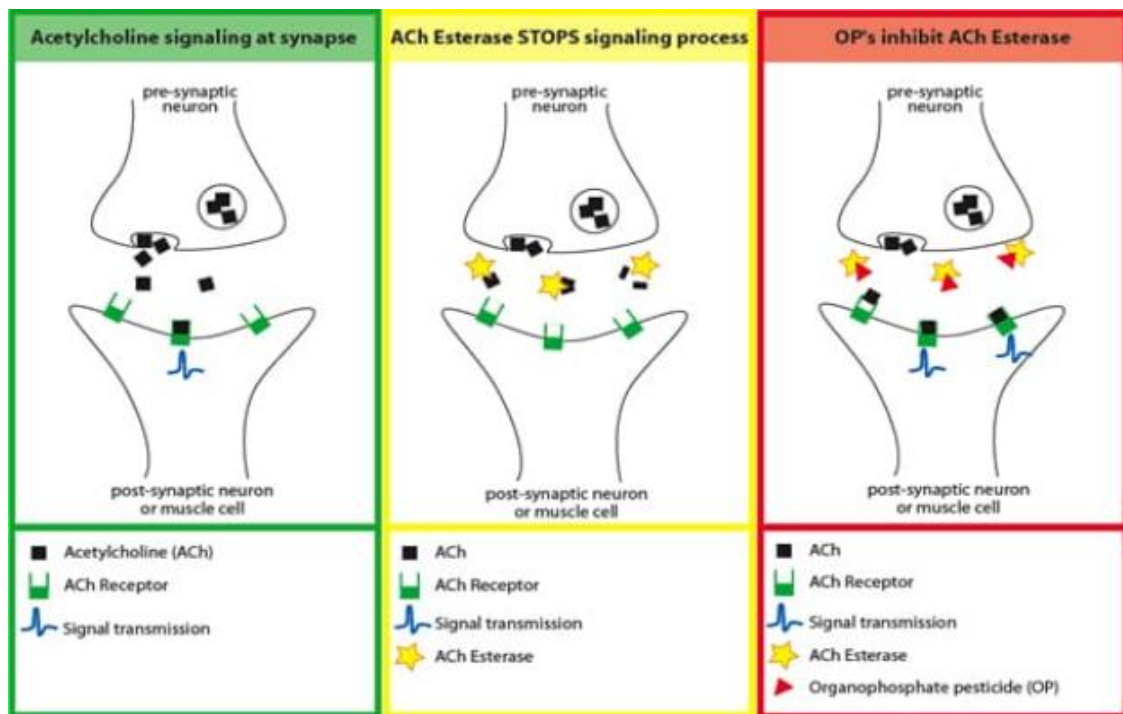


Fig. 3. Mechanism of action of organophosphate (Department of Environmental & Occupational Health Sciences, 2007)

3. CONCLUSION

We have come to realize that organophosphates are chemical compounds used in the production of some pesticides, the widespread use of these organophosphate compound has been effective

in its pesticidal role, however the detrimental health and environmental effects are becoming critical public health concern especially to those not adhering to the preventive protocols required in organophosphate pesticides usage. Hence it has been recommended from the literature read

that people should be sensitized on the preventive methods such as the use of safety gears.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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