Review Article

Organophosphates: Pathophysiology, Diagnosis, and Treatment

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ABSTRACT

Pesticides are chemical substances that are utilized in killing, repelling, mitigating and controlling the excessive growth of organisms that are harmful to the environment, plants and animals of agricultural and domestic use. They can be classified based on their mode of action, mode of entry, chemical composition and target organisms. Based on their target options they are classified as insecticide, rodenticide, herbicide, and molluscicide and, based on their chemical composition they are classified as organochlorine, carbamates, pyrethroids, organophosphates. Organophosphate compound is one of the major ingredient in pesticide production which is very toxic, it is a phosphorylated hydrocarbon formed from the esterification of phosphoric acid and alcohol, this compound has some detrimental effects because of its inhibition of acetylcholinesterase enzyme activity, some of these health effects are neurologic e.g. Parkinson; reproductive e.g. infertility; carcinogenic e.g. lung cancer in children; defect in brain development; etc. Organophosphate toxicity can be investigated in the laboratory through evaluating serum cholinesterase level, urinary alkylphosphates and Liver function test (LFT). Basically this toxicity can be prevented by reading instructions from manuals before application and use of safety gears to avoid contact poisoning. In the long run organophosphate pesticides toxicity can be treated with the use of emetics and antioxidants. Generally Organophosphate pesticides have been effective in their pesticidal role but have become a critical public health concern. Hence it has been recommended by different literatures that sensitization should be made in the preventive measures like the use of safety gears and routine health checkup by users.

Keywords: *Pesticides, organophosphate, toxicity*

INTRODUCTION

Pesticides and other organophosphate containing compounds have been beneficial in agriculture (insecticides are used to prevent crop damage; fungicides are used to prevent plant disease), in forestry, industry (for material preservatives in paints or metal working fluids), and in society (used for personal insect repellents). Pesticides consist of chemical substances that can be used to control pest or to lessen the detrimental effects of pest. Despite their benefits, pesticides can be hazardous to both humans and the environment[1]. Because some pesticides can persist in the environment, they can remain there for years. Environmental contamination or occupational use can expose the general population to pesticides residues, including physical and biological degradation products present in the air, water, and food[2]. US Environmental Protection Agency (2018) defines pesticides as substances that are used to control pests. It includes the following: herbicide, insecticides (which may include insect growth regulators, termiticides.) nematicide,

molluscicide, piscicide, avicide, rodenticide, bactericide, insect repellent, animal repellent, antimicrobial, and fungicide[3].

Organophosphates (OP) are chemical substances which are produced through the process of esterification between phosphoric acid and alcohol. Organophosphates can undergo hydrolysis with the liberation of alcohol from the esteric bond. These chemicals are the main components of herbicides, insecticides and pesticides[4]. Organophosphates can be classified as: Insecticides, nerve gases, ophthalmic agents, antihelmintics, herbicides, industrial chemical (plasticizer). Organophosphates has been found in different environmental compartments like air, dust, water, sediment, soil and biota samples at higher frequency and concentration[5]. Their toxicity can result from household or occupational exposure, military or terrorist action, or iatrogenic mishap. [6,7]. In farm workers, chronic occupational exposure to organophosphate insecticides has been linked to neuropsychological effects in some studies. These have included difficulties in executive functions, psychomotor speed, verbal, memory, attention, processing speed, visual-spatial functioning, and coordination[8].

Herbicides and insecticides are generally referred to as pesticides. The most common of them all are the herbicides which account for approximately 80% of all pesticide use. Their significant benefit in public health is to increase food production productivity and reduce food-borne and vector-borne diseases. Most pesticides are intended to serve as plant protection products (also known as crop protection products),[9] which in general, protect 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 organophosphates containing compounds can be absorbed cutaneously (through the skin), ingested, inhaled, or injected. Although most patients rapidly become symptomatic, the onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation[10].

Organophosphate pesticides (OPP) are of particular importance because of the cholinergic symptoms and toxicity produced from exposure [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 2017, long-term exposure to pesticides may cause chronic diseases such as cancer, and damage to the reproductive system, the liver, the brain, and other parts of the body. The study further stated that, some pesticides like lindane, mankozeb and pentachlorophenol are categorized as carcinogenic and may cause cancer. Several of the pesticides are categorized as harmful to reproduction,[12] either by causing adverse side effects of the unborn baby or by causing spontaneous abortions. Pesticides and organophosphates are harmful to man and the environment. Effective management of pesticides/organophosphates may help reduce and prevent health risk on humans and the environment.[13]

2.0 Pesticides.

Pesticides are chemicals (such as carbamate) or biological agents (such as viruses, bacteria, or fungi) that deter, incapacitate, kill, or otherwise discourage pests. Target pests can include insects, plant pathogens, weeds, molluscs, birds, mammals, fish, nematodes (roundworms), and microbes that destroy property, cause nuisance, or spread disease, or are disease vectors. Along with these benefits, pesticides also have drawbacks, such as potential toxicity to humans and other species. US Environmental Protection Agency (2018) defines pesticides as substances that are used to control pests. It includes the following: herbicide, insecticides (which may include insect growth regulators, termiticides, etc.) nematicide, molluscicide, piscicide, avicide, rodenticide, bactericide, insect repellent, animal repellent, antimicrobial, and fungicide [1]. The most common of them all are the herbicides which account for approximately 80% of all pesticide use.

Fig 1: Different pesticides

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2.2 Classifications of Pesticides Based on Their Target Pest Specie

In this type of classification, pesticides are named after the name of the corresponding pest in target, they include:

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.

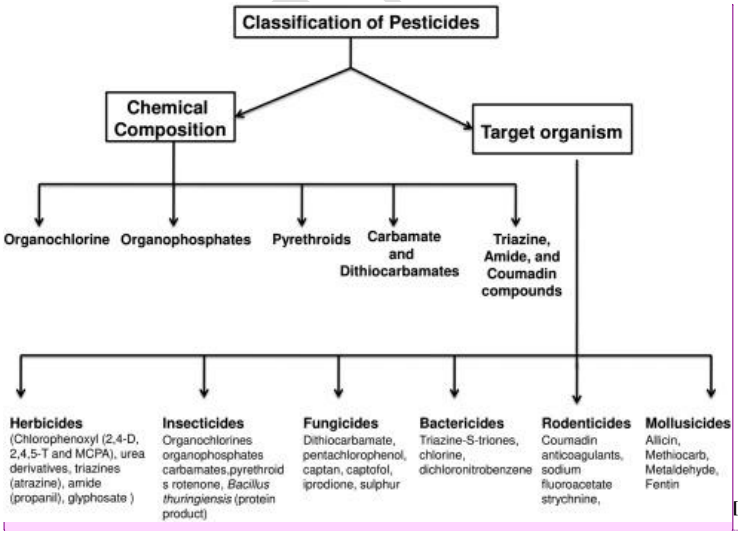
Avicides –These are used to kill birds.

Molluscicides–They inhibit or kill mollusc's i.e snail's usually disturbing growth of plants or crops.[4,6.10]

2.3 Classifications of Pesticides Based on Their Composition

The word "pesticide" is an umbrella term for all insecticides, herbicides, fungicides, rodenticides, wood preservatives, garden chemicals and household disinfectants that may be used to kill some pests. The most common and useful method of classifying pesticides are based on their chemical composition and nature of active ingredients. It is such kind of classification that gives the clue about the efficacy, physical and chemical properties of the respective pesticides. The information on chemical and physical characteristics of pesticides is very useful in determining the mode of application, precautions that need to be taken during application and the application rates. Based on chemical composition, pesticides are classified into four main groups namely; organochlorines, organophosphorus, carbamates and pyrethrin and pyrethroids. [3,7].

Fig 2: Classification of pesticides



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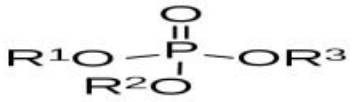
2.4 PESTICIDES CONTAINING ORGANOPHOSPHATE

Some of the widely used organophosphate insecticides include parathion, malathion, diaznon and glyphosate. Organophosphates (OP) are chemical substances produced by the process of esterification between phosphoric acid and alcohol. Organophosphates can undergo hydrolysis with the liberation of alcohol from the ester bond. These chemicals are the main components of herbicides, pesticides, and insecticides. OPs are also the main components of nerve gas. Acute or chronic exposure to organophosphates can produce varying toxicity levels in humans, animals, plants, and insects[12,13]. Organophosphates also are widely used in the production of plastics and solvents. From the clinical perspective, OPs are of interest because of the toxicity produced from exposure. Nerve gas and organophosphate pesticides (OPP) are particularly important from a clinical standpoint because of the cholinergic symptoms produced from exposure. [4]

2.4.1 Structure of Organophosphates

Organophosphates are a class of organophosphorus compounds with the general structure O=P(OR)3, a central phosphate molecule with alkyl or aromatic substituents[14]. They can be considered as esters of phosphoric acid. Like most functional groups organophosphates occur in a diverse range of forms, with important examples including key biomolecules such as DNA, RNA and ATP, as well as many insecticides, herbicides, nerve agents and flame retardants.[15]



2.4.2 Mechanism of Action of Organophosphates

The primary mechanism of action of organophosphate pesticides is inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase (AChE). AChE is an enzyme that degrades the neurotransmitter acetylcholine (ACh) into choline and acetic acid. ACh is found in the central and peripheral nervous system, neuromuscular junctions, and red blood cells (RBCs)[16]. Organophosphates inactivate AChE by phosphorylating the serine hydroxyl group located at the active site of AChE. Over a period of time, phosphorylation is followed by loss of an organophosphate leaving group and the bond with AChE becomes irreversible, a process known as aging.[7] Once AChE has been inactivated, ACh accumulates throughout the nervous system, resulting in overstimulation of muscarinic and nicotinic receptors. Clinical effects are manifested via activation of the autonomic and central nervous systems and at nicotinic receptors on skeletal muscle. Once an organophosphate bind to AChE, the enzyme can undergo one of the following:

- Endogenous hydrolysis of the phosphorylated enzyme by esterases or paraoxonases
- Reactivation by a strong nucleophile such as pralidoxime (2-PAM)
- Irreversible binding and permanent enzyme inactivation (aging)[17]

Organophosphates can be absorbed cutaneous, ingested, inhaled, or injected. Although most patients rapidly become symptomatic, the onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation. [18]

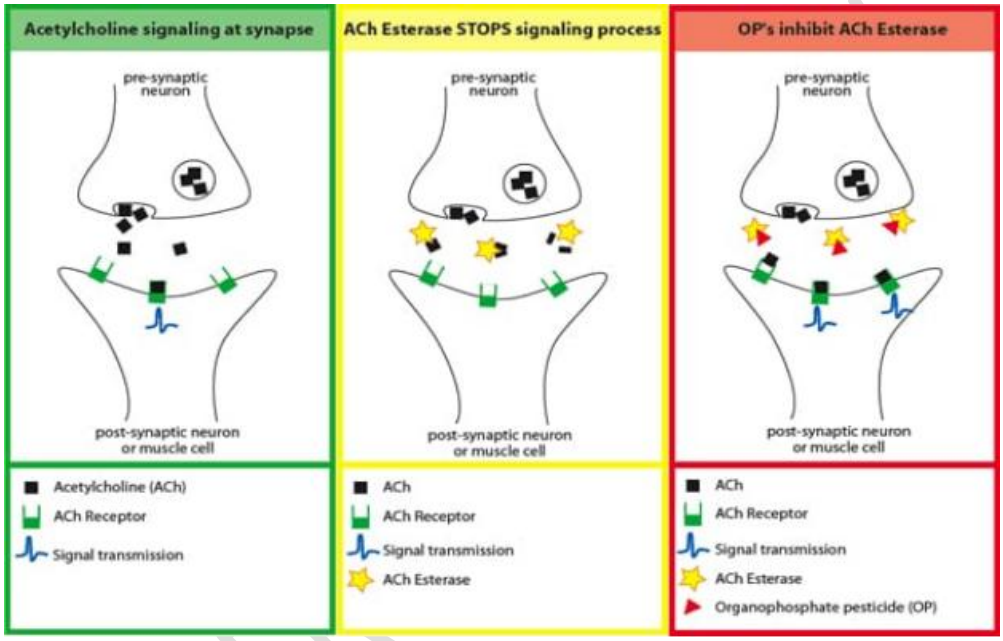


Figure 3: Mechanism of action of organophosphate (Department of Environmental & Occupational Health Sciences, 2007)

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2.5 Health Effects of Pesticides containing organophosphates

Pesticides have improved the standard of human health by controlling vector-borne diseases, however, their long term and indiscriminate use has resulted in serious health effects. Human beings especially infants and children are highly vulnerable to deleterious effects of pesticides due to the non-specific nature and inadequate application of pesticides[19]. According to World Health Organization, each year, about 3,000,000 cases of pesticide poisoning and 220,000 deaths are reported in developing countries[10,20]. Examples of acute health effects include stinging eyes, rashes, blisters, blindness, nausea, dizziness, diarrhea and death. Examples of known chronic

effects are cancers, birth defects, reproductive harm, immunotoxicity, neurological, renal toxicity, hepatotoxicity and disruption of the endocrine system.

2.5.1 Neurologic effects

Pesticides has different effects on human health, but the most common and typical adverse health effect of pesticides is their effect in the human nervous system. This is in particular typical for insecticides, and here some of these are described in more detail. Many of these are called nerve gases, and they are actually used as chemical weapons in wars, in addition to the use in agriculture. This indicates the seriousness of the health effects from these substances.[21]

One type of pesticide that affects the nervous system is dichlorodiphenyltrichloroethane (DDT). This compound has been used a lot, not only in agriculture, but also in the struggle against malaria and typhoid fever. This substance is a very toxic neurotoxin; meaning it affects the nervous system seriously. After high exposures DDT can cause tremor, seizures and even death. This toxin may also cause long term, chronic effects after exposure to lower levels of the substance for a longer period, and may cause ataxic gait and tremor in the affected workers. When DDT is sprayed on plants, animals and humans can eat DDT in the plants afterwards. Humans can eat animals with DDT as well, and this consumption increases the DDT exposure[22]. Due to this, DDT can cause adverse effects for many years, as it accumulates in the environment. It can be difficult to avoid this exposure, both for humans and animals, when the spraying is performed over large field areas. DDT has been banned in many countries, as it is stored in the fat tissue of the body of both humans and animals for a long time (years) before it is excreted.[23]

2.5.2 Cancer

The studies on cancer analyze the risks associated with the consumption of specific products which have some organophosphate pesticide residues. These consumption products include: fish, water [11,20] seafood [12] and milk or other dairy products[24]. In general, these studies find a small but statistically significant association between cancer risks and some specific pesticide residues, such as Malathion and Chopyrifos , but not for other organophosphates. Specifically, Echothiophate present a higher risk for consumers[25]. The risk of pesticides to human health has been of public concern since the 1970s. The benefits of pesticide use then started being weighed against their costs, which led to research being conducted monetizing the benefits and the costs. When there is sufficient evidence of carcinogenicity in humans pesticides are additionally classified by the International Agency for Research on Cancer (IARC)[26]

2.5.3 Reproductive disorders

Effects on male reproductive system

Dysfunction of male reproductive system represents a fundamental issue for livestock industry. Impairment of spermatogenesis, anti-androgenic effects, alterations in reproductive enzyme pathways, decreased sperm quality and motility are key elements in insecticide-induced male infertility[27]. Insecticides exert their toxic outcomes on male reproductive system by directly affecting reproductive organs (testes, sertoli cells, leydig cells) and germ cells or impairing hormonal balance in secondary endocrine system[28]. It has been demonstrated in laboratory animals that carbamates have toxic effects on male reproductive system. Alterations of testicular weight and male accessory gland morphology, degeneration of seminiferous tubules and epididymis, spermatogenesis arrest, abnormalities of sperm motility and number, impairment of serum hormone and total proteins levels and estrogen receptor expressions were observed in several studies.[28] However, detailed underlying molecular mechanisms of carbamate toxicity on male reproductive organs are still unclear[29,23,10]. Organophosphates could alter the spermatozoon chromatin structure, DNA, acrosome, motility and have toxic effects on HPG axis. Reduced levels of testosterone were measured with organophosphate exposure due to inhibition of testosterone synthesis, which possibly occurs through reduction of steroidogenic enzymes' expression levels[31]. Organophosphates have dose-dependent detrimental effects on the morphology of testis and seminiferous tubules by causing atrophy and inducing germ cell death [17]. Additionally, organophosphate exposure is associated with decreased levels of sialic acid, glycogen alkaline phosphatase activity and increased levels of total protein, cholesterol and acid phosphatase. Organophosphate insecticides induce DNA damage in sperm chromatin and that alters spermatogenesis pathway and causes infertility in male animals[32].

Effects on female reproductive system

Toxic effects of insecticides on female reproductive system were shown in different studies; and, it is concluded that insecticides disrupt female endocrine system and cause alterations in reproductive organs and germ cells [33] Insecticides disrupt ovarian physiology. This is a two-way street as altering organ functions causes hormone secretion changes and this endocrine changes mostly affect the female reproductive system and result with dysfunctions via HPG axis. Disrupted hormone synthesis, altered follicular maturation, disrupted ovarian cycle, pregnancy time prolong, stillbirth and infertility are linked to oxidative imbalance in the cells, and eventually lead to DNA damage, inflammation and apoptosis induction[34]

It has been speculated that organophosphate pesticides have important role in slaughtering buffaloes reproductive defects. This could be associated with follicle membrane permeability features that permit xenobiotics entrance to the system. Higher concentrations of insecticides including Paraquat, Malanthion, endosulphan and chlopyrifos were detected in ovary than serum. This could make a way for follicular wall alterations and more insecticide entrance to the cellular system. In addition, insecticides could affect germ cells at primordial phases resulting in infertility in adult stage [35].

2.5.4 Effects on the liver

The liver is the main metabolic organ in the body and is considered a viable defense system against environmental xenobiotics and metabolic toxins[36]. In the current study, its integrity was assessed through two biochemical markers, serum ALT, and AST. Results revealed a significant increase in ALT in agro pesticide users, while AST remained unchanged. ALT is a cytosolic enzyme mainly expressed by the hepatocytes, and high activity in serum samples from the farmers implies lysis of the liver cells and leakage of the enzyme into the blood, and therefore a cytotoxic effect of the agrochemicals on the liver. [37]The increase in ALT without a significant change in AST is more indicative of liver alteration, as AST is also found in other organs such as the heart and skeletal muscle, while ALT has low concentrations in the skeletal muscle and kidney, and is chiefly produced in the hepatocyte[38] The use of the organophosphate active principles metalaxyl and copper oxide was also associated with elevated ALT activity in the farmers, and corroborate previous reports on hepatotoxicity of these chemicals in rodents [39,40]. Other pesticide active principles used by the farmers such as malathion and cypermethrin, though not associated with elevated ALT in the current study, were shown to induce hepatotoxicity in experimental animals [41,3].

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2.5.5 Effects on the kidney

Acute organophosphate poisoning may cause kidney Impairment, This type of injury is more frequent in severe poisoning, although the effects do not seem to be related to the degree of acetylcholinesterase inhibition. There have been reports of oliguric and non-oliguric acute renal failure, proteinuria and acute tubular necrosis. The pathogenesis is unknown because of the lack of experimental data. In laboratory animals, an increase in low-osmolarity urinary flow has been reported, suggesting a direct influence on tubular function, so several mechanisms have been advanced: direct damage to the distal convoluted tubule, an increase in oxidative stress, rhabdomyolysis and hypovolaemia due to dehydration [42].

Determination of serum acetylcholinesterase activity is useful for diagnostic purposes but not for the determination of the involved agent and prognosis. Kidney failure may be fatal, since substitutive renal treatments have proved unsatisfactory and do not appear to improve survival. This could be due to the particular toxikinetics of the agents: a high distribution volume, with a low blood level, tissue accumulation and slow release; however, there is a report of successful treatment with hemofiltration[42]. In addition, an increase in creatinine and urea levels indicated a kidney dysfunction. These disruptions were observed with several cases of OPs poisoning in rats such as chlorfenvinfos, fenthion and dimethoate [43,44].

2.6 Laboratory Investigation of Organophosphate Toxicity

Serum Cholinesterase test: Red blood cells (RBC) cholinesterase level is a sensitive indicator, but its estimation is difficult and is usually not available. Serum cholinesterase level, which can be routinely estimated locally, is depressed after OP poisoning. Serum cholinesterase levels have no prognostic value in acute organophosphate poisoning. Thus, a grading system to identify high-risk patients based on this measurement is most likely unreliable[45].

Urine Alkylphosphate: Studies have been conducted studies of non-occupational exposure and human volunteer studies looking at the kinetics of chlorpyrifos, propetamphos, diazinon and malathion. In non-occupationally exposed people, 95% of urinary alkyl phosphates do not exceed 72 μmol/mol creatinine. In occupationally exposed people, the corresponding 95th percentile of total urinary alkyl phosphates is 122 μmol/mol creatinine. In volunteer studies with 1 mg oral doses of chlorpyifos, diazinon and propetamphos the mean peak values were 160, 750 and 404 μmol/mol creatinine, respectively, and were not associated with any reduction in blood cholinesterase activity.[46] The levels of OP metabolites seen in urine from workers potentially exposed to OPs are generally low and unlikely to cause significant reduction in blood cholinesterase activity.[47]

Liver Function test: The different enzymes are co-related and in organophosphate poisoning the ALT increases significantly above AST.[1]

2.7 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 organophosphates of most toxic types should be banned.
- Adequate use of personal protective equipment, washing hands and exposed skin during as well as after work, changing clothes between work shifts, and having first aid trainings and protocols in place for workers.[47]
- Take a bath or shower at the end of the working day and wash before eating or drinking.
- Know which products contain organophosphates and how to recognize them.
- Keep products in a secure place and label them clearly to avoid pesticides poisoning at home.
- Stay indoors with the windows closed if spraying occurs nearby.
- Wash all fruits and vegetables before use.

- Reduce or eliminate home use of organophosphate pesticides, especially if pregnant women or young children are in the home.
- Don't store highly toxic pesticides, especially agricultural pesticides at homes.
- Don't re-enter areas of application until after the interval specified on label[48,49,50].

2.8 Treatment of Organophosphate pesticide toxicity

Antioxidants: The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of acetylcholine at end-organs having muscarinic receptors. Atropine does not reactivate the cholinesterase enzyme or accelerate disposition of organophosphate. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off, and multiple doses will be required.[51,52] Atropine is effective against muscarinic manifestations, but it is ineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression. Despite these limitations, atropine is often a life-saving agent in organophosphate poisonings. Favorable response to a test dose of atropine can help differentiate poisoning by anticholinesterase agents from other conditions [53,54]

Test Dosage of Atropine

• Adults: 1 mg

• Children under 12 years: 0.01 mg/kg[55]

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

3.0 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 DISCLAIMER:

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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