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A REVIEW ON EFFECT OF ORGANOPHOSPHATE PESTICIDES ON NON- TARGET ORGANISMS WITH SPECIAL REFERENCE TO FISH

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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

ABSTRACT

Fishes are exposed to various kind of toxicants that are life- threatening. Organophosphates are one of the major and hazardous contaminants found in water bodies. It reaches water bodies through surface runoff and leaching. Exposure to pesticides can cause impairment in the internal organs of organism, which may lead to the alternation in the physiology and functioning of the organs. Organophosphates can induce damages to nervous system by inactivating neurotransmitter acetylcholinesterase. It can also cause excessive release of reactive oxygen species and thereby cause oxidative stress. Oxidative stress activates antioxidant enzyme system of an organism, to cope up with the massive generation of free radicals. This review gives a brief account on the effects of organophosphates and the detrimental damages it can cause on organisms.

Keywords: Organophosphates; acetylcholinesterase; neurotoxicity; antioxidant system.

1. INTRODUCTION

Since tropical climate favours pest breeding, pesticides play a very important role in agricultural development and public health care in India [1]. These pesticides along with other chemicals ca n leach out and damage nearby aquatic ecosystem. Surface run off of these synthetic chemicals can cause pollution in rivers. Fishes are most likely to affect, as they can absorb them from water through gills, skin and food they intake [2]. Fishes from downstream may have severe effects due to pollution since it can be easily transported through water [3]. Fish exposed to a broad spectrum strobilurin fungicide (Convoy) caused damages in erythrocytes and deoxyribonucleic acid (DNA) content lowering

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in vital organs. Erythrocyte cellular abnormalities, erythrocytic nuclear abnormalities and micronucleus assay values increased with increase in exposure to pesticides [4]. Effect of glyphosate, an herbicide, on *Channa punctatus* was studied and found that, it severely damages gill tissues, stomach and intestinal walls. It also interfered in enzyme activity of these tissues [5].

Organophosphates are used as stomach and contact poison, fumigants and systemic insecticides for different types of pests [6]. These are known to act as anticholinesterase agents by inhibiting the cholinesterase enzyme. 70% inhibition of acetylcholinesterase can result in death [7]. Inhibition from 20%-70% can cause adverse effects like problems in reproduction, reduced stamina and change in behaviour [8]. Chronic exposure can affect swimming and social interaction [9,10].

The phosphorus (P) of organophosphate pesticides is pentavalent and tetracoordinate with three single bonds attaching three constituents to the P while the fourth constituent attach with P by a double bond. P=O is highly electrophilic and reactive at P atom. That makes it a toxic chemical [11].

Once organophosphate enters an organism, it undergoes metabolic process that convert it into non-toxic secondary conjugates. But it has an active P-O bond, which is really unstable and get easily destroyed, which can inhibit the activity of animal acetylcholinesterase. Some studies have shown that marine and freshwater organisms undergo many metabolic changes when get exposed to organophosphates, that result in the interference in overall physiological processes [12-14]. Most of the genomic and biochemical molecules showed damages and decrease in content due to pesticide pollution [15].

Sunanda and his co-workers [16] concluded that presence of chlorpyrifos, an organophosphate, in water can cause variations in the chemical properties of water along with impairing the delicate balance in the environment. It can easily enter food chain and can cause physiological damages in the vital organs of the aquatic organisms. Even though, lethal and sub-lethal concentrations of chlorpyrifos is a threatening factor, long term exposure can induce abnormalities and can reduce the lifespan of various aquatic species.

Mostly aquatic contaminants show primary effects on brain transcripts for neurotransmitter production [17]. Gruber and Munn [18] conducted a study on common carp fish from a lake where the water is affected by an irrigation return flow. These fish showed decreased cholinesterase activity by 34.2% when compared with the common carp from an unaffected lake by the irrigation system. Detailed study revealed that the affected lake had pollution by pesticides leached from the near agricultural region. Pesticides like chlorpyrifos, azinphosmethyl, carbaryl and ethoprop were identified from the water sample. This clearly represents the harmful effects of pesticides and also the vulnerability on non-target organisms.

Fish showed decreased antipredator behaviours and preferred brighter areas of resting upon pesticide exposure. Low concentration exposure to pesticide can induce the reduction in ecological fitness of the fish [19]. During exposure period to organophosphate pesticides, *Anguilla anguilla* showed significant variations in metabolism. Blood glucose and lactate levels of the gill and liver increased. While the protein content of gills and liver decreased significantly during the exposure. Recovery phase after the exposure showed normalization of the above metabolic variations [20]. In *Labeo rohita*, pesticide exposure impaired the function of brain, gills, muscle, kidney, liver and blood cells of the fish [21]. *Labeo rohita* upon exposure to phenthoate, an organophosphate, showed decreased glycogen as well as protein content that eventually contributed to the mortality of the fish [22]. *Oreochromis niloticus* exposed to diazinon in sub-lethal concentration showed variation in behavioural pattern. Fish showed somersaulting, convulsion and erratic swimming as an after effect of pesticide exposure. Protein content in the plasma, muscle, liver, gills and kidney decreased with increase in dosage of pesticides [23]. These reviews represent the deleterious effects of organophosphate pesticides on fishes which also indicate the effects on aquatic organisms and other non-target organisms including humans.

2. EFFECT ON ORGANS AND PHYSIOLOGICAL PARAMETERS

Organophosphates can cause various damages to the physiology and functioning of internal organs in fish. It may degrade or induce structural aberrations in the organs, which result in the reduction or alternation of function of the organ. Exposure to quinalphos, an organophosphate, caused degeneration of epithelial lining of gills within 96 hours in *Anabas testudinesis* [24]. *Oreochromis species* exposed to quinalphos showed hypertrophy of gill tissues along with lifting of lamellar epithelium, degeneration of gill filament and lamellar epithelium and also vasodilation of lamellar axis [25]. Organophosphate, monocrotophos can cause thinning of microridges, upliftment of epithelial cells, development of hyperplasia, decrease in the density of mucous cells and dystrophy of epithelial tissues of gills in *Cyprinus carpio* [26].

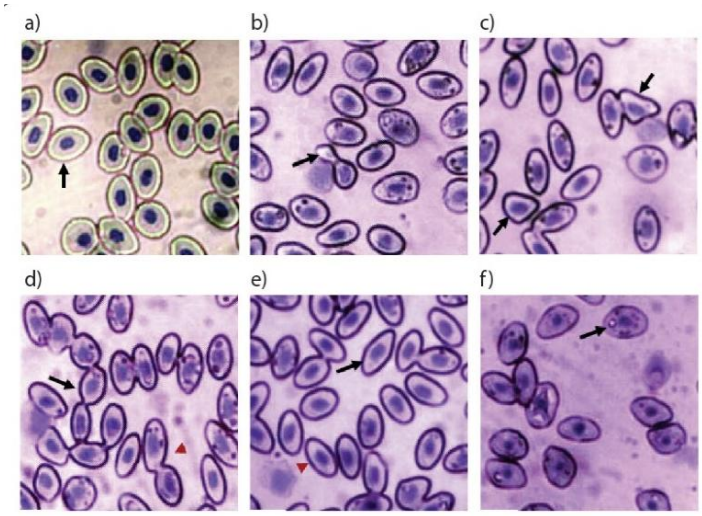

Fig. 1. Blood smear of fish treated with sub-lethal concentration of quinalphos showing erythrocytic cellular abnormalities reproduced from Sadiqul et al. [4]

When *Oreochromis mossambicus* were exposed to sub-lethal concentrations of quinalphos, there was a decrease in hemoglobin content, increase in white blood cell (WBC) content, and decrease in red blood cell (RBC) count and reduction in plasma and tissue protein [27]. Silver barb showed significant decline in protein and lipid content along with increase in morphological and nuclear abnormalities of erythrocytes on exposure to quinalphos [28]. Sub-lethal exposure of quinalphos (Kinalux) on Nile tilapia showed variations in the histology of kidney and liver along with varied RBC and WBC count [29]. Muscle tissue showed significant reduction in protein content when compared with other tissues, after exposure to quinalphos [30]. Studies conducted by Bakry [31] and Brezenoff [32] suggests that organophosphate agents have serious effect on cardiac functions of the organisms. Hepatic hypertrophy, necrosis, ruptured vein and vacuolation were found in liver tissue, degenerated kidney tubules and hematopoietic tissue, along with degeneration of renal corpuscle, vacuolation and necrosis in the kidney tissues were identified in silver barb after chronic exposure to quinalphos [33]. Pesticides have no effect on reproductive system in fish, if given for short-term. But long-term subjection, even in sub-lethal concentrations can cause severe effects on reproductive organs and reproduction [34]. Quinalphos can induce release of cytochrome c from the mitochondria to cytoplasm and cleavage of caspase-3 and caspase-9 [35].

Intermediate metabolites of quinalphos such as quinalphos oxon, O- Ethyl- O-.quinoxalin -2-yl phosphoric.acid, 2- hydroxyquinoxaline and ethyl.phosphoric acid were identified in rats treated with quinalphos. These metabolites of quinalphos were persistent for longer period [36]. Quinalphos can decrease number of viable sperms. Abnormalities on sperm was also found in quinalphos induced mice. It decreased testicular cholesterol by impairing the biosynthesis of testicular tissues along with reduced steroidogenesis by down-regulating expression of cytochrome P450, 3β- HSD and 17β-HSD which resulted in lowering of testosterone level [37]. *Clarias batrachus* exposed to quinalphos pesticide showed decrease in steroidogenic enzyme activity in testis [38]. Silver barb showed vacuolation and necrosis of kidney tubules and liver cells when exposed to quinalphos at sub-lethal concentration [39]. Quinalphos exposure can impair aerobic oxidation of nutrients, and glycogen synthesis and breakdown in liver and can induce formation of micronuclei and chromosomal aberrations in bone marrow cells and germ cells [40]. Chlorpyrifos exposure of a zebrafish hatchlings caused slowing of swimming activity and impairment in spatial discrimination. The dangerous part is that, it prevails tills adulthood and the fish showed decreased response to stimuli. It simply indicates that exposure during early developmental stages can cause damages that lasts even in adult stages of life [41].

3. EFFECT ON ACETYLCHOLINEST-ERASE ENZYME

Acetylcholinesterase (AchE) is a cholinergic enzyme found at the postsynaptic neuromuscular junctions. It hydrolyses the neurotransmitter acetylcholine in cholinergic synapses of the central and peripheral nervous system, both in vertebrates and invertebrates [42].

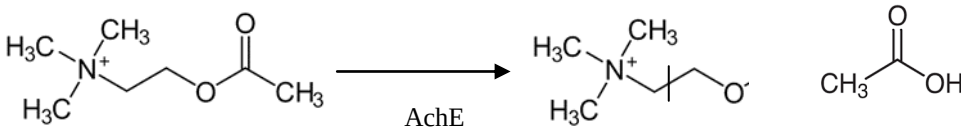

Fig. 2. Degradation of acetylcholine into acetic acid and choline by acetylcholinesterase

AchE inhibition is a better biomarker for neurotoxicity in research work [43]. Studies conducted on organophosphate pesticides have revealed its influence on cholinesterases especially AchE. Organophosphates like chlorpyrifos, diazinon and parathion are proved to affect AchE in larval zebrafish [44]. Giant freshwater prawns (*Macrobrachium rosenbergii*) also showed inhibition and accumulation of AchE at the synaptic terminals of nerves, on exposure with organophosphate quinalphos and dimethoate [45]. Fish exposed to chlorpyrifos showed increased expression of acetylcholine esterase enzyme by 12.4 times at 43µM concentration exposure when compared with the control group [42]. Diazinon, an organophosphate, was able to inhibit AchE activity by 77% within 24 hours. Within one hour of exposure, lipid peroxidation and carbonyl group formation increased dramatically. Meanwhile, antioxidant power significantly decreased [46]. Rainbow trout showed depression in cholinesterase activity after getting exposed to pesticide. Fish showed successful recovery after keeping them in uncontaminated water for 48 hours [47]. Exposure to quinalphos by common carp at sub-lethal concentration showed irregular, erratic and darting swimming movements, hyper excitability, loss of equilibrium and sinking to the bottom. This could be due to the inactivation of AchE enzymes in the nerve terminals [48]. Organophosphate pesticides have additive effect on inhibition of cholinesterase activity when given in combination with other organophosphate pesticides [49]. Nerve agent like Sarin can also cause inactivation of AchE enzyme resulting in the accumulation of acetylcholine and continuous stimulation of cholinergic receptors [50]. AchE activity can be used as an assay in the study of pollution in marine species, since its activity is found in the highest level, especially in fish [51]. Goldfish exposed to azinphosmethyl, parathion and carbaryl pesticides showed inhibition of brain cholinesterase enzymes. During recovery from exposure, the fish was able to overcome the effect by 35 days or more [52].

Chlorpyrifos, a widely used organophosphate pesticide in agriculture, due to its efficiency to control pest has increased its exposure to human and other non- target organisms [53-55]. When early life stages of zebrafish get exposed to chlorpyrifos, they showed decrease in body length, restricted egg hatching and morphological aberrations. It also caused changes in response to light to dark photoperiod transition. AchE activity and many neurotoxicity genes were affected [56]. Some researchers use brain AchE activity to diagnose chlorpyrifos toxicity [57].

Chlorpyrifos become an active compound when it undergoes oxidative desulfuration in target body to chlorpyrifos oxon which can induce neurotoxicity by inhibition of esterases in the nervous system [58-60]. This product is more water- soluble than chlorpyrifos and thus, it is easily eliminated from organisms like fish, rats and human, which indicate its low potential to get accumulated after multiple exposure [56,60-63]. But, chlorpyrifos oxon shows a particular selectivity for acetylcholinesterase as a target esterase [64,65]. Inhibition of AchE results in the accumulation of acetylcholine at the nerval synapses and causes hyperexcitation of neurons and related end organs [66-68]. Lipophilic nature of chlorpyrifos supports sustained inhibition of AchE and delayed toxicity after sub-lethal tolerated doses get stored and released slowly [65, 69-72].

Johnson [73] suggested that occurrence of delayed neurotoxicity is associated with the inhibition of an esterase. Bloch and Hottinger [74] proposed the involvement of AchE in neurotoxicity. This inhibition of esterase in the brain is only an early event of delayed neurotoxicity caused by organophosphate compounds. Delayed neurotoxicity was also identified by some researchers, in animals exposed to organophosphate after 8-14 days of dosing. It has a connection with the phosphorylation of a site in nervous system with in some hours of exposure [74]. Organophosphorus can inhibit AchE by phosphorylation of serine hydroxyl moiety at the active site of the enzyme. Phosphorylated enzyme is more stable that make the enzyme irreversibly inhibited [75]. If a compound capable of making complex with this site, were added before phosphorylation, neurotoxicity could be prevented [74].

Acetylcholine is designated to bind at two cholinergic receptors- muscarinic and nicotinic receptors.

Accumulation of acetylcholine causes some variations in these receptors which in turn alters the function of autonomous nervous system, the somatic motor neuron and brain. These receptors are distributed in many organs and mostly in brain and spinal cord. Brain seems to have more muscarinic receptors while spinal cord has nicotinic receptors. Organophosphate pesticides have direct effect on muscarinic and nicotinic receptors. Binding of organophosphate on receptors can modulate the function of receptors [31,76-79]. Some organophosphates bind with the receptor in high affinity which make them important in modulating toxicity. It binds with muscarinic receptors. and can induce activation or inhibition of the receptor, that is, it can activate an inhibitory effect or can inhibit an activatory action. Thus, it can impair the entire system related with the receptors. In the case of nicotinic receptors, organophosphate bind at allosteric sites and cause desensitization [80]. It was also identified that organophosphate or their metabolites can interact with various other biological target molecules other than cholinesterase [81].

Muscarinic acetylcholine (m-Ach) receptors have regulation at the biochemical and electrophysiological actions. It deals with intracellular cAMP (cyclic Adenosine monophosphate), cGMP (cyclic guanosine monophosphate), inositol phospholipid levels and opening and closing of K^+ and Ca^{2+}channels [31,82]. Even though organophosphate have no direct effect on m-Ach receptors, but excess acetylcholine at the synaptic gaps can induce decreased synthesis or increased breakdown of these receptors. This is due to the inhibited AchE enzyme [83]. Most of these m-Ach receptors are regulated by agonists whose binding sites get altered upon acute exposure to organophosphate, that indirectly affect m-Ach receptors [84,85]. Many studies were conducted by interacting drug with nicotinic acetylcholine (n-Ach) and m-Ach receptors using radio-labelled ligand binding or receptor -induced responses like ion transport or generation of second messengers [86-92].

Stimulation of muscarinic receptors.by toxins induce signs of toxicity with increased salivation and lacrimation, bronco secretion, bronco-constriction, constriction of eye pupil, brachycardia, gastrointestinal cramps, diarrhoea and urination while signs of toxicity induced by the stimulation in nicotinic receptors include tachycardia, muscle fasciculation, hypertension, muscle weakness and tremors. Restlessness, ataxia, emotional liability, loss of memory, mental confusion, convulsions, cyanosis, generalised weakness, coma and depression of respiratory centres are combined effect of nicotinic and muscarinic receptors. There are reported cases of deficits in memory and neurophysiological functions in humans exposed to organophosphate pesticides or nerve agents [93-96].

Psychology and mental state of an animal can be affected by the administration of cholinergic agonists and antagonists. Behaviours like aggression, learning and conditioning, emotional behaviour etc are depended on the cholinergic neurotransmission in limbic system. This limbic system includes parts of nervous system like thalamus, hypothalamus, reticular formation, cortex, hippocampus, basal ganglia etc [97,98]. Cholinergic agonists have effect on memory in humans as well [99], thus these are used in the treatment of Alzheimer's disease and for memory loss due to old age [100,101]. Organisms may develop tolerance after many sub-lethal exposures to organophosphate compounds [102]. This tolerance is the result of decreased regulation of muscarinic and nicotinic receptors in the nervous system [103,104] due to the increased neurotransmitter level [105,106].

4. EFFECT ON ANTIOXIDANT SYSTEM

Exposure to pesticides can result in the induction of oxidative stress in many organisms, due to the increased generation of reactive oxygen species. Pesticides can have effects on antioxidative and detoxifying enzymes that neutralizes the oxidative stress, at very low concentration [107]. In humans, many lifestyle diseases such as diabetes, cancer, atherosclerosis, neurodegenerative disorders *etc* can be a result of oxidative stress. When the ability of antioxidant mechanism to remove free radicals get exceeded by the generation of reactive oxygen species, oxidative stress occurs. Oxidative stress can activate certain environmental pollutants entered in the body, which may impair signalling pathways during metabolism [108]. Oxygen radicals can damage proteins in the system. For example, a study conducted suggests that hydroxyl radical is able to make protein degradation and modifications. When a protein subjects to hydroxyl radical, it results in the loss of tryptophan and produce bityrosine phenol. On the other hand, superoxide anion can act synergistically with hydroxyl radical in protein fragmentation [109]. Firstline defence antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were found to be effective against superoxide anion radical, a free radical formed during metabolism. SOD catalyse dismutation of two molecules of superoxide anion to hydrogen peroxide and a molecular oxygen. Catalase on the other hand, convert hydrogen peroxide to water and molecular oxygen [110].

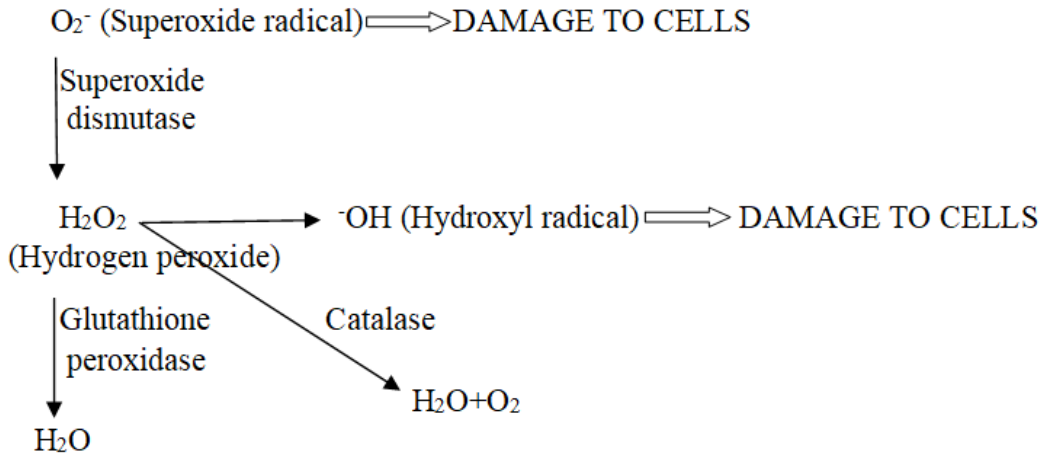

Fig. 3. Mechanism of neutralizing free radicals by antioxidant enzymes

Table 1. Commonly used Organophosphate pesticides and its application in agriculture

Organophosphate pesticides	Application in agriculture
Parathion	Applied to cotton, rice and fruit trees.
Malathion	Applied to crops especially vegetables, used in the eradication of mosquitoes
Methyl parathion	Applied to crops including cotton
Monocrotophos	Applied to crops especially against the pests of cucumber
Chlorpyrifos	Applied on crops with the most use include cotton, corn, almonds, and fruit trees, including oranges, bananas, and apples.
Diazinon	Applied to most crops
Dichlorvos	Applied to greenhouse and outdoor crops, effective against parasitic worms
Dimethoate	Applied on fruit crops specially to control fruit fly
Phenthoate	Applied on rice, vegetables, fruits and tea specially against chewing and sucking insects
Quinalphos	Applied to common crops

Acute toxicity of organophosphate pesticides like diazinon can induce oxidative stress and are able to impair antioxidant defence system [46]. SOD, CAT and glutathione S-Transferase (GST) activity were increased in liver tissues of *Cyprinus carpio* after quinalphos exposure [111]. Malathion is also known for causing oxidative damage in fish along with variation in AchE, hematological profiles, antioxidant enzymes status and lipid peroxidation rate [112,113]. Quinalphos induces generation of free radicals that causes lipid peroxidation [114]. It decreased antioxidant enzymes [115]. Antioxidant enzyme such as SOD, catalase and glutathione reductase showed decline in production of mitochondrial, microsomal and nuclear fractions of gills, after subjecting to sub-lethal dosage of quinalphos [116]. Quinalphos is able to reduce cell viability by increasing the generation of intracellular reactive oxygen species, DNA condensation and cell apoptosis [35]. There were significant variations in the antioxidant enzyme, glutathione system and lipid peroxidation rate on sub-lethal exposure to quinalphos [117]. Methyl parathion can also induce severe damages in fish by increasing the production of ROS [118]. A study conducted in *Oreochromis niloticus* showed that organophosphate, dimethoate, has various effect on different antioxidant enzymes present in different tissues of the fish. For example, enzymes like SOD, GPx and lipid peroxidation (LPO) activity showed increased activity while CAT, GSH and glutathione reductase (GR) activity showed decrease in liver tissues. On the other hand, GR and LPO have increased activity in kidney and GPx and GSH decreased significantly [119].

While examining the relation between the oxidation stress and gene expression of antioxidant enzyme, Limaya and his co-researchers [120] identified certain features regarding enzyme activity. When rats were induced with oxidative stress, RT-PCR results showed increase in mRNA generation of antioxidant enzymes like SOD, GPx and CAT but the enzyme activity was decreased. This suggests that there could be some post- translation modifications that lead to the inactive enzymes. Gene expression of paraoxonase (PON) and GPx was found to be decreased while CAT genes showed increase in expression by 1.1-fold after

4 hours of exposure to organophosphates [120]. Expression of GST gene and vitellogenin (Vtg) gene, which are oxidative stress indicators, were found decreased along with significant DNA damage in the liver cells was observed when fish were exposed to pesticide residues [121].

5. ADVANCES IN TECHNOLOGY TO CONTROL THE USAGE OF PESTICIDES

To control the excessive usage of pesticides in agriculture, advanced technologies such as nanotechnology have contributed by the introduction nanobiosensors and nanoformulation of agrochemicals. Nanobiosensors, to detect the presence the organophosphate agents were developed, to measure its presence in food particles. The sensors are mostly based on acetylcholinesterase, since it is the primary target of organophosphates [122]. Development of nanoformulations of agrochemicals as an alternative for pesticides and fertilizers are being considered due to hazardous effects of these chemicals on non-target organisms [123].

6. CONCLUSION

Uncontrolled usage of pesticides in the agricultural field was always been a concern in terms of effects on the non- target organisms. Aquatic organisms are mostly affected by pesticides since it can simply get into aquatic ecosystem by surface runoff and leaching. According to the above reviews, application of pesticides such as organophosphates can cause serious nervous complications and organ damages to the pests and the non-target organisms as well. It can easily enter food chain and can cause physiological damages in these organisms. Organophosphates are known for its effect on AchE, the enzyme that get inactivated by means of phosphorylation of the serine moiety. This inactivation can cause accumulation of acetylcholine on the nerve terminals leading to the continuous activation of nerve. It can lead to various complications like neurodegeneration, delayed neurotoxicity, brachycardia, losing control over muscles, respiratory arrest and even death. Organophosphates can also induce oxidative stress by increasing the generation of reactive oxygen species. ROS takes electrons from the lipids in the cell membrane and can cause cell damage. This process known as lipid peroxidation. The destruction of membrane lipids and the end-products of such lipid peroxidation are dangerous for the viability of cells, even tissues. ROS can interfere with various signalling pathways and result in impairment of many physiological functions. Various detailed studies are being done in order to find the basis of these causes.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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