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Adverse effects of organophosphorus pesticides on the liver: a brief summary of four decades of research

Somayyeh Karami-Mohajeri[1,2], Ahmad Ahmadipour[2], Hamid-Reza Rahimi[1,2], and Mohammad Abdollahi[3,4]

Pharmaceutics Research Center, Institute of Neuropharmacology[1], Department of Toxicology and Pharmacology, Faculty of Pharmacy[2], Kerman University of Medical Sciences, Kerman, Pharmaceutical Sciences Research Center[3], Department of Toxicology and Pharmacology[4], Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

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Organophosphorus pesticides (OPs) are widely used volatile pesticides that have harmful effects on the liver in acute and chronic exposures. This review article summarises and discusses a wide collection of studies published over the last 40 years reporting on the effects of OPs on the liver, in an attempt to propose general mechanisms of OP hepatotoxicity and possible treatment. Several key biological processes have been reported as involved in OP-induced hepatotoxicity such as disturbances in the antioxidant defence system, oxidative stress, apoptosis, and mitochondrial and microsomal metabolism. Most studies show that antioxidants can attenuate oxidative stress and the consequent changes in liver function. However, few studies have examined the relationship between OP structures and the severity and mechanism of their action. We hope that future *in vitro*, *in vivo,* and clinical trials will answer the remaining questions about the mechanisms of OP hepatotoxicity and its management.

KEY WORDS: *apoptosis; hepatotoxicity; mitochondrial metabolism; molecular toxicity, organophosphorus; oxidative stress*

Organophosphorus pesticides (OPs) have harmful effects on human health through environmental or occupational exposure. Roughly 0.1 % of the applied pesticides reach the target pests, and the rest spreads through water, soil, and food (1-3). These pesticides are readily available on the market. Suicidal poisoning with OPs is common, particularly in rural areas (4). Acute poisoning with OPs is a global threat to human health that causes more than 100,000 deaths a year (5, 6).

They primarily affect the nervous system of the exposed organisms by inhibiting acetylcholinesterase (AChE) and raising acetylcholine levels in the cholinergic synapse. Beside cholinergic effects, OPs induce oxidative stress (7, 8), affect metabolic pathways (9), and cause multiple organ dysfunctions such as hypoxia and inadequate tissue perfusion of the liver and heart (10). In the liver they cause ultrastructural, biochemical, metabolic, and mitochondrial damage, evidenced by changes in hepatic biomarkers such as serum aminotransferase and direct and indirect bilirubin (11-31).

Their mechanisms of action on the liver and metabolism have not yet been fully clarified, and finding an effective therapy against OPs still remains a major challenge.

Correspondence to: Mohammad Abdollahi, Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
e-mail: *mohammad@tums.ac.ir*

This review article summarises and discusses a wide collection of studies published over the last 40 years reporting on the effects of OPs on the liver, in an attempt to propose general mechanisms of OP hepatotoxicity and possible treatment.

Literature collection

To screen for and select relevant literature we ran the keywords "Organophosphate", "organophosphorus", "hepatotoxicity", and "liver toxicity" through all relevant bibliographic databases, including Google Scholar, Scopus, Web of Science, PubMed, Medline, and Embase. The screening yielded more than 300 papers between the years 1977 and 2015. The obtained corpus was further sifted for the following search terms "acetylcholinesterase", "acetylcholine", "oxidative stress", "lipid peroxidation" "metabolic disorders", "mitochondrial toxicity", "genotoxicity", "histopathological", and "therapeutics" to narrow the choice of relevant articles to over 170, covering the last four decades of research.

Histopathological evidence of OP hepatotoxicity

Many studies confirm that the liver tissue is the primary target organ of OP toxicity (Figure 1).

Chlorpyrifos is a typical representative of the OPs, which causes detrimental effects both on liver function and

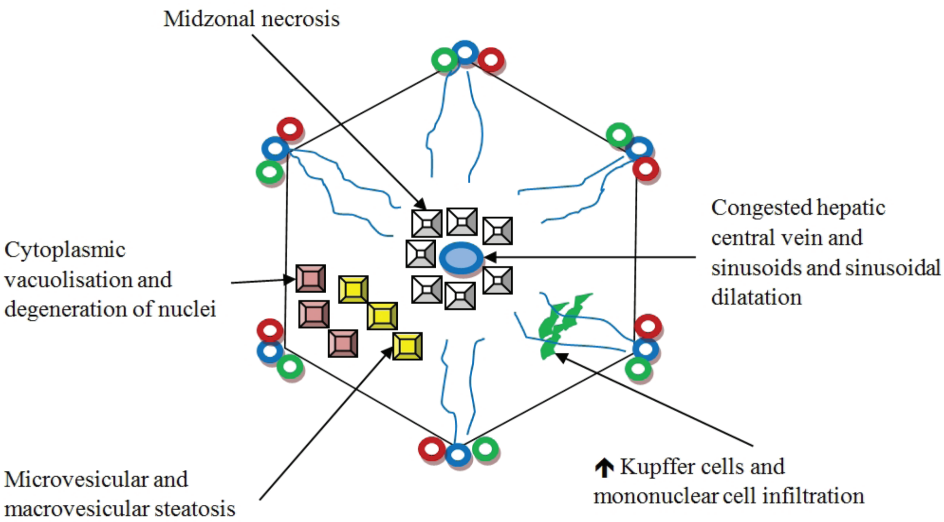

Figure 1 *Histopathological disorders in the hepatic lobule after exposure to organophosphorus pesticides*

structure. Almost forty years ago, Mikhail et al. (32) found that a two-day i.p. exposure to a sub-lethal dose of this insecticide resulted with mid-zonal liver necrosis, fatty deposition at the periphery, and glycogen deposition at one side of the hepatic cell and around the central vein. Goel et al. (33) studied liver histoarchitecture in chlorpyrifos-treated rats and observed hepatocyte vacuolisation and necrosis, sinusoidal dilatation, and increase in binucleated cells at higher doses and longer exposure to chlorpyrifos. Recent findings by Ezzi et al. (34) suggest that chlorpyrifos had a dose-dependent effect on dilated sinusoids, central vein, and portal triad in rats.

An excessive amount of liver blood and degenerative changes were found in the liver of fish exposed to chlorpyrifos through contaminated water (35).

Another OP compound associated with liver damage in experimental animals is triazophos. Sharma et al. (36) observed a variety of histopathological findings, such as infiltration, vacuolisation, enlarged sinusoids, and necrosis in female albino rats exposed to triazophos.

Sub-chronic exposure of rats to methidathion caused mononuclear cell infiltration in all portal areas, sinusoidal dilatation, focal micro-vesicular steatosis, and parenchymal degenerations (17, 26).

Dose-dependent liver changes, including necrosis, cytoskeleton disarray, vacuolisation of the endothelial cells, damages in Disse's space, changes in nuclear shape, and heterochromatin distribution were evidenced in the liver of fish and rats exposed to sub-lethal doses of diazinon for a long time (37, 38).

Acute high dose of diazinon caused hypertrophy and swelling of hepatocytes, vacuolisation of cytoplasm, and macrovascular steatosis (39). Forty-minute inhalation of diazinon every other day in pregnant mice induced a dose-dependent increase in the hepatocyte area, hepatocyte apoptosis, and a decrease in the sinusoid area of the foetal liver (40).

Malathion caused macrovesicular steatosis, apoptotic nuclei, granulovacuolar dystrophy lesions, and pericentrilobular vasodilatation in the liver of rats after about one month of low-dose exposure (41, 42). In contrast, Chakraborty et al. (43), reported only discrete to mild histological changes in the liver of rats exposed to a malathion dose about four times higher than in the study of Baconi et al. (41) for 15 days. A four-week daily oral exposure to sub-lethal doses of malathion caused hepatomegaly, necrotic lesions in the periportal lobules, cytoplasmic vacuolation around nuclei, and sinusoid expansion and atrophy of hepatocytes in rat liver (44, 45).

Parathion in the study by Chakraborty et al. (43), just like malathion, caused mild histopathological changes over 15 days of exposure. However, methyl parathion in the study by Undeger et al. (46) increased liver weight and caused hepatomegaly at lower doses than parathion. A sub-lethal dose of methyl parathion also caused cloudy swelling, bile stagnation, focal necrosis, atrophy, and vacuolisation in the liver tissue after contamination through water (47).

Dimethoate led to dose-dependent histological changes in rat liver, such as mononuclear cell infiltration, Kupffer cell count increase, congestion and dilatation of veins and sinusoids, necrosis, cytoplasmic vacuolisation, and degeneration of hepatocyte nuclei (22).

All of these studies investigated thion OPs that caused liver damage regardless of their structural differences. The exception is the study by Chakraborty et al. (43), but its comparison with Undeger et al. (46) may explain why. Namely, the presence of a bulky group in the side chain of OPs can make a great difference in the severity of liver injury.

As for oxon OPs, studies have reported hyalinisation, vacuolisation, nucleus necrosis, and hepatocellular oedema, and fatty degeneration in sub-acute exposure to low-dose of trichlorfon and acute exposure to omethoate (48, 49).

These disturbances in the morphological structure of the liver could be associated with a disruption of the tissue function, which could also be related to lower antioxidative capability, change in fatty and glycogen content in the liver, and the inhibition of some enzymes contributing to lipid, protein, and carbohydrate metabolism needed to preserve the integrity of the liver tissue.

Biochemical evidence of OP hepatotoxicity

Figure 2 shows some of the possible biochemical changes in the serum and liver after OP exposure. The most common serum biomarkers of liver damage are aspartate transaminase (AST) and alanine transaminase (ALT). There is strong evidence that both are increased by dimethoate, monocrotophos, methyl parathion, dichlorvos, fenitrothion, omethoate, chlorpyrifos, 2-butenoic acid-3-(diethoxyphosphinothioyl) methyl ester (RPR-II), diazinon, and methidathion (21, 33, 39, 49-64). It is interesting to note that the increases in AST and ALT are often accompanied by increases in the inflammatory mediator tumour necrosis factor alpha (TNF-α) (39, 49, 51, 65). In humans, higher AST and ALT were reported in tobacco farmworkers in India (66) and farm workers in Gadap Karachi, Pakistan exposed to a mixture of pesticides, including OPs (67).

Other biomarkers of liver damage include acid phosphatase (AcP) and alkaline phosphatase (ALP). Sub-lethal concentrations of methamidophos, phorate, and RPR-II seem to increase AcP and ALP in plasma and lower them in the liver tissue of animals (60, 68, 69). Similar findings have been reported for sub-chronic monocrotophos, methyl parathion, and dimethoate effects on ALP and AcP levels in plasma, but not in the liver, where they also increased (21, 59).

Impaired bile flow and biliary excretion could also serve as indirect indicators of liver damage (70). Goel and Dhawan (71), for example, suggested that poor biliary excretion and longer half-life of 99mTc-mebrofenin in chlorpyrifos-treated rats reflected impaired hepatobiliary function.

As impaired liver function affects the metabolism, consequently it also affects the concentrations of waste products. Several animal studies have pointed to the indirect effects of sub-lethal doses of phorate, fenitrothion, and dimethoate on urea and bilirubin (58, 64, 72). In humans occupationally exposed to a wide range of OPs, blood urea nitrogen and albumin along with serum aminotransferases are frequently elevated (30, 73). Since, there are limited data about the hepatotoxicity of OPs in humans, it is not certain whether changes in biochemical parameters indicate actual liver damage.

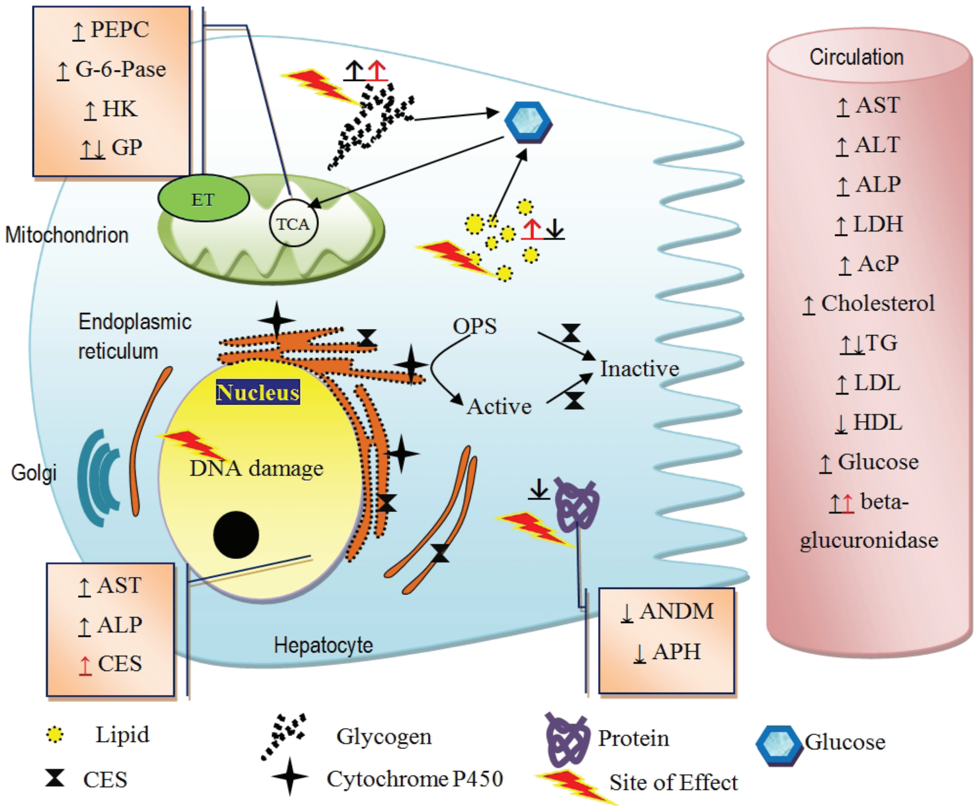

Figure 2 *Possible disturbance pathways in the liver tissue after exposure to organophosphorus pesticides. Black arrows indicate long-term exposure and red ones acute poisoning.*
Abbreviations: AcP = acid phosphatase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANDM = aminopyrine-N-demethylase; APH = aniline-p-hydroxylase; AST = aspartate aminotransferase; CES= carboxylesterase; G6Pase = glucose-6-phosphatase; GP= glycogen phosphorylase; HDL = high-density lipoprotein; HK = hexokinase; LDL = low-density lipoprotein; PEPC = phosphoenolpyruvate carboxykinase; TG = triglyceride

Possible effects of OPs on hepatic carbohydrate, lipid, and protein metabolism

Histological disorders are related to the metabolic capacity of the liver. Figure 2 illustrates how disturbances in the histoarchitecture of the liver induced by OPs can affect its performance in the enzymatic pathways involved in the metabolism of lipids, carbohydrates, and proteins in the cytoplasm, mitochondria, and peroxisomes (9). Animal studies suggest that the activity of glycogen phosphorylase (GP), the enzyme that breaks glycogen into glucose and reduces the hepatic glycogen content, increases after fenitrothion and malathion exposure (74, 75). This is supported by a drop in hepatic glycogen concentration after fenthion exposure in fish (76). In a study by Rezg et al. (44), however, sub-chronic exposure to malathion decreased GP activity by 50 % and increased hexokinase activity by 10 % but had no effect on blood glucose levels. Phosphoenolpyruvate carboxykinase (PEPCK) plays a crucial role in gluconeogenesis, and several studies have reported that malathion and diazinon increase the activity of both GP and PEPCK (75, 77-79). Two other hepatic gluconeogenesis enzymes, namely glucose-6-phosphatase and malate dehydrogenase, are affected by acute exposure to OPs, as reported for acephate (80). In contrast, Sharma et al. (23), found no significant changes in glucose-6-phosphate dehydrogenase (G6PD) activity in acute exposure to dimethoate. In another study (81), hepatic malate dehydrogenase involved in the citric acid cycle and gluconeogenesis was downregulated in rats exposed to a sub-lethal dose of diazinon. OPs also seem to lower glucokinase, a liver enzyme contributing to glycogen synthesis, as reported for dichlorvos exposure (82). All of these studies indicated changes in carbohydrate metabolism, but their inconsistencies may be owed to the type of the investigated OP, route of administration, as well as animal species and strain.

On the other hand, diazinon-poisoned rats showed increased lactate production (83). This increase may be due to an increase in liver lactate dehydrogenase (LDH) activity, a key cytosolic enzyme in glycolysis, reported for the exposure to quinalphos, dimethoate, acephate, fenitrothion, and methidathion (21, 61, 84-86). In a study by Mukhamedzhanov et al. (87) acute treatment of rats with intramuscular chlorophos and trichlorometaphos activated aldolase and LDH, which are both glycolytic enzymes. Higher hepatic LDH activity may represent a shift from mitochondrial respiration toward anaerobic glycolysis. Parallel changes in serum LDH and aminotransferases also suggest substantial liver involvement during exposure.

As a primary site of cellular energy generation and oxygen consumption, mitochondrion is a likely target for OPs, which may explain their non-cholinergic toxicity (88, 89). Recent research has focused on the possible roles of mitochondrial dysfunction in OP-induced toxicity through mitochondrial respiration rate, respiratory chain enzymes (90-94), energy production (93, 95-97), and cell death (98-100). Several studies have found an association between mitochondrial dynamics and malathion-induced drop in mitochondrial ATP synthesis in rat liver (9) or quinalphos and acephate effects on liver succinic dehydrogenase (84, 85, 101) and ATPase activities (87) - all of them the key enzymes for oxidative phosphorylation. Two studies in rats (90, 93) point to an OP-induced drop in the liver mitochondrial respiratory control ratio (RCR), especially by dichlorvos. This decline may be related to changes in the inner mitochondrial membrane permeability caused by lipid peroxidation. A time-dependent decrease in carbonic anhydrase activity was reported in fish exposed to chlorpyrifos (35). Carbonic anhydrase in hepatocyte mitochondria plays a vital role in the regulation of ionic balance, which is required in metabolic reactions, production of ATP, and transport processes (102).

The effects of OPs, most notably diazinon and fenitrothion, on liver protein metabolism include the reduction of total protein, albumin, calcium-binding protein, and regucalcin (which is involved in Ca^{2+} transport) (51, 64, 72, 81, 86).

Diazinon can lower the liver activity of fumarylacetoacetase, which catalyses the hydrolysis of 4-fumarylacetacetate to acetoacetate and fumarate as part of the phenylalanine and tyrosine catabolism pathways and contributes to mental retardation (81). It can also affect carbamoyl-phosphate synthase, which catalyses the synthesis of carbamoyl phosphate from glutamine or ammonia and bicarbonate, and S-adenosylmethionine synthetase, which is vital for nucleic acid and protein synthesis (81).

One study revealed that methyl parathion affected the liver expression of chaperones and proteins regulating the cytoskeleton system, cell metabolism and signalling, electron transport, and hormone receptors in zebrafish (103).

Some studies reported OP-induced changes in liver lipid profiles. Nagaraju et al. (104) reported dyslipidaemia, including higher triglycerides and lower HDL-C in rats chronically exposed to monocrotophos. Sub-lethal fenitrothion reversibly increased triglycerides and cholesterols in mice after 90 days of exposure. All values returned to normal, except for triglycerides (72). Trichlorfon at the concentration of 2 mg L^{-1} decreased hepatic hormone-sensitive lipase, very-low-density lipoprotein, and apolipoprotein B100 levels, which is associated with impaired lipid transport and accumulation of lipids in hepatocytes (105). However, low-dose OPs may not be contributing to lipid metabolism. In an *in vitro* study by Takeuchi et al. (106) reported that OPs at concentrations as low as 10^{-5} mol L^{-1} did not activate peroxisome proliferator-activated receptors, which are ligand-dependent transcription factors and key regulators of lipid metabolism.

Possible effects of OPs on hepatic oxidative stress pathways

Formation of reactive oxygen species (ROS) and reactive intermediates after exposure to pesticides can cause hepatotoxicity (107). Extensive data suggest that free radical formation and oxidative stress can be a major contributor to the toxicity of pesticides (108-113). OPs are oxidants and impair enzymatic antioxidant defences, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) (23, 34, 44, 114-129). Malathion, methyl parathion, and parathion in HepG2 cell lines, as well as chlorpyrifos, methidathion, chlorfenvinphos, and dimethoate in rat liver and diazinon in fish most probably disrupt membrane lipids through oxidative stress (23, 35, 61, 116, 118, 130-135). Table 1 summarises the key changes in antioxidant defence and oxidative stress biomarkers caused by OPs. Oxidative stress contributes to OP-induced toxicity through peroxidation of cellular macromolecules, which leads to a degradation of membrane phospholipids and proteins and cellular deterioration.

The main role in the induction of oxidative stress is played by the mitochondria. Leakage of electrons from the respiratory chain leads to the formation of ROS, triggers apoptotic pathways, and affects metabolism and ATP generation (136-138). Mitochondria are susceptible to oxidative damage, which manifests itself as changes in their transmembrane potential and weakened membrane integrity (137, 138). Mitochondrial oxidative damage is a major cause of many liver disorders, including chronic hepatitis, steatosis, ischemic injuries, aging, and inflammatory damage (140, 141). Several studies have evidenced the involvement of mitochondria in hepatotoxicity induced by OPs. For example, acute exposure to malathion and chronic exposure to dichlorvos and chlorpyrifos can increase the release of cytochrome C from mitochondria to cytosol and activate caspase-3 by disrupting cellular antioxidant defences (88, 99, 142). Diazinon can trigger apoptotic pathways by activating caspase-9 and caspase-3, increase the Bax/Bcl-2 ratio and protein disulphide isomerase (with pro-apoptotic function), and suppress endoplasmic

Table 1 *Summary of oxidative stress processes in the liver tissue triggered by organophosphorus pesticides*

Pesticide type	Route of administration	Exposure duration	Dose	Animal	Antioxidant enzymes	Oxidative stress products	Antioxidants
Chlorpyrifos (141)	gavage	8 w	6.75 mg kg^{-1} per day	rat	-	▲LPO, ▲PC ▲ROS	▼TAC
Chlorpyrifos (121)	water	24, 48, & 96 h	single dose 15.3 and 51 μg L^{-1}	fish	▲SOD, ▼CAT	▲LPO	▼TAC
Chlorpyrifos (122)	intramuscular	7 d	single dose 50, 100, and 200 mg kg^{-1}	rat	▼SOD, ▼CAT, ▼G_6PDH, ▼GR, ▲GPx	▲LPO	▼GSH, ▲GSSG
Chlorfen-vinphos (133)	gavage	14 & 28 d	0.3 mg kg^{-1} per day	rat	-	▲H_2O_2	▼GSH
Diazinon (134)	water	12 or 24 h	0.97, 1.95, and 3.95 mg L^{-1}	fish	-	▲LPO, ▲PC	-
Diazinon (39)	gavage	7 d	single dose 335 mg kg^{-1}	rat	▲SOD, ▼MPO	-	-
Diazinon (37)	water	4 w	0.1 and 0.2 mg L^{-1}	fish	-	▲LPO	▲TAC
Diazinon (123)	drinking water	1 w	10 mg kg^{-1}	rat	▼GPx, ▼GST, ▼CAT	-	▼GSH
Diazinon (124)	water	1, 7, 15, & 30 d	0.1, 1, and 2 mg L^{-1}	fish	▲GST	▲ LPO	▲GSH
Diaxinon (125)	water	5, 15, & 30 d	0.0036, 0.018, and 0.036 μg L^{-1}	fish	▲SOD, ▲GPx, ▲CAT	NC LPO	-
Dichlorvos (126)	gavage	3 w	0.64, 1.60, and 4.00 mg kg^{-1} per day	rat	▲SOD, ▲CAT	▲LPO, ▲PC	-

Table 1 *continued*

Pesticide type	Route of administration	Exposure duration	Dose	Animal	Antioxidant enzymes	Oxidative stress products	Antioxidants
Dimethoate (118)	gavage	30 d	0.6, 6 and 30 mg kg^{-1} per day	rat	▼GST	▲ LPO	▼GSH
Dimethoate (21)	gavage	8 w	20 mg kg^{-1} per day	rat	▲SOD, ▲GPx, ▼CAT	▲LPO	-
Dimethoate (23)	gavage	24 h	single dose 45, 75, and 90 mg kg^{-1}	rat	▲SOD, ▲GPx, ▲CAT, ▲GR	▲ LPO	▼GSH
Dimethoate (127)	intraperitoneal	1 w	1, 5, 10, 15 and 30 mg kg^{-1}	rat	▲CAT	▲LPO, ▲PC	-
Fenitrothion (128)	water	1 w	0.04 mg L^{-1}	fish	▲SOD, ▲CAT, ▲GST	-	-
Malathion (129)	gavage	4 w	200 mg kg^{-1} per day	rat	-	▲LPO	▼GSH, ▼TAC
Malathion (45)	water	4 w	150 mg kg^{-1} per day	rat	▼ SOD, ▼ CAT	▲ LPO	▼GSH
Malathion (116)	drinking water	4 w	100, 316, 1000 and, 1500 mg L^{-1}	rat	▲SOD, ▲CAT	▲ LPO	-
Methidathion (17, 26, 61)	gavage	24 h	single dose 8 mg kg^{-1}	rat	-	▲ LPO	-
Trichlorfon (48)	water	4 w	0.01, 0.1, 1.0 mg L^{-1}	frog	▲SOD, ▲CAT	▼ LPO	-
Triazophos (36)	gavage	4 w	8.2, 4.1, and 2.05 mg kg^{-1}	rat	▼SOD, ▼GPx, ▼CAT, ▼GR, ▼GST	▲ LPO	-

Abbreviations: CAT = catalase; G_6PDH = glucose-6-phosphate dehydrogenase; GPx = glutathione peroxidase; GR = glutathione reductase; GSH = reduced glutathione; GSSG = oxidized glutathione; GST= glutathione S-transferase; H_2O_2 = hydrogen peroxide; LPO = lipid peroxidation; MPO = myeloperoxidase; NC = no change; PC = protein carbonyl; SOD = superoxide dismutase; TAC = total antioxidant capacity

chaperone (with anti-apoptotic properties) in the liver (81, 143).

Possible effect of OPs on hepatic biotransformation

Animal studies of OP effects on important cytochromes and microsomal enzymes that affect biotransformation of compounds and drug metabolism report controversial results. Several studies reported chlorpyrifos, malathion, and parathion as potent inhibitors of cytochrome P 450 (CYP) 3A and 2C11, cytochrome b5, and aminopyrine *N*-demethylase (ANDM) (42, 144, 121), but some reported no effect (parathion on CYP 2A1, 2A2, and 2C6) (144) or an increase (iprobenfos on CYP 1A mRNA transcription) (143). Low-dose dimethoate administered for two weeks increased the mRNA expression of CYP 2D1 and higher metabolism of metoprolol in rats (145). Parathion and paraoxon decreased the activity of rat liver benzo(a)pyrene hydroxylase, which is governed by CYP 1A1 (146).

In humans, Van der Meer et al. (147) reported complete inhibition of atropine metabolism in OP-poisoned patients and that this was owed to the inhibition of hepatic microsomal enzymes.

Several *in vitro* studies have also indicated OP effects on aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that regulates genes involved in xenobiotic metabolism (148-150).

Possible mutagenic, genotoxic, and carcinogenic effects of OPs

Mutagenic and genotoxic effects of pesticides have been evidenced by a variety of tests showing gene mutations, chromosomal aberrations, and micronucleus formation (151-154). The mutagenic effects of OPs are owed to the direct alkylating ability of the parental molecule and its metabolites (130, 131, 155).

The genotoxic potential of pesticides has been demonstrated by the comet assay in exposed workers in India and Iran (156, 157). Several *in vivo* and *in vitro* studies reported that the genotoxicity of OPs such as dimethoate, methyl parathion, chlorpyrifos, phorate, and malathion in hepatocytes was associated with oxidative damage (130, 131, 127, 149-159). A study by Hreljac et al. (160) showed that methyl paraoxon was less genotoxic in HepG2 cells than its parent OP methyl parathion. This suggests that the genotoxicity of methyl parathion and methyl paraoxon is AChE-independent and that other mechanisms are involved in this process. In the same study, on the other hand, dimefox, a highly toxic OP, did not induce DNA strand breaks but showed mitogenic activity.

As for carcinogenicity, Reuber (161) reports that dimethoate and omethoate, its toxic metabolite, can cause benign and malignant neoplasms in the liver. However, the International Agency for Research on Cancer (IARC) could not find enough evidence to classify dimethoate as potential carcinogen (162). Furthermore, a study by Bonner et al. (163) did not associate malathion with cancer in pesticide applicators. All these findings suggest that the agents causing low DNA damage are generally not mutagenic or carcinogenic, and those causing sustained DNA and cell damage (but not cell death) are mutagenic and/or carcinogenic (164).

Conclusions and recommendations to control OP-induced liver damage

This literature review abundantly evidences that OPs can have significant and harmful effects on the liver and points to the need of regular liver function monitoring in long-term occupational and short-term accidental exposure to OP insecticides.

The presented research (summarised in the supplementary Table 2 at the end of the review) suggests that the key mechanisms of OP action are disturbances in the liver metabolism and mitochondrial metabolic pathways caused by oxidative damage. This conclusion is reinforced by other OP effects, such as apoptosis, cell toxicity, genotoxicity, and tissue damage induced by ROS triggered by OP exposure.

The best course of action to counter OP liver and mitochondrial toxicity in acute, subacute, sub-chronic, or chronic exposure is therefore to use antioxidants (89, 119, 165, 166). The choice of antioxidants is wide, but several have been evidenced as potent against OP toxicity, including selenium (167), *N*-acetylcysteine (NAC), pentoxifylline (PTX), and alpha-tocopherol. NAC has been reported to significantly decrease lipid peroxidation, hospital time, and mortality in poisoned patients (168), whereas PTX and alpha-tocopherol reverse OP-induced effects on glutathione, nitrotyrosine, CAT, and GPx (65, 169, 170). Recently, a new generation of possible antidotes to OP poisoning has raised interests, the so called OP hydrolases produced by bacteria, but research has not yet reached clinical stage (171).

Since few studies have compared the effects of OPs with different structures, little is known about the exact relationship between the severity and mechanism of liver damage and the chemical structure of these toxins.

We hope that future *in vitro*, *in vivo,* and clinical trials will answer the remaining questions about the mechanisms of OP hepatotoxicity and its management.

Conflict of interest

None to declare.

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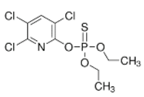
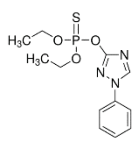
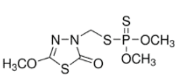
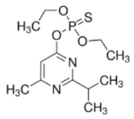
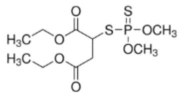
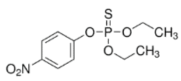
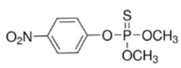
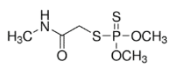
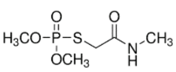
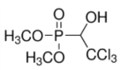
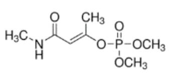
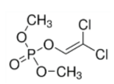
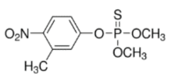
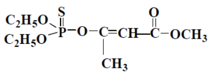
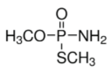
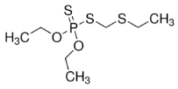
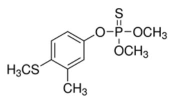
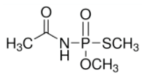
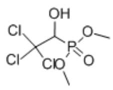
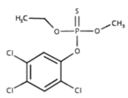
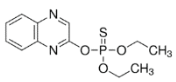
Table 2 (supplementary) *Summary of the key hepatotoxic effects by organophosphorus pesticides*

Name	Structure	[1] Pesticide type [2] Chemical formula [3] CAS number	Hepatotoxic effects
Chlorpyrifos (33, 34, 35, 53, 71, 132, 141, 121, 158, 122)		[1] Insecticide [2] $C_9H_{11}Cl_3NO_3PS$ [3] 2921-88-2	- Histopathological changes (rat and fish) - Changes in hepatobiliary system (rat) - Changes in serum liver damage biomarkers (rat) - Downregulation of CYP 3A (fish) - Oxidative stress induction (rat and fish) - DNA damages (rat) - Apoptosis induction (rat)
Triazophos (36)		[1] Acaricide, insecticide, and nematicide [2] $C_{12}H_{16}N_3O_3PS$ [3] 24017-47-8	- Histopathological changes (rat) - Oxidative stress induction (rat)
Methidathion (17, 26, 61)		[1] Acaricide and insecticide [2] $C_6H_{11}N_2O_4PS_3$ [3] 950-37-8	- Histopathological changes (rat) - Oxidative stress induction (rat)

Name	Structure	[1] Pesticide type [2] Chemical formula [3] CAS number	Hepatotoxic effects
Diazinon (13, 37-40, 51, 63, 78, 81, 83, 154, 167, 172-125)		[1] Insecticide [2] $C_{12}H_{21}N_2O_3PS$ [3] 333-41-5	- Histopathological changes (rat and fish) - Changes in serum liver damage biomarkers (rat) - Glucose, lipid, and protein metabolism (rat) - Oxidative stress induction (rat and fish) - DNA damages (rat) - Apoptosis induction (rat)
Malathion (12, 20, 25, 41-45, 75-77, 94, 95, 116, 169, 129)		[1] Insecticide [2] $C_{10}H_{19}O_6PS_2$ [3] 121-75-5	- Histopathological changes (rat) - Changes in serum liver damage biomarkers (rat) - Glucose, lipid, and protein metabolism (rat) - Oxidative stress induction (rat) - Metabolism (chicken) - Apoptosis induction (rat)
Parathion (43, 103, 133, 146)		[1] Insecticide [2] $C_{10}H_{14}NO_5PS$ [3] 56-38-2	- Histopathological changes (rat) - Changes in serum liver damage biomarkers (rat) - Downregulation of CYP 3A and 2C11 (fish) - Lipid metabolism (fish) - Oxidative stress induction (rat) - Decrease in benzo(a)pyrene metabolism (rat) - Apoptosis induction (rat)
Methyl parathion (46, 47, 103)		[1] Insecticide [2] $C_8H_{10}NO_5PS$ [3] 298-00-0	- Histopathological changes and hepatomegaly (rat) - Changes in serum liver damage biomarkers (rat) - Lipid metabolism (fish)
Dimethoate (21-23, 58, 60, 118, 145, 127)		[1] Acaricide and insecticide [2] $C_5H_{12}NO_3PS_2$ [3] 60-51-5	- Histopathological changes (rat) - Changes in serum liver damage biomarkers (rat) - Upregulation of CYP 2D1 (rat) - Cause benign and malignant neoplasm (rat) - Oxidative stress induction (rat)
Omethoate (49, 161)		[1] Acaricide and insecticide [2] $C_5H_{12}NO_4PS$ [3] 1113-02-6	- Histopathological changes (rat) - Changes in serum liver damage biomarkers (rat) - Cause benign and malignant neoplasm (rat)
Trichlorfon (48,105, 115)		[1] Insecticide [2] $C_4H_8Cl_3O_4P$ [3] 52-68-6	- Histopathological changes (frog) - Lipid metabolism (fish) - Oxidative stress induction (rat and frog)
Monocrotophos (59, 65, 104)		[1] Insecticide [2] $C_7H_{14}NO_5P$ [3] 6923-22-4	- Changes in serum liver damage biomarkers (rat) - Glucose and lipid metabolism (rat)
Dichlorvos (82, 88, 93, 126)		[1] Insecticide [2] $C_4H_7Cl_2O_4P$ [3] 62-73-7	- Histopathological changes (rat) - Changes in serum liver damage biomarkers (rat) - Glucose and lipid metabolism (rat) - Oxidative stress induction (rat) - Apoptosis induction (rat)
Fenitrothion (54, 64,72, 74, 86, 128)		[1] Insecticide [2] $C_9H_{12}NO_5PS$ [3] 122-14-5	- Changes in serum liver damage biomarkers (rat) - Glucose and lipid metabolism (fish) - Oxidative stress induction (rat)

Name	Structure	[1] Pesticide type [2] Chemical formula [3] CAS number	Hepatotoxic effects
RPR-II (60)		[1] Insecticide [2] $C_6H_{10}O_2$ [3] 924-50-5	- Changes in serum liver damage biomarkers (fish)
Methamidophos (69)		[1] Insecticide [2] $C_2H_8NO_2PS$ [3] 10265-92-6	- Changes in serum liver damage biomarkers (rat) - Histopathological changes (rat) - Oxidative stress induction (rat)
Phorate (68, 159)		[1] Acaricide and insecticide [2] $C_7H_{17}O_2PS_3$ [3] 298-02-2	- Changes in serum liver damage biomarkers (rat) - DNA damages (rat) - Oxidative stress induction (rat)
Fenthion (76, 133)		[1] Acaricide, avicide, and insecticide [2] $C_{10}H_{15}O_3PS_2$ [3] 55-38-9	- Glucose metabolism (fish) - Oxidative stress induction (fish)
Acephate (80,84)		[1] Insecticide [2] $C_4H_{10}NO_3PS$ [3] 30560-19-1	- Changes in serum liver damage biomarkers (rat) - Glucose metabolism (rat)
Chlorophos (87)		[1] Insecticide and vermicide [2] $C_4H_8Cl_3O_4P$ [3] 52-68-6	- Changes in serum liver damage biomarkers (rat) - Glucose metabolism (rat)
Trichlorometaphos (87)		[1] Insecticide [2] $C_9H_{10}Cl_3O_3PS$ [3] 2633-54-7	- Changes in serum liver damage biomarkers (rat) - Glucose metabolism (rat)
Quinalphos (85)		[1] Insecticide [2] $C_{12}H_{15}N_2O_3PS$ [3] 13593-03-8	- Glucose metabolism (fish)

Abbreviations: CYP = cytochrome P 450; RPR-II = 2-butenoic acid-3-(diethoxyphosphinothioyl)methyl ester

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Štetno djelovanje organofosfornih pesticida na jetra: kratki pregled četrdesetogodišnjeg istraživanja

Organofosforni pesticidi (OP) imaju veoma široku primjenu, ali i štetno djeluju na jetru pri akutnoj i kroničnoj izloženosti. Ovaj članak daje pregled 40 godina istraživanja djelovanja OP-ova na jetru s namjerom da predloži neke zajedničke mehanizme njihova toksičnog djelovanja na jetru i liječenje. U istraživanjima se izdvaja nekoliko ključnih bioloških procesa koji sudjeluju u hepatotoksičnosti OP-ova, poput narušavanja antioksidacijskoga obrambenog sustava, oksidacijskoga stresa, apoptoze te mitohondrijskoga i mikrosomalnoga metabolizma. Rezultati većine istraživanja potvrdili su da antioksidansi uspješno ublažavaju posljedice oksidacijskoga stresa u jetri. Međutim, gotovo da i nije istražena povezanost između strukture OP-ova i njihove štetnosti odnosno mehanizama djelovanja. Nadamo se da će buduća *in vitro* i *in vivo* istraživanja te klinička ispitivanja odgovoriti na preostala pitanja vezana uz mehanizme hepatotoksičnoga djelovanja OP-ova i njegova uspješnoga liječenja.

KLJUČNE RIJEČI: *antioksidansi, apoptoza; hepatotoksičnost; mitohondrijski metabolizam; oksidativni stres; OP*