Nature Environment and Pollution Technology
An International Quarterly Scientific Journal

p-ISSN: 0972-6268
(Print copies up to 2016)
e-ISSN: 2395-3454

Vol. 22 | No. 4 | pp. 1867-1880 | 2023

Review Research Paper

https://doi.org/10.46488/NEPT.2023.v22i04.014

Open Access Journal

Chemistry, Metabolism and Neurotoxicity of Organophosphorus Insecticides: A Review

Ashutosh Singh*, Abhishek Singh†, Akhilesh Singh*, Priti Singh*, Vivek Singh***, Yogender Singh****, Hardeep Singh Tuli*****, Hadi Sajid Abdulabbas****** and Abhishek Chauhan*******(*)**

*Department of Chemistry, K.S. Saket Post Graduate College, Ayodhya-224001, India
**Department of Chemistry, Udai Pratap College, Varanasi-221002, India
***Departments of Botany, Udai Pratap College, Varanasi-221002, India
****Department of Chemistry, Government Degree College, B.B. Nagar, Bulandshahr-203402, India
*****Department of Bio-Sciences and Technology, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala 133207, India
******Biology Department, College of Science, University of Babylon, Babylon Province-Hilla City, Iraq
*******Amity Institute of Environmental Toxicology, Safety, and Management, Amity University, Noida-201303, India
†Corresponding author: Abhishek Singh; abhupc@yahoo.com

Nat. Env. & Poll. Tech.
Website: www.neptjournal.com

Received: 13-02-2023
Revised: 21-03-2023
Accepted: 07-04-2023

Key Words:
Organophosphorus
Acetylcholine (AChE)
Paraoxon
Malathion
Cytochrome P450

ABSTRACT

Organophosphorus compounds (OPs) are phosphoric acid derivatives represented by the formula ($R_2XP=O/S$), R as organic groups; however, they need not contain a direct carbon-phosphorus bond. The organophosphorus compounds can be categorized into three classes, *viz*., organophosphates, carbamates nerve agents. The OPs having application as insecticides are generally phosphorothioates (i.e., containing P=S bond). These sulfur analogs are first bioactivated (*in vivo*) and converted to oxygen analogs responsible for exerting toxic action. These organophosphorus compounds are esters, fluorides, anhydrides, and amides of phosphoric, phosphorothioate, and phosphorodithioic acids. The toxicity of OPs is related to their molecular structure, metabolism in the targeted organisms, concentration, mode of decomposition, application, ingestion in organisms, etc. Exposure to OPs leads to the appearance of neurological symptoms followed by acute poisoning by targeting the target primarily, acetylcholine (AChE). However, secondary targets and other harmful effects besides nerve system problems are also reported. Organophosphates poison insects and other animals, including birds, amphibians, and mammals. These chemicals can have neural effects (Neurotoxicity), non-neuronal effects, or acute toxicity, which may also result in fatality. Their uncontrollable widespread became a significant threat to the environment; thus, corrective measures have been essential to save living beings and the environment from further damage.

INTRODUCTION

Organophosphorus compounds (OPs) are phosphoric acid derivatives represented by the formula ($R_2XP=O/S$), R as organic groups; however, they need not contain a direct carbon-phosphorus bond. The organophosphorus compounds can be categorized into three classes: organophosphates and carbamates nerve agents. The phosphorous can have five, three, and less than three oxidation states in the compounds. Among these, pentavalent phosphorous is the most prevalent in these chemicals. These chemicals display various fuel additives, insecticides, flame retardants, lubricants, and plasticizers (Fig. 1). The OPs insecticides act as nerve agents by inhibiting acetylcholinesterase (AChE), resulting in acute toxicity. Organophosphorus-based insecticides have been used exhaustively for agriculture and other applications in the last century. Soil bacteria attack these insecticides and, upon hydrolysis in the presence of sunlight and air, may quickly degrade the insecticides (Khalid et al. 2016). However, the persistence of these moieties in food and water in small amounts is noticed (Amir et al. 2019, Akhtar et al. 2009). These have also been toxic and have led to environmental bioaccumulation (Ricardo et al. 2018, Soltaninejad & Shadnia 2014). The OPs' intoxication is a reason for sickness and death worldwide (Petroianu 2015). The wide applications of OPs and their toxicity have been

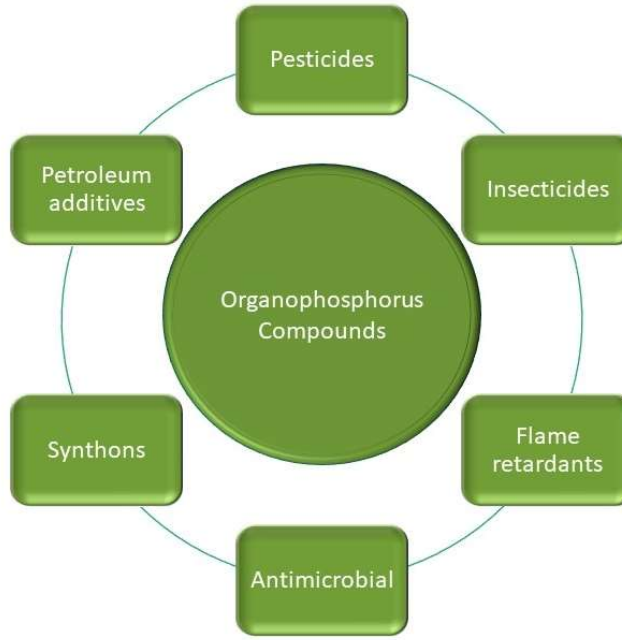


Fig. 1: Pictorial representation of applications of phosphorous compounds.

the reason for their extensive research. This encouraged us to discuss the history of organophosphorus-based insecticides, chemistry, metabolism, and neurotoxicity in the present review article.

Looking back into the past through binoculars of publication, it may be taken that the beginning of research on organic compounds containing phosphorus was marked by the work of Lassaignein 1820 (Lassaigne 1820, Thenard 1847). The scientist also investigated the alcohol and phosphoric acid interaction as well as demonstrated the presence of phosphonic derivatives. For the first time, organophosphorus compounds were described in 1847 by Thenard *via* preparation phosphines series (Hofmann et al. 2009). Hofmann was the first to prepare alkane phosphonic acids in 1872 (Michaelis et al. 1897). The German Michaelis and his coworkers are pioneers of classic but modern phosphorus ester chemistry (Lange & Krueger 1932). Although organophosphorus compounds were synthesized as early as the 19th century, their toxicity effects were reported in 1932 when the Russian scientists Arbuzov Lange and Krueger observed the potent bioactivity of organophosphorus compounds. Investigations of these compounds' biocidal effect elucidated toxicity not only in warm-blooded animals but also in insects. The development of organophosphorus compounds (OPs) was mainly the preparation of active pesticides and insecticides against insects and pests (Petroianu 2015, Soltaninejad & Shadnia 2014, Jayasinghe et al. 2012). Tetraethyl pyrophosphate (TEPP), discovered by De Clermont and Moschnine in 1854, is the first reported organophosphorus (OPs) known for cholinesterase inhibition. During the time 1934 to1944, many OPs were developed by Schrader, namely parathion, paraoxon, soman, tabun, and sarin which were found to be nerve agents (Savage et al. 1981, Taylor et al. 2007, Squibb 2013). In 1943 parathion was introduced and widely used (Savage et al. 1981, Galli et al. 1988, IOMC & WHO 2010). After World War II, concern for public health and agricultural toxicity due to organophosphorus (Ops) pesticides rose significantly (Galli et al. 1988). The decade 1950s to the 160s showed extensive organophosphorus (OPs) pesticide use. The introduction of Malathion by Cyanamid Company in1950 (Savage et al. 1987, Taylor et al. 2007, Squibb 2013, Galli et al. 1988, WHO 2010), the development of dichlorvos, trichlorfon, and diazinon in 1952 and the creation of Vxin 1958 were marked invention the decade. Mass-produced was also started for VX by the military as a chemical warfare agent (Masson & Nachon 2017). A lot of research has been done in this field for selecting insecticides for better efficacy action, low toxicity, and activity. Current ways of plant protection are successful due to OPs. Which are far better than the chlorinated hydrocarbon insecticides, which have more bioaccumulation in the environment and humans (Galli et al. 1988, Testai et al. 2010). The drawbacks of chlorinated hydrocarbons resulted in bringing degradable organophosphates to market. Organophosphorus insecticides were found to be the only alternatives to chlorinated hydrocarbon insecticides at that time.

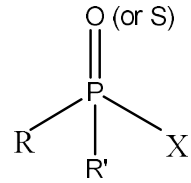
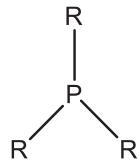
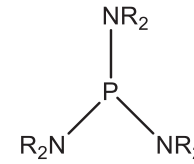
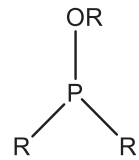
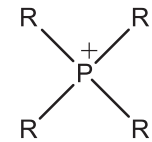
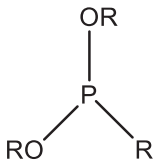
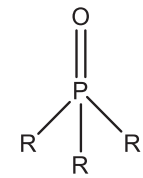
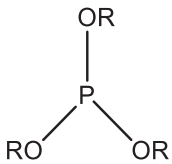
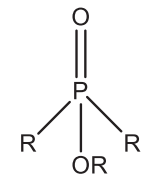
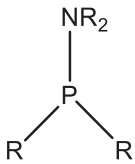
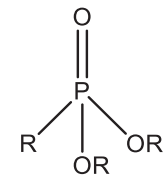
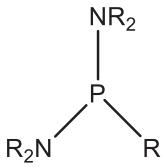
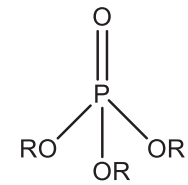


Fig. 2: General Structure of Organophosphorus (OPs).

CHEMISTRY OF ORGANOPHOSPHORUS (OPS)

Schrader, in 1937, was the first to reveal the chemistry and general structure of organophosphorus (OPs), as shown in Fig. 2. It was observed that phosphorus was pentavalent in these compounds to which sulfur/oxygen was attached through the double bond, R & R' were either alkoxy groups or isopropyl substitutes, and X was found

Table 1: Types of Organophosphorus Compounds.

1.		7.	
	Phosphines		Triamides
2.		8.	
	Phosphinites		Phosphonium salts
3.		9.	
	Phosphonites		Phosphine oxides
4.		10.	
	Phosphites		Phosphinates
5.		11.	
	Phosphinousamides		Phosphonates
6.		12.	
	Diamides		Phosphates

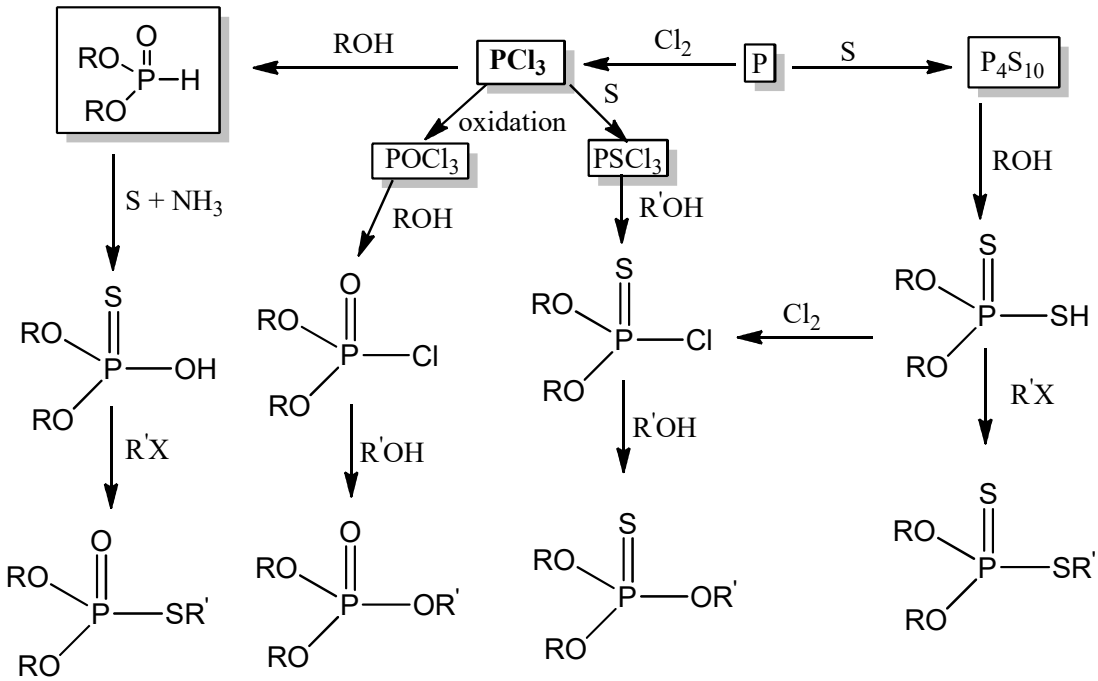
to be the most crucial sensitive towards hydrolysis and was hence called leaving group (Galli et al. 1988). There are numerous subclasses of OPs, viz. phosphorothioates, phosphoramidates, phosphonates, and others (Kurt 2004, Bader 2005). These organophosphorus compounds showed their primary application as insecticides after World War II and are still in use (Kumar et al. 2016).

Most phosphorus-based insecticides are not actual organophosphorus compounds, as these do not have direct P-C bonds. These compounds are esters, amides, anhydrides, and fluorides of phosphoric, phosphorothioic, and phosphorodithioic acids (Van der Oost et al. 2003). The primary classification of organophosphorus compounds is shown in Table 1. The application of these compounds as insecticides may be due to their facile synthetic routes. The synthesis of a few essential phosphorus organo-compounds and their intermediates used as insecticides is summarized in Scheme 1. Some commercially available organophosphates registered under Section 9(3) of the Insecticides Act, 1968, for use in the country are summarized in Table 2.

STRUCTURE-ACTIVITY RELATIONSHIPS (SAR)

The metabolic effect of Organophosphorus (OPs) insecticides was investigated between the 1950s and 1960s. The structures of OPs are related to their activity. These OPs have Oxon, i.e., P = O moiet, (e.g., dichlorvos, methamidophos, or the nerve agents sarin or soman), which is an effective inhibitor of acetylcholinesterase (Ginsberg et al. 2014). However, the maximum OPs used as insecticides are phosphorothioates and contain Thion, i.e., P=S moiety. The P=S bond needs bioactivation to form toxic oxygen analog axons to exert their harmful action. After bioactivation, OPs display their insecticidal properties via cytochrome P450 (CYPs) mediated oxidative desulfuration (Klaassen et al. 2013, ATSDR's Toxicological Profiles 2003). The formation of oxygen analogs is known as oxon during bioactivation primarily because of their toxicity. Other bioactivation, such as the formation of sulfone by cytochrome P450 (CYP) catalysis (Kurt 2004) or hydrolyticesterases (e.g., carboxylesterase, paraoxonase-1), results in metabolites with lesser or no toxicity (Bader 2005, Sakai & Matsumura 1971). The rest of the biotransformation reactions result in secondary intermediates with toxicity. Few of them are mediated by enzyme CYPs, and few esterases (e.g., paraoxonase, carboxylesterase) (Auf et al. 2007, Malina 2006).

It is mentioned in the literature that the conversion of organophosphorus esters involves metabolic enzymes like transferases, oxidase, hydrolases, etc. The sites for metabolic conversion on an OPs molecule are shown in (Fig. 3). The conversion of thion to oxon group is enzymatically mediated oxidative desulfuration, as shown in Fig. 4. This modification exemplifies intoxication because oxon analog is more potent for the inhibition of anticholinesterase. The conversion of the



Scheme 1: Synthesis of the essential types of phosphorus ester insecticides.

Table 2: Organophosphates registered under Section 9 (3) of the Insecticides Act, 1968, for use in the country as of 31 Dec. 2014. (adopted and modified from Kumar et al. 2016, Chambers et al. 2010).

Organophosphates	Trade Name	Molecular Formula
Acephate	Orthene	$C_4H_{10}NO_3PS$
Chlorpyrifos	Dursban, Lorsban	$C_{13}H_{19}ClNO_2PS_3$
Chlorpyrifos	Dursban, Lorsban	$C_9H_{11}Cl_3NO_3PS$
Chlorpyriphos-methyl	Reldan	$C_7H_7Cl_3NO_3PS$
Diazinon	Spectracide	$C_{12}H_{21}N_2O_3PS$
Dichlorvos	Vapona, DDVP	$C_4H_7Cl_2O_4P$
Dimethoate	Cygon, De-Fend	$C_5H_{12}NO_3PS_2$
Edifenphos	Hinosan, EDDP	$C_{14}H_{15}O_2PS_2$
Ethion	Ethanox, Ethiol, Hylemox, Nialate	$C_9H_{22}O_4P2S_4$
Ethoprop	Mocap 2	$C_8H_{19}O_2PS$
Fenamiphos	Nemacur	$C_{13}H_{22}NO_3PS$
Fenitrothion	Sumithion	$C_9H_{12}NO_5PS$
Fenthion	Baytex, Tiguvon	$C_{10}H_{15}O_3PS_2$
Iprobenfos	Vikita	$C_{13}H_{21}O_3PS$
Malathion	Carbophos, American Cyanamide 2	$C_{10}H_{19}O_6PS$
Monocrotophos	Wankophos P	$C_7H_{14}NO_5P$
Oxydemeton-methyl	Meta systox-R	$C_6H_{15}O_4PS_2$
Parathion-methyl	Zofos, Azaopho	$C_{10}H_{14}NO_5PS\text{-}CH_4$
Phenthoate	PAP	$C_{12}H_{17}O_4PS_2$
Phorate	Thimet	$C_7H_{17}O_2PS_3$
Phosalone	Zolonc	$C_{12}H_{15}ClNO_4PS_2$
Phosphamidon	Dimecron	$C_{10}H_{19}ClNO_5P$
Pirimiphos-methyl	Actellic	$C_{11}H_{20}N_3O_3PS$
Profenofos	Dyfonate	$C_{11}H_{15}BrClO_3PS$
Propetamphos	Blotic, Safrotin, and Seraphos	$C_{10}H_{20}NO_4PS$
Quinalphos	Chemidor, Chemolux	$C_{12}H_{15}N_2O_3PS$
Temophos	Abate	$C_{16}H_{20}O_6P_2S_3$
Terbufos	Counter, Contravene	$C_9H_{21}O_2PS_3$
Triazophos	Hostathion	$C_{12}H_{16}N_3O_3PS$
Trichlorfon	Dylox, Neguvon	$C_4H_8Cl_3O_4P$

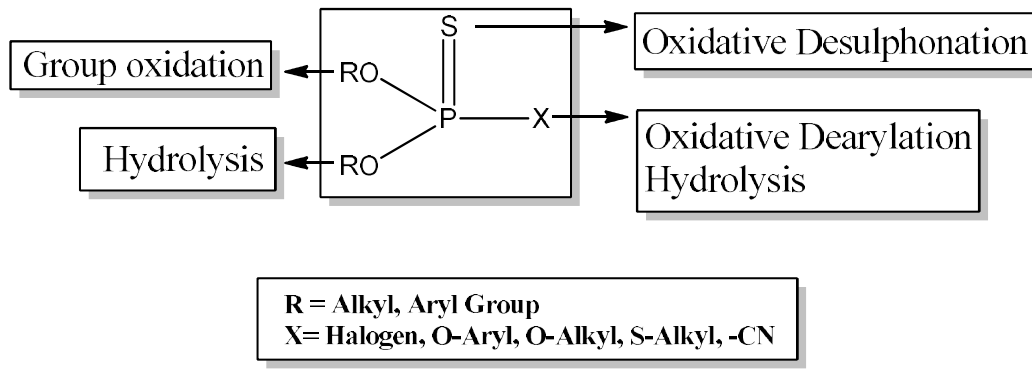


Fig. 3: Metabolic conversion sites in organophosphorus esters.

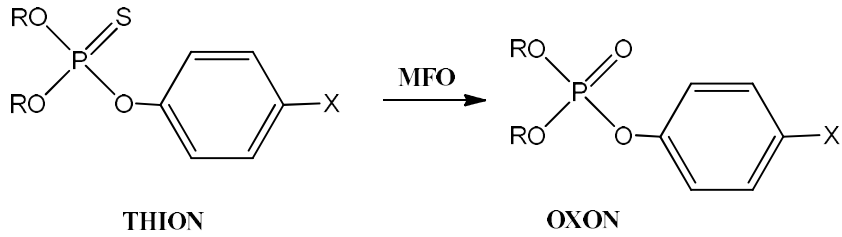


Fig. 4: Parathion: metabolic conversion activation.

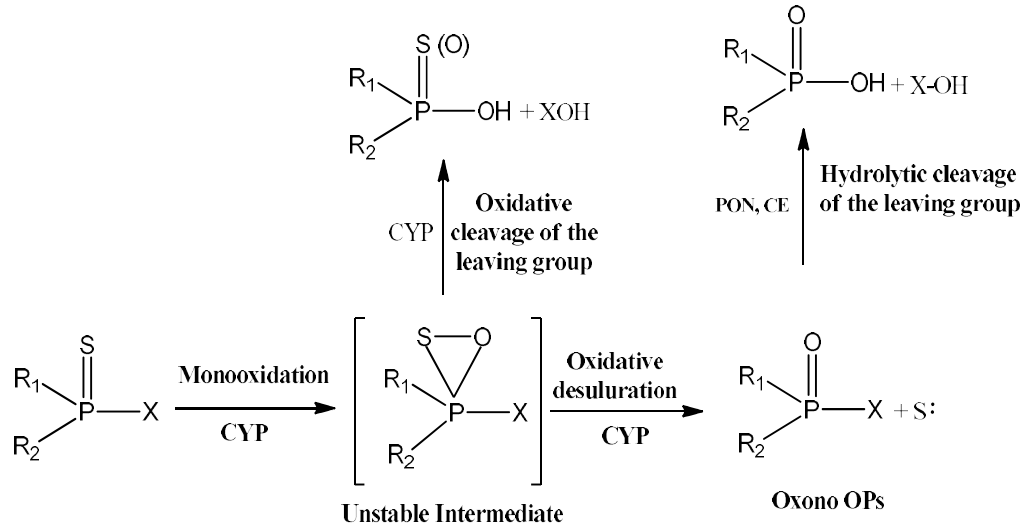


Fig. 5: Reaction of phase I OP metabolism. CYP, cytochrome P_{450}, PON, paraoxonase CE, carboxylesterase (Adapted from Hrejac 2009).

thion group to the oxon group has already been observed in mammals as well as in insects (News Agencies Monopolies 1900).

METABOLISM MECHANISM OF OPs

The OP compounds are more readily absorbed in the living system leading to easy metabolism and excretion (Toxicology of Organophosphate and Carbamate Compounds, 2011). Similarly, to other xenobiotics, OPs metabolism occurs mainly in the liver and, to a lesser extent, in the lungs and intestines. Two phases of the pathway are suggested for the chemical metabolism of OPs. In phase I, the metabolic enzymes activate the OPs by functional group introduction (Maxwell et al. 1992). Phase I of OP metabolism involves oxidation and hydrolysis (Fig. 5). In phase II reactions, enzymes get attached to various hydrophilic groups, like glucuronic acid, sulfate, glycine, and glutamic acid, enabling excretion of the metabolite from the organism Metabolism of includes initial activation via oxidation followed by hydrolysis of activated metabolites (Ziegler et al. 1964).

Oxidation is the most critical reaction in activating the OP thion, leading to the formation of oxons which are active inhibitors of AchE. The sulfur atom in the thion binds to oxygen in the presence of cytochrome P_{450} enzymes (CYP). This results in I formation of an unstable intermediate via oxidative desulphuration. These activated intermediates are strong inhibitors of AChE, responsible for the neurotoxic effects of OPs (Colovic et al. 2013). The influence of the active sulfur atom, as this reaction's side product, is still unclear. It may also interact with neighboring proteins, inactivating cytochrome P_{450} (CYP) enzymes.

The reaction is responsible for the detoxification of OPs. OPs' paraoxonase cleaves dialkyl phosphate and (X) leaving group present on OP molecule. OPs can also be hydrolyzed by the enzyme carboxylesterase. This enzyme is different from paraoxonase in one factor: self-inactivation upon hydrolysis. Metabolism occurs in two phases. In phase I, initially, oxidative desulphuration and then hydrolysis occurs. This is followed by dealkylation or removal of leaving the group (Moser & Padilla, 2011, Grlić 1988). The process involves the intermediate formed with cytochrome P450(CYP), which

ends with a desulphurization reaction. Thus, detoxification involves desulphuration leading to activation of OPs, and then oxidation resulting in cleavage of leaving group equilibrium between desulfuration and oxidative cleavage reactions is responsible for the toxicity of OPs. In phase II metabolism, the reaction results in detoxification and excretion. The oxidation results in the hydrophilic compound, which can conjugate in phase II metabolism via enzymatic catalysis and, finally, excretion (Sogorb et al. 2008). OPs hydrolytic detoxification by phosphotriesterases is also known with a precise mechanism. The enzyme cleaves the bond between P–X of OPs (X is the leaving group), resulting in more polar and less toxic metabolites Enzyme phosphotriesterases are found in mammals, marine animals, birds, bacteria, etc. The serum and liver of mammals have shown a high level of detoxication of OPs by the enzyme (Vilanova & Sogorb 1999, Royo et al. 2007).

TOXICOLOGY OF ORGANOPHOSPHORUS COMPOUNDS

OPs toxicity includes acute toxicity, neurotoxicity, inhibition of the enzyme AChE, etc., resulting in depression, suicide, and fatality. The toxicity of OPs is related to their molecular structure, concentration, application, decomposition, ingestion, metabolism, excretion, etc. (Camacho et al. 2022). Organophosphorus (OPs) insecticides have high acute toxicity. Organophosphates have toxic effects on insects and other animals, including birds, amphibians, and mammals. For simplicity toxicity of OPs can be studied as (i) neural effects (Neurotoxicity), (ii) non-neuronal effects, and (iii) e toxicity.

Neurotoxicity

Two major factors, (a) AChE and (b) paraoxonase (PON1) activity levels in interaction with OPs, are responsible for their toxicity.

Acetylcholinesterase (AChE) inhibition: The primary reason for OPs toxicity is enzyme AChE inhibition, which hydro (Karalliedde 2001) lyses neurotransmitter acetylcholine in nervous systems. The hydrolytic degradation of AChE occurs in synaptic membranes producing choline and acetate from acetylcholine. OP cholinesterase inhibitors stop the functioning of acetylcholinesterase, leading to excessive accumulation of acetylcholine in the synaptic cleft (Fig. 6 & 7). OP compounds generally form covalent bonds between OP and the active site of AChE thus, inhibiting its functioning. Hydrolysis of OP from the active site is irreversible and slow, thus leading to long-term effects. Novel OPs are altered to accelerate spontaneous hydrolysis of the OP-AChE complex. This causes neurotoxicity and neuro-muscular paralysis (Camacho et al. 2022).

AChE inhibition causes acetylcholine accumulation at cholinergic synapses, thereby overstimulating cholinergic receptors, resulting in a "cholinergic syndrome," which includes excessive salivation, sweating, tremors, bronchial secretion, gastrointestinal motility, diarrhea, muscular

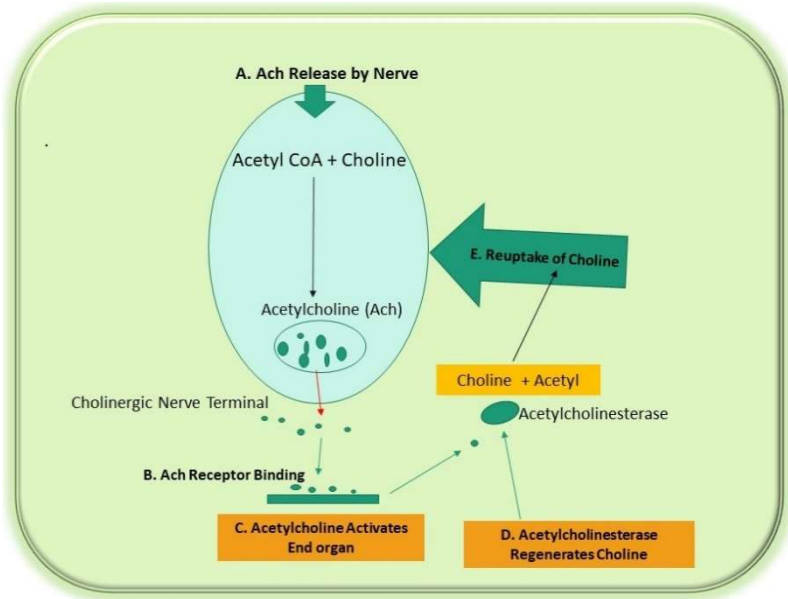


Fig. 6: Normal function of AChE esterase.

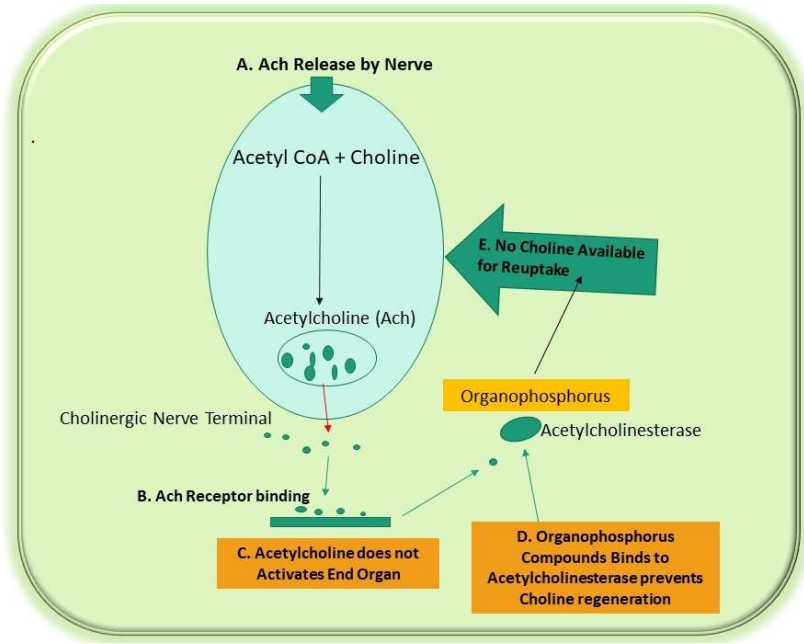


Fig. 7: AChE Esterase breaking down AChE.

twitching, etc., finally death due to respiratory failure caused by inhibition of respiratory centers in the brainstem (WHO 2006, La Du et al. 1999).

Hydrolysis of phosphorylated AChE is slow, but oximes may help accelerate the process. However, oximes may be unable to reactivate phosphorylated AChE on aging (loss of one alkyl group by nonenzymatic hydrolysis), resulting in irreversibly inhibiting enzymes. Atropine is an antidote for poisoning caused by OP and prevents the accumulation of acetylcholine on these receptors. Pralidoxime shows its application in treating OP poisoning. Diazepam is also an anti-anxiety or antagonize convulsions agent for OP toxicity (La Du et al. 1999). Prolonged cholinergic stimulation by OPs also causes acute OP poisoning (Herńandez et al. 2003), developing intermediate syndrome after a few days of exposure leading to symptoms such as marked weakness of muscles in the limb respiratory system and neck (La Du et al. 1999). Long-term CNS effects of high doses of OPs in animals and humans due to neurotoxicity (Costa et al. 2013, Ellison et al. 2012, Needham et al. 2005).

In contrast, low, chronic exposure to OPs does not result in significant neuropsychological effects, neuropsychiatric problems, or nerve dysfunction (Hoppin et al. 2006, Menini & Gugliucci 2014, Hodgson & Rose 2006, Simcox et al. 1995, Gordon et al. 1999). Young animals and children are reported to have a greater sensitivity towards acute toxicity of OPs which may be due to their low detoxication abilities (Needham et al. 2005). However, young animals show greater resistance toward delayed organophosphate-induced polyneuropathy. Pre- and/or post-natal exposure also results in the accumulation of OPs, thus causing neurotoxicity. OPs inhibit DNA replication, and neuronal survival, alter non-cholinergic processes, and enhance oxidative stress and other abnormalities (Ellison et al. 2012, Needham et al. 2005, Berlin & Yodaiken 1984, NRC 2006, La Du et al. 1999, Costa 2018, Hamblin 1960). Malathion shows a broad range against sucking and chewing insects but is less toxic to warm-blooded animals (Odinets 1971). Malathion is metabolized by its enzymatic oxidation of tomalaoxon, thus increasing the toxicity values. In the first step, hydrolysis of ester bonds by enzyme malathionase results in formation of monocarbonic acid, which is non-toxic for warm-blooded animals (Storm et al. 2000). The O,O-Dimethyl-S-(N-2-chlorophenyl-butyramido) methyl phosphorodithioate also found to be effective against many phytophagous insects (Costa et al. 2013).

Paraoxonase (PON1): The active metabolites of compounds such as diazinon, chlorpyrifos, and parathion may be hydrolyzed by Paraoxonase (PON1), a polymorphic enzyme. PON1 is produced in the liver and transported to plasma along with high-density lipoprotein (Menini & Gugliucc 2014, Hodsgon et al. 2006, Ellison et al. 2012, Hofmann et al. 2009, Hodgson & Rose 2006). Herńandez et al. (2003) reported decreased PON1 – 909 G/C polymorphism activity on longer exposure to OPs pesticides (Costa et al. 2013). Ellison et al. demonstrated PON1 activity influenced by PON1 55

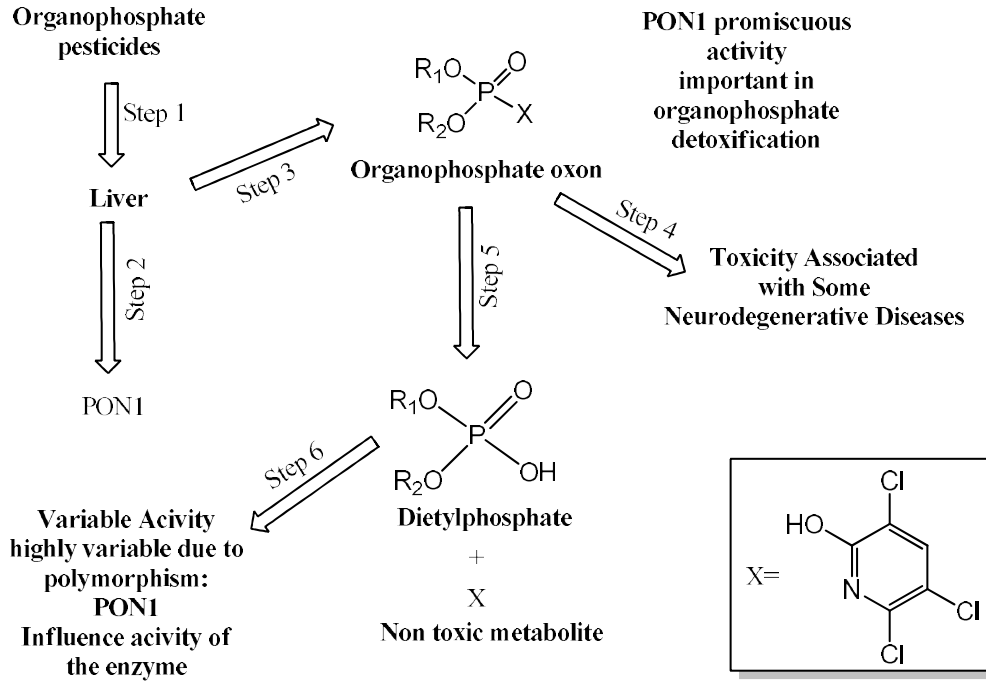


Fig. 8: Role of PON1 in Organophosphate metabolism.

and PON1 192 genotypes in agricultural workers in Egypt (Needham et al. 2005). The agricultural pesticide handlers in Washington State were studied, and it was found that lower plasma levels of PON1 activity show greater BuChE inhibition (Hodgson et al. 2006). Costa et al. (2013) found PON1 to be a crucial factor in diazinon and chlorpyrifosoxon toxicity in rats and mice (Ellison et al. 2012, Needham et al. 2005, Hoppin et al. 2006, Menini & Gugliucc 2014, Hodgson & Rose 2006, Simcox et al. 1995). (Fig. 8).

Non-Neuronal Molecular Effects of OPs

The non-neuronal effects of OP exposure on humans are little known (Naughton & Terry Jr. 2018, Quistad et al. 2006). A report revealed several non-neuronal tissues, upon exposure to OPs, may disturb biological processes such as carboxylase inhibition by blocking chemical transformation (Simcox et al. 1995). Xenobiotic metabolism disturbance and cytochrome P450 enzyme (CYP) inhibition by active sulfur during desulphuration (phase I metabolism) is also reported (Bomser et al. 2002). OPs also inhibit enzyme lipases and protein kinase (PKC), which are vital in cell signaling (Oral et al. 2006, Mostafalou & Abdollahi 2013). OP-induced generation of reactive oxygen species leading to oxidative stress and thus resulting apoptosis in tissues is also known, which inhibits steroid androgen (AR) receptors resulting in hormones in the organism (Than et al. 2013).

Chronic Effects

The toxicity of OPs at high levels may lead to cancer, cardiovascular diseases, Alzheimer's disease, congenital disabilities, reproductive disorders, Parkinson's disease, diabetes, nephropathies, chronic respiratory problems, etc. (Singh & Sharma 2000). Organophosphate exposure at certain levels leads to COPIND, i.e., chronic organophosphate-induced neuropsychiatric disorders such as hyperactivity disorder, confusion, and neurobehavioral changes (Savage et al. 1988) resulting in respiratory and cardiac diseases (Kumari. et al. 2008). The very high-level exposure may even be fatal (Kojima et al. 2004). Table 3 summarizes the WHO-recommended classifications (Galli et al. 1988) of organophosphates by a hazard registered in India (2009).

OPs CONTAMINATION IN THE ENVIRONMENT

OPs compounds initially replaced fewer organochlorines due to their less stable nature. Later their uncontrollable widespread became a major environmental threat, depicted in Fig. 9.

A lot of literature is available that reports the environmental contamination, particularly sediments, soil, and water, such as contamination of sediments by phorate, malathion, etc., in Tarnadmund, Nedugula, and Bison swamp wetlands of Nilgiris district (Chambers et al. 2010, Kaushik 2022, Bishnu

Table 3: Organophosphates by a hazard which are registered in India.

Highly Toxic		Moderately Toxic	
Organophosphates	Trade Name	Organophosphates	Trade Name
Azinphos-methyl	Guthion, Gusathion	Acephate	Orthene
Bomyl	Swat	Bensulide	Betasan, Prefar
Carbophenothion	Trithion	Bromophos-ethyl	Nexagan
Coumaphos	Co-Ral, Asuntol	Bromophos	Nexion
Chlorfenvinphos	Apachlor, Birlane	Chlorphoxim	Baythion-C
Chlormephos	Dotan	Chlorpyrifos	Dursban, Lorsban, Brodan
Chlorthiophos	Celathion	Crotoxyphos	Ciodrin, Cypona
Coumaphos	Co-Ral, Asuntol	Crufomate	Ruelene
Cenophosphon	Trichloronate, Agritox	Cyanophos	Cyanox
Cyanofenphos	Surecide	Cythioate	Proban, Cyflee
Demeton	Syntox	DEF	De-Green, E-Z-Off D)
Dalifor	Torak	Demeton-S-methyl	Duratox, Metasystox-R
Dicrotophos	Bidrin	Diazinon	Spectracide
Dimefos	Hanane, Pestox XIV	Dichlofenthion	VC-13 Nemacide
Dioxathion	Delnav	Dichlorvos	DDVP, Vapona
Disulfoton	Disyston	Edifenphos	
Endothion	EPN	EPBP	S-Seven
Ethyl parathion	E605, Parathion, Thiophos	Ethion	Ethanox
Famphur	Famfos, Bo-Ana, Bash	Ethoprop	Mocap
Fenamiphos	Nemacur	Etrimfos	Ekamet
Fensulfothion	Dasanit	Fenitrothion	Accothion, Agrothion, Sumithion
Fonofos	Dyfonate, N-2790	Fenthion	mercaptophos,Entex, Baytex, Tiguvon
Fosthietan	Nem-A-Tak	Formothion	Anthio
Isofenphos	Amaze, Oftanol	Heptenophos	Hostaquick
Mephosfolan	Cytrolane	IBP	Kitazin
Methamidophos	Monitor	Iodofenphos	Nuvanol-N
Methidathion	Supracide, Ultracide	Isoxathion	E-48, Karphos
Methyl parathion	E601,Penncap-M	Leptophos	Phosvel
Mevinphos	Phosdrin, Duraphos	Malathion	Cythion
Mipafox	Isopestox, Pestox XV	Merphos	Folex, Easy Off-D
Monocrotophos	Azodrin	Methyl trithiondimethoate	Cygon, DeFend
Phorate	Thimet, Rampart, AASTAR	Naled	Dibrom
Phosfolan	Cyolane, Cylan	Oxydemeton-methyl	Metasystox-R
Phosphamidon	Dimecron	Oxydeprofos	Metasystox-S
Prothoate	Fac	Propyl thiopyrophosphate	Aspon
Schradan	OMPA	Phenthoate	Dimephenthoate, Phenthoate
Sulfotep	Thiotepp, Bladafum, Dithione	Phosalone	Zolone
Terbufos	Counter, Contraven	Phosmet	Imidan, Prolate
Tetraethyl pyrophosphate	TEPP	Propetamphos	Safrotin

et al. 2009), as well as detection of ethion and chlorpyrifos in tea fields' soils sample of West Bengal and South India (Bishnu et al. 2012, Sreenivasan & Muraleedharan 2011, Jacob et al. 2014) and also contamination of cardamom field of Idukki district, Kerala by chlorpyriphos, ethion, and quinalphos (Jacob et al. 2014, Mathur & Tannan 1999).

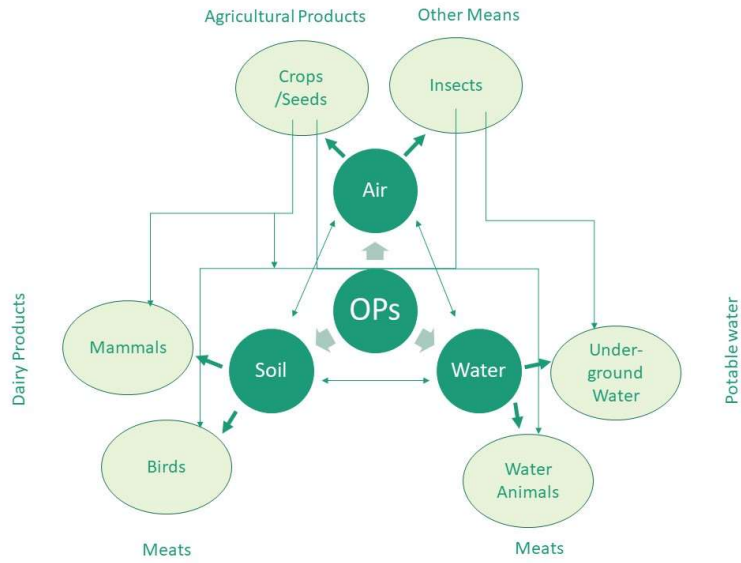


Fig. 9: Routes of exposure of humans to organophosphates (OPs).

The organophosphates are also causing water pollution due to pesticide usage in crop production of vegetables, cotton, and horticultural crops (Pujeri et al. 2008, Bhanti & Taneja 2007, Kumari et al. 2005). Agricultural products such as vegetables, fruits, tea, sugars, etc., are contaminated OPs, including big brands like Tata, Hindustan Unilever, Wagh Bakri, etc. OPs like methyl parathion, chlorpyriphos, and malathion vegetable contamination have been reported at a low level in northern India. However, long-term usage may lead to bioaccumulation may become fatal at a later stage (Lushchak et al. 2018, Leska et al. 2021, Choudhary & Sharma 2008). The presence of organophosphates residues such as malathion and chlorpyriphos residues have also been detected in other food products like butter, honey, cold drinks, etc. (CSE 2006, 2005, Sanghi et al. 2005, Srivastava et al. 2008), indicating the accumulation of these chemicals in living beings. Although OPs are degradable and thus lead to lesser bioaccumulation residues, however, these have been detected in human urine, blood, semen, breast milk, animal milk, etc. (Bajwa & Sandhu 2014, Tamaro et al. 2018, Li et al. 2020, Huen et al. 2012, Ibigbami et al. 2019, Pirsaheb et al. 2015, Lakshmi et al. 2020, Akter et al. 2020) as well as fishes and aquatic animals (Sandoval-Herrera et al. 2019, Ross et al. 2010).

EVIDENCE FOR PSYCHOLOGICAL EFFECTS OF ORGANOPHOSPHATE COMPOUNDS

Organophosphorus compounds (OPs) are used exclusively for agricultural, industrial, and domestic purposes worldwide; therefore, developing countries correspond to public health issues. Approximately 3 million poisonings and more than 200,000 deaths occur yearly due to OP compounds. The issue of mental health is a major public health concern worldwide. 970 people worldwide are affected by mental disorders such as depression and anxiety. OP inhibits acetylcholinesterase activity and gives rise to neuropsychiatric disorders along with adverse health issues (Sandoval-Herrera et al. 2019, Harrison & Ross 2016). In addition, several studies revealed eminent depression links and associated anxiety with exposure to organochlorines, organophosphates, carbamates, pyrethroids, and herbicides like phenoxy and paraquat dichloride. After 24 h of application of OP, the most common symptoms experienced were headache, dizziness, excessive sweating, fatigue/tiredness, and skin irritation. Individuals exposed earlier are more prone to increased risk of psychiatric disorders (Koh et al. 2017, Keifer et al. 1997). Limited studies on chronic exposure to OP believe psychological dysfunction is a possible effect. Short–term memory, learning, eye-hand coordination, and reaction time in simple and complex reactions are frequently examined. The peripheral nervous system (PNS) effects of OP, which occur by inhibiting cholinesterase, include paresthesias, weakness, foot and wrist drop, and paralysis. Peripheral Neuropathy related to OP was named organophosphate-induced delayed polyneuropathy (OPIDP). It takes 2 to 5 weeks for OPIDP development after exposure to OP. Neuropathy target esterase enzyme obstruction seems to be the biochemical mechanism of the OP that caused OPIDP. The acute central nervous system (CNS) effects of OP included concentration, vigilance, memory, information

processing, psychomotor speed, language impairment, anxiety, irritability, and depression. Cognitive impairment and personality changes are the generalized changes observed in individuals exposed to OP (Keifer et al. 1997).

CONCLUSIONS

Organophosphorus compounds (OPs) are phosphoric acid derivatives represented by the formula ($R_2XP=O/S$), R as organic groups; however, they need not contain a direct carbon-phosphorus bond. The organophosphorus compounds can be categorized into three classes: organophosphates and carbamates nerve agents. Most OPs used as insecticides are phosphorothioates (i.e., they have a P=S bond) and need to be bioactivated in vivo to their oxygen analogs to exert their toxic action. These compounds are esters, amides, anhydrides, and fluorides of phosphoric, phosphorothioate, and phosphorodithioic acids.

The toxicity of OPs is related to their molecular structure, concentration, application, decomposition, ingestion, metabolism, excretion, etc. Organophosphorus (OPs) insecticides have high acute toxicity. Organophosphates have toxic effects on insects and other animals, including birds, amphibians, and mammals. For simplicity toxicity of OPs can be studied as neural effects, non-neuronal effects, and acute toxicity. The primary reason for OPs toxicity is enzyme AchE inhibition, which hydrolyses neurotransmitter acetylcholine in nervous systems. Potential secondary targets and harmful effects outside the nerve system are also reported. Organophosphates poison insects and other animals, including birds, amphibians, and mammals. These chemicals can have neurotoxicity, non-neuronal effects, or acute toxicity, which may also result in fatality. Their uncontrollable widespread became a major threat to the environment, and thus corrective measures have been an essential requirement to save living beings and the environment from further damage.

REFERENCES

Akhtar, W., Sengupta, D. and Chowdhury, A. 2009. Impact of pesticides use in agriculture: Their benefits and hazards. Interdisc. Toxicol., 2(1): 1-12. https://doi.org/10.2478/v10102-009-0001-7

Akter, R., Pervin, M. A., Jahan, H., Rakhi, S. F., Reza, A. H. M. and Hossain, Z. 2020. Toxic effects of an organophosphate pesticide, envoy 50 SC on the histopathological, hematological, and brain acetylcholinesterase activities in stinging catfish (Heteropneustes fossilis). J. Basic Appl. Zool., 81(1): 1-14.

ATSDR's toxicological profiles (Web version). 2003. CRC Press.

Auf der Heide, E. 2007. Cholinesterase inhibitors; including pesticides and chemical warfare nerve agents. Agency for Toxic Substances and Disease Registry.

Bader, R.F.W. 2005. Erratum to "complementarity of QTAIM and MO theory. Coord. Chem. Rev., 249(24): 3198. https://doi.org/10.1016/j.ccr.2005.05.004

Bajwa, U. and Sandhu, K. S. 2014. Effect of handling and processing on pesticide residues in food-a review. J. Food Sci. Technol., 51: 201-220.

Berlin, A.R. and Yodaiken, B. 1984. Assessment of toxic agents at the workplace. Role of ambient and biological monitoring. In: Proceedings of NIOSH-OSHA-CEC Seminar, Luxembourg, December 1980.

Bhanti, M. and Taneja, A. 2007. Contamination of vegetables of different seasons with organophosphorous pesticides and related health risk assessment in northern India. Chemosphere, 69(1): 63-68.

Bishnu, A., Chakrabarti, K., Chakraborty, A. and Saha, T. 2009. Pesticide residue level in tea ecosystems of Hill and Dooars regions of West Bengal, India. Environ. Monit. Assess., 149: 457-464.

Bishnu, A., Chakraborty, A., Chakrabarti, K. and Saha, T. 2012. Ethion degradation and its correlation with microbial and biochemical parameters of tea soils. Biol. Fert. Soils, 48: 19-29.

Bomser, J. A., Quistad, G. B. and Casida, J. E. 2002. Chlorpyrifos oxon potentiates diacylglycerol-induced extracellular signal-regulated kinase (ERK 44/42) activation, possibly by diacylglycerol lipase inhibition. Toxicol. Appl. Pharmacol., 178(1): 29-36.

Camacho-Pérez, M.R., Covantes-Rosales, C.E., Toledo-Ibarra, G.A., Mercado-Salgado, U., Ponce-Regalado, M.D., Díaz-Resendiz, K.J.G. and Girón-Pérez, M.I. 2022. Organophosphorus pesticides as modulating substances of inflammation through the cholinergic pathway. International Journal of Molecular Sciences, 23(9), 4523.

Chambers, J.E., Meek, E.C. and Chambers, H.W. 2010. The metabolism of organophosphorus insecticides. In Testai, E., Buratti, F.M. and Di Consiglio, E (eds), Hayes' Handbook of Pesticide Toxicology, Academic Press, Cambridge, MA, pp. 1407-1399.

Choudhary, A. and Sharma, D.C. 2008. Pesticide residues in honey samples from Himachal Pradesh (India). Bulletin of Environmental Contamination and Toxicology, 80(5), 417-422.

Colovic, M.B., Krstic, D.Z., Lazarevic-Pasti, T.D., Bondzic, A.M. and Vasic, V.M. 2013. Acetylcholinesterase inhibitors: pharmacology and toxicology. Current neuropharmacology, 11(3), 315-335.

Costa, L.G. 2018. Organophosphorus compounds at 80: Some old and new issues. Toxicol. Sci., 162(1): 24-35.

Costa, L.G., Giordano, G., Cole, T.B., Marsillach, J. and Furlong, C.E. 2013. Paraoxonase 1 (PON1) is a genetic determinant of susceptibility to organophosphate toxicity. Toxicology, 307: 115-122.

CSE Report 2005. Analysis of pesticide residues in blood samples from Villages of Punjab, CSE/PML/PR-21/2005. https://cdn.cseindia.org/userfiles/Punjab_blood_report.pdf

CSE Report 2006. August analysis of pesticide residues in soft drinks. http://www.indiaenvironmentportal.org.in/files/labreport2006.pdf

Ellison, C.A., Crane, A.L., Bonner, M.R., Knaak, J.B., Browne, R.W., Lein, P.J. and Olson, J.R. 2012. PON1 status does not influence cholinesterase activity in Egyptian agricultural workers exposed to chlorpyrifos. Toxicol. Appl. Pharmacol., 265(3): 308-315.

Galli, C.L., Manzo, L. and Spencer, P.S. (Eds.). 1988. Recent Advances in Nervous System Toxicology. Springer, US. https://doi.org/10.1007/978-1-4613-0887-4

Ginsberg, G., Sonawane, B., Nath, R. and Lewandowski, P. 2014. Methylmercury-induced inhibition of paraoxonase-1 (Pon1)-Implications for cardiovascular risk. Journal of Toxicology and Environmental Health, Part A, 77(17): 1004-1023. https://doi.org/10.1080/15287394.2014.919837

Gordon, S.M., Callahan, P.J., Nishioka, M.G., Brinkman, M.C., O'Rourke, M.K., Lebowitz, M.D. and Moschandreas, D.J. 1999. Residential environmental measurements in the national human exposure assessment survey (NHEXAS) pilot study in Arizona: Preliminary results for pesticides and VOCs. J. Expo. Sci. Environ. Epidemiol., 9(5): 456-470.

Grlić, L. 1988. A small chemical lexicon. Zagreb: Forward, 198 p.

Hamblin, D.O. 1960. Some phosphate ester insecticides are of lesser toxicity for man. J. Occup. Med., 2(5): 211-213.

Harrison, V. and Ross, S.M. 2016. Anxiety and depression following cumulative low-level exposure to organophosphate pesticides. Environ. Res., 151: 528-536.

Herńandez, A.F., Mackness, B., Rodrigo, L., López, O., Pla, A., Gil, F. and Mackness, M.I. 2003. Paraoxonase activity and genetic polymorphisms in greenhouse workers with long-term pesticide exposure. Hum. Exp. Toxicol., 22(11): 565-574.

Hodgson, E. and Rose, R.L. 2006. Organophosphorus chemicals: potent inhibitors of the human metabolism of steroid hormones and xenobiotics. Drug metabolism reviews, 38(1-2), 149-162.

Hofmann, J.N., Keifer, M.C., Furlong, C.E., De Roos, A.J., Farin, F.M., Fenske, R.A. and Checkoway, H. 2009. Serum cholinesterase inhibition in relation to paraoxonase-1 (PON1) status among organophosphate-exposed agricultural pesticide handlers. Environ. Health Persp., 117(9): 1402-1408.

Hoppin, J.A., Adgate, J.L., Eberhart, M., Nishioka, M. and Ryan, P.B. 2006. Environmental exposure assessment of pesticides in farmworker homes. Environmental Health Perspectives, 114(6), 929-935.

Hrejac, I. 2009. Genotoxic, cogenotoxic and potential carcinogenic activity of model organphosphorous pesticides. University of Ljubljana, Ljubljan Slovenia 2009.

Huen, K., Bradman, A., Harley, K., Yousefi, P., Barr, D.B., Eskenazi, B. and Holland, N. 2012. Organophosphate pesticide levels in blood and urine of women and newborns living in an agricultural community. Environ. Res., 117: 8-16.

Ibigbami, O.A., Aiyesanmi, A.F., Adesina, A.J. and Popoola, O.K. 2019. Occurrence and levels of chlorinated pesticides residues in cow milk: A human health risk assessment. J. Agric. Chem. Environ., 8(01): 58.

Inter-Organization Programme for the Sound Management of Chemicals (IOMC) & World Health Organization (WHO). 2010. WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009. World Health Organization, Geneva, Switzerland.

Jacob, S., Resmi, G. and Mathew, P.K. 2014. Environmental pollution due to pesticide application in cardamom hills of Idukki, District, Kerala, India. Int. J. Basic. Appl. Res., 1: 27-34.

Jayasinghe, S. S., Pathirana, K. D. and Buckley, N. A. 2012. Effects of acute organophosphorus poisoning on the function of peripheral nerves: a cohort study. PloS ONE, 7(11): e49405. https://doi.org/10.1371/journal.pone.0049405

Karalliedde, L. (ed.). 2001. Organophosphates and health. World Scientific Pub. Co., India.

Kaushik, G. 2022. A review on phorate persistence, toxicity and remediation by bacterial communities. Pedosphere, 32(1): 171-183.

Keifer, M.C. and Mahurin, R.K. 1997. Chronic neurologic effects of pesticide overexposure. Occup. Med., 12(2): 291-304.

Khalid, M., Rasul, S., Hussain, J., Ahmad, R., Zia, A., Bilal, M., Pervez, A. and Naqvi, T.A. 2016. Biodegradation of organophosphorus insecticides, chlorpyrifos, by *Pseudomonas putida* CP-1. Pakistan Journal of Zoology, 48(5).

Klaassen, C.D., Casarett, L.J. and Doull, J. (eds). 2013. Casarett and Doull's Toxicology: The Basic Science of Poisons. Eight Edition. McGraw-Hill Education, NY.

Koh, S.B., Kim, T.H., Min, S., Lee, K., Kang, D.R. and Choi, J.R. 2017. Exposure to pesticide as a risk factor for depression: A population-based longitudinal study in Korea. Neurotoxicology, 62: 181-185.

Kojima, H., Katsura, E., Takeuchi, S., Niiyama, K. and Kobayashi, K. 2004. Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro reporter gene assays using Chinese hamster ovary cells. Environmental health perspectives, 112(5), 524-531.

Kumar, S., Kaushik, G. and Villarreal-Chiu, J.F. 2016. Scenario of organophosphate pollution and toxicity in India: A review. Environ. Sci. Pollut. Res., 23: 9480-9491.

Kumari, B., Madan, V.K. and Kathpal, T.S. 2008. Status of insecticide contamination of soil and water in Haryana, India. Environmental monitoring and assessment, 136, 239-244.

Kumari, B., Singh, J., Singh, S. and Kathpal, T.S. 2005. Monitoring of butter and ghee (clarified butter fat) for pesticidal contamination from a cotton belt of Haryana, India. Environ. Monit. Assess., 105: 111-120.

Kurt, T.L. 2004. A Textbook of Modern Toxicology, E. Hodgson (ed), Wiley-Interscience, John Wiley & Sons, Hoboken, NJ. p. 557.

La Du, B.N., Aviram, M., Billecke, S., Navab, M., Primo-Parmo, S., Sorenson, R.C. and Standiford, T.J. 1999. On the physiological role (s) of the paraoxonases. Chem. Biol. Interac., 119: 379-388.

Lakshmi, J., Mukhopadhyay, K., Ramaswamy, P. and Mahadevan, S. 2020. A systematic review on organophosphate pesticide and type II diabetes mellitus. Current Diabetes Rev., 16(6): 586-597.

Lange, W. and Krueger, G. 1932. About esters of monofluorophosphoric acid. Rep. German Chem. Soc., A B Ser., 65(9): 1598-1601.

Lassaigne, I. L. 1820. Ann. Chimie. Physique., 13, Strie. 2, 294

Leska, A., Nowak, A., Nowak, I. and Górczyńska, A. 2021. Effects of insecticides and microbiological contaminants on Apis mellifera health. Molecules, 26(16): 5080.

Li, A. J., Banjabi, A. A., Takazawa, M., Kumosani, T. A., Yousef, J. M. and Kannan, K. 2020. Serum concentrations of pesticides, including organophosphates, pyrethroids, and neonicotinoids in a population with osteoarthritis in Saudi Arabia. Sci. Total Environ., 737: 139706.

Lushchak, V. I., Matviishyn, T. M., Husak, V. V., Storey, J. M. and Storey, K. B. 2018. Pesticide toxicity: a mechanistic approach. EXCLI J., 17: 1101.

Malina, D. 2006. Book review narrative medicine: Honoring the stories of illness by rita charon. Oxford University Press, NY, p. 256

Masson, P. and Nachon, F. 2017. Cholinesterase reactivators and bioscavengers for pre‐and post‐exposure treatments of organophosphorus poisoning. J. Neurochem., 142: 26-40.

Mathur, S.C. and Tannan, S.K. 1999. Future of Indian pesticides industry in next millennium. Pesticide information, 24(4), 9-23.

Maxwell, D.M. 1992. The specificity of carboxylesterase protection against the toxicity of organophosphorus compounds. Toxicol. Appl. Pharmacol., 114(2): 306-312. https://doi.org/10.1016/0041-008X(92)90082-4

Menini, T. and Gugliucci, A. 2014. Paraoxonase 1 in neurological disorders. Redox Report, 19(2): 49-58. https://doi.org/10.1179/1351000213Y.0000000071

Michselis, A. and Becker, T. 1897. Ueber die Constitution der phosphorigen Säure. Berichte der deutschen chemischen Gesellschaft, 30(1): 1003-1009.

Miodovnik, A., 2019. Prenatal exposure to industrial chemicals and pesticides and effects on neurodevelopment. Encyclopedia of Environmental Health, pp. 352-342, Elsevier.

Moser, V.C. and Padilla, S. 2011. Esterase metabolism of cholinesterase inhibitors using rat liver in vitro. Toxicology, 281(1–3): 56-62. https://doi.org/10.1016/j.tox.2011.01.002

Mostafalou, S. and Abdollahi, M. 2013. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicology and applied pharmacology, 268(2), 157-177.

National Research Council (NRC). 2006. Human biomonitoring for environmental chemicals. National Academies Press, NY.

Naughton, S.X. and Terry Jr, A. V. 2018. Neurotoxicity in acute and repeated organophosphate exposure. Toxicology, 408: 101-112.

Needham, L.L., Özkaynak, H., Whyatt, R.M., Barr, D.B., Wang, R.Y., Naeher, L. and Zartarian, V. 2005. Exposure assessment in the National Children's Study: introduction. Environ. Health Persp., 113(8): 1076-1082.

News Agencies. Monopolies. Inter-ocean publishing co. V. Associated press, 56 n. E. 822(Ill.). 1900. The Yale Law Journal, 9(8), 376. https://doi.org/10.2307/782184

Odinets, A.A. 1971. Toxicity of malathion for warm-blooded

animals: A review of the literature. Farmakol. Toksikol., 34(1): 113-116.
Oral, B., Guney, M., Demirin, H., Ozguner, M., Giray, S.G., Take, G. and Altuntas, I. 2006. Endometrial damage and apoptosis in rats induced by dichlorvos and the ameliorating effect of antioxidant vitamins E and C. Reprod. Toxicol., 22(4): 783-790.
Petroianu, G. 2015. History of organophosphorus cholinesterase inhibitors & reactivators. Milit. Med. Sci. Lett., 84(4): 182-185.
Pirsaheb, M., Limoee, M., Namdari, F. and Khamutian, R. 2015. Organochlorine pesticides residue in breast milk: a systematic review. Med. J. Islamic Rep. Iran., 29: 228.
Pujeri, U.S., Pujar, A.S., Hiremath, S.C. and Yadawe, M.S. 2008. The status of pesticide pollution in surface water (lakes) of Bijapur. Int. J. Appl. Biol. Pharm. Technol. 1,436-441.
Quistad, G. B., Liang, S. N., Fisher, K. J., Nomura, D. K. and Casida, J. E. 2006. Each lipase has a unique sensitivity profile for organophosphorus inhibitors. Toxicol. Sci., 91(1): 166-172.
Ricardo., A., Torres-Palma, E. and Serna-Galvis, A. 2018. Advanced Oxidation Processes for Waste Water Treatment. Elesvier, The Netherlands
Ross, S.J.M., Brewin, C.R., Curran, H.V., Furlong, C.E., Abraham-Smith, K.M. and Harrison, V. 2010. Neuropsychological and psychiatric functioning in sheep farmers exposed to low levels of organophosphate pesticides. Neurotoxicol. Teratol., 32(4): 452-459.
Royo, S., Martínez-Máñez, R., Sancenón, F., Costero, A.M., Parra, M. and Gil, S. 2007. Chromogenic and fluorogenic reagents for chemical warfare nerve agents' detection. Chemical Communications, 46, 4839. https://doi.org/10.1039/b707063b
Sakai, K. and Matsumura, F. 1971. Degradation of certain organophosphate and carbamate insecticides by human brain esterases. Toxicology and Applied Pharmacology, 19(4), 660-666. https://doi.org/10.1016/0041-008X(71)90297-3
Sandoval-Herrera, N., Mena, F., Espinoza, M. and Romero, A. 2019. Neurotoxicity of organophosphate pesticides could reduce the ability of fish to escape predation under low doses of exposure. Scie. Rep., 9(1): 1-11.
Sanghi, R., Pillai, M.K., Jayalekshmi, T.R. and Nair, A. 2003. Organochlorine and organophosphorus pesticide residues in breast milk from Bhopal, Madhya Pradesh, India. Hum. Exp. Toxicol., 22(2): 73-76.
Savage, E.P., Keefe, T.J., Mounce, L.M., Heaton, R.K., Lewis, J.A. and Burcar, P.J. 1988. Chronic neurological sequelae of acute organophosphate pesticide poisoning. Archives of Environmental Health: An International Journal, 43(1), 38-45.
Savage, E.P., Keefe, T.J., Wheeler, H.W., Mounce, L., Helwic, L., Applehans, F., Goes, E., Goes, T., Mihlan, G., Rench, J. and Taylor, D.K. 1981. Household pesticide usage in the united states. Arch. Environ. Health Int. J., 36(6): 304-309. https://doi.org/10.1080/00039896.1981.10667642
Serrano-Medina, A., Ugalde-Lizárraga, A., Bojorquez-Cuevas, M. S., Garnica-Ruiz, J., González-Corral, M.A., García-Ledezma, A. and Cornejo-Bravo, J.M. 2019. Neuropsychiatric disorders in farmers associated with organophosphorus pesticide exposure in a rural village of northwest México. Int. J. Environ. Res. Pub. Health, 16(5): 689.
Simcox, N.J., Fenske, R.A., Wolz, S.A., Lee, I.C. and Kalman, D.A. 1995. Pesticides in household dust and soil: Exposure pathways for children of agricultural families. Environ. Health Persp., 103(12): 1126-1134.
Singh, S. and Sharma, N. 2000. Neurological syndromes following organophosphate poisoning. Neurology India, 48(4), 308.
Sogorb, M.A., Garcia-Arguelles, S., Carrera, V. and Vilanova, E. 2008. Serum albumin is as efficient as paraxonase in the detoxication of paraoxon at toxicologically relevant concentrations. Chem. Res. Toxicol., 21(8): 1524-1529.
Soltaninejad, K. and Shadnia, S. 2014 History of the use and epidemiology of organophosphorus poisoning. Basic Clinic. Toxicol. Organophos. Comp., 4: 25-43.
Squibb, K. Pesticides: Program in Toxicology. Available from www.uobabylon.edu.iq/eprints/publication34640659.pdf. Accessed on October 1, 2013.
Sreenivasan, S. and Muraleedharan, N. 2011. Survey on the pesticide residues in tea in south India. Environmental monitoring and assessment, 176, 365-371.
Srivastava, S., Narvi, S.S. and Prasad, S.C. 2008. Organochlorines and organophosphates in bovine milk samples in Allahabad region.
Storm, J.E., Rozman, K.K. and Doull, J. 2000. Occupational exposure limits for 30 organophosphate pesticides based on inhibition of red blood cell acetylcholinesterase. Toxicology, 150(1-3): 1-29.
Tamaro, C.M., Smith, M.N., Workman, T., Griffith, W.C., Thompson, B. and Faustman, E. M. 2018. Characterization of organophosphate pesticides in urine and home environment dust in an agricultural community. Biomarkers, 23(2), 174-187.
Taylor, E.L., Holley, A.G. and Kirk, M. 2007. Pesticide development: A brief look at the history. South. Reg. Ext. For., 1: 1-7.
Testai, E., Buratti, F.M. and Di Consiglio, E. 2010. Hayes' Handbook of Pesticide Toxicology. Academic Press, Cambridge, MA.
Than, K. 2013. Organophosphates: a common but deadly pesticide. National Geographic.
Thenard, P. 1847. Compte. Rend., 25, 892.
Van der Oost, R., Beyer, J. and Vermeulen, N.P. 2003. Fish bioaccumulation and biomarkers in environmental risk assessment: A review. Environ. Toxicol. Pharmacol., 13(2): 57-149.
Vilanova, E. and Sogorb, M.A. 1999. The role of phosphotriesterases in the detoxication of organophosphorus compounds. Crit. Rev. Toxicology, 29(1), 21-57.
World Health Organization (WHO). 2006. Air quality guidelines: global update 2005: particulate matter, ozone, nitrogen dioxide, and sulfur dioxide. World Health Organization.
Ziegler, D.M. 1964. Metabolic oxygenation of nitrogen and sulphur compounds. In: J.K.Mitchell&M.G.Horning (eds), Drug metabolism and drug toxicity, (Raven Press, Iuew York), 33-53.

ORCID DETAILS OF THE AUTHORS

Abhishek Singh: https://orcid.org/0000-0002-3931-1047
Abhishek Chauhan: https://orcid.org/0000-0001-6475-1266
Hardeep Singh Tuli: https://orcid.org/0000-0003-1155-0094