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Organophosphorous Pesticide: An Environmental Pollutant Perspective

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ABSTRACT

Organophosphorus pesticides are widely used as insecticides all over the world because it possesses high biocidal activity. Currently organophosphorus insecticides enhanced usage in agriculture and public health has resulted in environmental pollution and can exert significant adverse effects in non-target organism including the mammalian species. This has increased concern of the consequence of organophosphorus pesticides to the environment. The majority of organophosphorus insecticides exert cholinergic toxicity in human, by phosphorylation of acetylcholinesterase and they are also classified as acetylcholinesterase insecticides. However, some have been shown to cause delayed polyneuropathy which is initiated by the attack on the neuropathy target esterase which is distinct from acetylcholinesterase. The currently investigated continuing issues of organophosphorus pesticides toxicology which includes; common mechanism of action; organophosphorus ester induced delayed neuropathy and risk assessment are discussed.

Keywords: Organophosphorus pesticides; Acetylcholinesterase; Delayed polyneuropathy; Environment; Risk assessment

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INTRODUCTION

Organophosphorus pesticides (OP) are derivatives of esters of phosphorothionic acid or phosphoric acid widely used as insecticides. About 200 different chemical structured organophosphorus insecticides are available commercially, formulated literally into thousands of sprays, liquids, and powders which may be used diluted or as supplied [1-4]. It is widely used in agriculture and public health programs, due to its lower environmental stability advantage when compared to organochlorine insecticides (for instance DDT), and high biocidal effects against different disease vector and insect by significant toxicity of mammalian species disadvantage [5]. Besides use in public health programmes and agriculture, organophosphorus compounds are also used in industry as flame retardant, solvents, plasticizers and in warfare as nerve gas [6-8]. Currently the occasional use of OP in indiscriminately large amount has resulted in the increase of environmental pollution. The detection of OP residues in grains, vegetables, food products, soil and water supplies has prompted a public health concern of its adverse effects [9,10]. Although several organophosphorus compounds were synthesized by Michealis between 1903 and 1915, their development into insecticides occurred in 1937 and early 1940s. The general chemical structure of organophosphorus ester was discovered by a German scientist, Gerhard Schrader and he is credited for the first commercialised insecticide, Balan with Tetraethylpyrophosphate (TEPP) as active ingredient in 1937, followed by dimefox in 1940, schardan in 1942, and parathion in 1944 [11-14]. The general chemical structure of organophosphorus insecticides according to Schrader [15,16] is illustrated below in Figure 1. This structure is categorized into four groups as shown in Table 1 with corresponding examples [17].

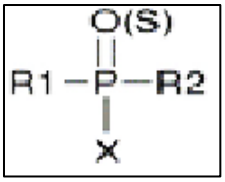

Figure 1: General chemical structure of an organophosphorus compounds. R1 and R2 are amido-, alkyl-, alkoxy-, or alkylthio-, groups. X is the acyl residue (cyano-, labile fluorine-, substituted or branched heterocyclic, aromatic, or aliphatic groups)

Table 1: Chemical structures of main groups of OP pesticides and examples in each group

Type of group	Outline of structure	Examples
Phosphate	O || $(R\text{-}O)_2$-P-O-X	Chlorfenvinphos, dicrotophos, crotoxyphos, dichlorvos,heptenphos, mevinphos
Phosphorothioate	S || $(R\text{-}O)_2$-P-S-X	Bromophos-ethyl, bromophos-methyl chlorpyriphos-methyl, coumaphos, dichlofenthion, fenchlorphos, Parathion
O-alkyl phosphorothioate	S || $(R\text{-}O)_2$-P-O-X	Demeton-S-methyl, omethoate, vamidothion, phoxim
Phosphorodithioate	S || $(R\text{-}O)_2$-P-S-X	Azinophos-ethyl, azinophos-methyl, malathion, mecarbam, menazon, morphothion, phenthoate

Most organophosphorus insecticides encountered are classified as highly hazardous - Class1b by the World Health Organization (WHO), and as moderately toxic by the (NTP) National Toxicology Programme [18,19]. The eight most commonly encountered organophosphorus insecticides at the National Poisons Information Service are malathion, fenitrothion, dichlorvos, diazinon, dementon s-methyl, heptenophos, dimethoate and pirimiphos-methyl other [20,21]. The majority of organophosphorus insecticides exert cholinergic toxicity in human, by phosphorylation of acetylcholinesterase and they are also classified as acetylcholinesterase insecticides. However, some have been shown to cause delayed polyneuropathy which is initiated by the attack on the neuropathy target esterase which is distinct from acetylcholinesterase. The currently investigated continuing issues of organophosphorus pesticides toxicology which includes common mechanism of action, organophosphorus ester induced delayed neuropathy and risk assessment is discussed.

Organophosphorus Insecticides Exposure

The mode of OP exposure to humans is usually accidental, occupational or homicidal [22]. The National Poisons Information service (NPIS) reported that in the UK , humans were exposed to OPs through the following routes: - 55% ingestion; 21% inhalation; 12% skin contact; 9% Eye contact, 9% Other, in 2000 cases of OP poisoning between 2002-2005 [23]. Over 300,000 cases of OP acute and chronic toxicity events have been estimated worldwide [24,25]. Zhang et al. stated that between 1996 and 2000, OP insecticide ingestion accounted for 62% of intoxication in China, which corresponded to 175 000 cases worldwide [26]. Although 2.2% of this case is based in suicide, 98% exposure occurs in children under the age of five worldwide. Retrospective published literature of OP intoxication has been reported in Australia [27] Asia [28-30] and Africa [31-35]. In the United States, 2,186 exposures to organophosphate insecticides, with two deaths and eighteen major outcomes was reported by the American Association of Poison Control Centers in 2015 [36]. OP insecticides a common cause of poisoning in developing countries when compared to the developed countries.

Absorption, Metabolism, Biotransformation and Excretion of Organophosphorus Pesticides

Organophosphorus insecticides are lipophilic compounds and are readily absorbed from the oral mucousa, skin membrane, conjunctiva, respiratory, gastrointestinal tracts and are rapidly distributed to the tissues of the body [37]. Organophosphorus Pesticides (OP) absorption into the bloodstream is fast through any of the routes mentioned but dermal uptake is slower than other routes. The onset to duration of toxicity is determined by physiochemical properties (e.g. partition coefficient, lipid solubility and Pka,) dose, route of exposure, rate of metabolism and $t_{1/2}$ of the type of organophosphorus insecticide involved. OP metabolism is dependent on the type of group attached to the

OP backbone structure (Table 1) and is highly specie specific [38]. Biotransformation of organophosphorus Pesticides occurs in the liver, where cytochrome P-450 converts P = S to P = O (reactive metabolite) in toxic or oxon form. OP readily undergo oxidation, reduction, hydrolysis (phase I biotransformation) and conjugation with glutathione (GSH) liver (Phase II biotransformation). Malathion provides a good illustration of the mechanisms involved in acute toxicity [39]. OP is mainly excreted through urine. For instance, conversion of methyl parathion to methylparaoxon occurs within minutes of administration. Methyl parathion or methylparaoxon are mainly detoxified in the liver through Phase I (hydrolysis, oxidation,) and dearylation with reduced glutathione (GSH). One of its metabolites is p-nitrophenol. Therefore, measuring the urinary excretion of p-nitrophenol would throw some light into method of elimination. The elimination of methyl parathion and its reactive metabolites occurs primarily via the urine. Studies conducted on mice with radiolabelled ('/P-methyl parathion) revealed 10% radioactivity in the faeces and 75% radioactivity in the urine [40].

Common Mechanism of Action

OP exerts their acute effect by acetylcholinesterase (AChE) inhibition in the nervous system (NS). The covalent reaction between the organophosphorus ester with the serine hyrodxyl group an active site for in the AChE protein, leads to the formation of an intermediate, which partially hydrolyses the X group of OP (Figure 2) [41]. This forms an irreversible inhibited enzyme when the phosphorylated AChE ages. Hence, leading to the accumulation of high levels of acetylcholine (ACh) at the cholinergic synapse with over stimulation of nicotinic and muscarinic receptors. [42,43].

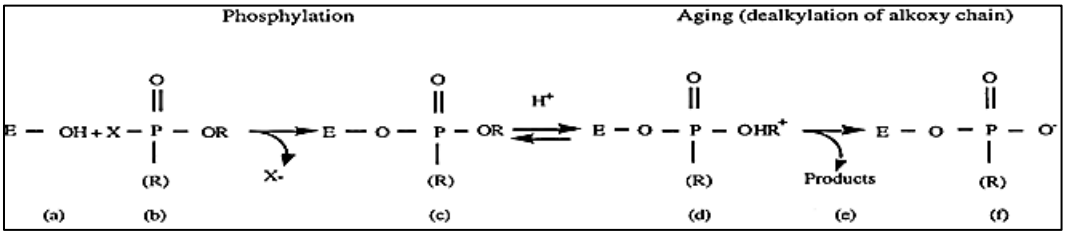

Figure 2: Illustrates the mechanism of phosphorylation and aging of cholinesterase. (a) free enzyme;(b) organophosphorus compound; (c) phosphorylated enzyme; (d) intermediate; (e) dealkylation products and (f) aged enzyme

Some of the cholinergic signs and symptoms includes salivation, sweating, and muscular twitching and could lead to death due to flaccid paralysis of the pulmonary muscle. However, some recently introduced OP like dicholorus and temephos are less tenacious AChE inhibitors. The phosphorylated enzyme is spontaneously and rapidly dissociated.

Organophosphorus Ester Induced Delayed Neuropathy

Few organophosphorus cause organophosphorus esters induced delayed neuropathy (OPIND) another type of toxicity. OPIND is distinct from AChE Inhibition. In the past four decades, comprehensive studies have demonstrated and identified the target, neuropathy target esterase (NTE) [44]. The chemical reaction involved in the NTE phosphorylation is quite similar to that of AChE phosphorylation. However, only different chemically structured OPs that cause NTE aging can result to OPIND. The first recognized episode of OPIND toxicity was happed in the USA during the 1930s. An epidemic of poisoning termed 'ginger jakes' caused by the adulterant tri-ortho-cresyl phosphate (TOCP) in Jamaican ginger. The flaccid paralysis that occurred in victims was not due TOCP but its reactive metabolite, saligenin cyclic phosphate [45].

Risk Management

In the UK**,** pesticides are regulated by a number of legislation including, COSHH (the Control of Substances Hazardous to Health). Protection Products Regulations (PPPR) and the Control of Pesticides Regulations (COPR). The agricultural pesticides are managed by Pesticides Safety Directorate while the non-agricultural pesticides are managed by the Health and Safety Executive (HSE) some organophosphorus insecticides are under review by the have been under review Chemicals Regulatory Directorate Pesticides. The exposure models used in risk assessment is the Reference Dose (RfD) approach. This is widely used for OP standard setting, since OPs produce systemic toxicity, involving primarily the nervous system. An RfD is calculated by a no-adverse-observed-effect level (NOAEL) by a series of uncertainty factors (UFs). Benchmark dose modelling is used in human risk management.

CONCLUSION

The understanding of persistence of OPs in the environment and its transport between air, water and soil is an essential element to understanding the effects of OPs in the environment on non-target organism including plants and human beings. OPs exhibit limited selectivity between target and non-target species. Thus, potential adverse effect of OP continues to be a problem amongst the mammalian population.

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