Nephrotoxicity issues of organophosphates

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Abstract

Organophosphates are a large class of chemicals, initially invented in 1850 and since then they have been applied in numerous aspects of science to serve our purposes. Their mechanism of action in living organisms involves the irreversible inhibition of acetylcholinesterase, therefore they interfere with neuromuscular signal transmission. Due to the systematic and exaggerated use of these chemicals, there is massive exposure to them, hence there is great concern regarding the ramifications to all mammalian organisms. It has been widely accepted that over-exposure to organophosphates, has a deleterious impact on the renal tissue and subsequently on the renal function. Despite the significance of this global issue, limited knowledge exists, regarding the effect
of these substances on our health. Therefore, new and extensive research is required to expand our knowledge and ensure proper guidance regarding the use of organophosphates as well the protection against their detrimental consequences. The aim of this review is to negotiate the effect of organophosphate exposure on renal tissue and kidney function.

**Abbreviations:** ACh (Acetylcholine), AChE (Acetylcholinesterase), AKI (Acute Kidney Injury), Organophosphates (OPs), Reactive oxygen species (ROS)

**Key words:** Kidney; Organophosphates; Toxicity

1. **Introduction**

Organophosphates (OPs) constitute a large class of chemicals. A huge number of OPs have been synthesized since their invention in 1850 for a wide range of purposes. They have been used as pesticides, nerve agents in World War II, flame retardants, and parasiticides. Noteworthy are their beneficial medical effects in various pathologies such as Alzheimer’s disease, myasthenia gravis, glaucoma and voiding dysfunction (Aggarwal and Zimmern 2016; Jiang et al. 2017). All OPs share structural similarities containing a phosphorus atom. Subsequently they are all considered esters of phosphoric acid with various attachments of oxygen, carbon, sulfur or nitrogen. Due to the vast variety of possible chemical combinations, there are hundreds of OPs in use. OPs such as parathion, malathion, methyl parathion, chlorpyrifos, diazinon, dichlorvos, phosmet, fenitrothion, tetrachlorvinphos, azamethiphos, azinphos-methyl, terbufos, disulfoton and fonofos are some of the chemicals that have been in use for agricultural purposes for many years. They all present a potential health risk since they can be ingested with food/drinking water, inhaled or trans-dermally absorbed.
Nerve agents such as sarin, tabun, soman, cyclosarin, diisopropylfluorophosphate and VX present another issue of great importance as they can be utilized in warfare conditions. They also pose a risk to military personnel and to general population that can become subject to accidental exposure during destruction/transportation (Vucinic et al. 2017). OPs irreversibly inhibit acetylcholinesterase (AChE), resulting in accumulation of acetylcholine (ACh) at the end-plate with an end-result of persistent depolarization. Consequently, neuromuscular signal transmission is impaired. OPs effects are categorized as acute, delayed and long term, depending on the timing of their presentation.

Owing to the increased infiltration of pesticides in our environment, human exposure to such compounds has become almost inevitable, not only in developing countries, where agricultural practices still rely widely on pesticides but also in developed ones where insecticides are more often used for public health purposes and food products and water are usually contaminated with pesticides. Thus, it is mandatory to thorough explore the potential health effects of these compounds. The potential association between exposure to endocrine disruptors such as OPs and the appearance of some human urogenital congenital abnormalities (such as cryptorchidism and hypospadias(Mamoulakis et al. 2002; Mamoulakis et al. 2017a; Petrakis et al. 2017)) has been recently investigated in a comprehensive review concluding that a trend towards a positive association between environmental/occupational exposure to some OPs and some congenital abnormalities appears to exist (Kalliora et al. 2018). The aim of this review is to negotiate the effect of exposure to OPs specifically on renal tissue and kidney function.

2. OP Toxicity

According to the Globally Harmonized System (GHS) the toxicity of a substance can be subcategorized to acute (≤24hrs), subacute (≤28 days), sub-chronic (<90 days), chronic (≥90days). The acute toxicity of OPs might become apparent with symptoms such as salivation, lacrimation, urination, defecation, gastrointestinal distress, emesis, tightness in the chest, wheezing, increased sweating, arrhythmia, headache, restlessness, confusion, ataxia, tremor, cramps, fasciculation, seizures and death results due to respiratory or cardiac arrest (Gupta 2006). Delayed neurotoxicity
OP-induced delayed neuropathy, presents with cramping, ataxia and weakness of the limbs manifesting at 10-14 days after exposure due to phosphorylation and dealkylation of an enzyme called neuropathy target esterase, which cause total loss of myelinated fibers in the white matter of the spinal cord and hypoxic ischemic encephalopathy (Kobayashi et al. 2017; Lotti and Moretto 2005). OP-induced intermediate syndrome is a distinct clinical entity, usually occurring after the acute phase but before the OP-induced delayed neuropathy, 2-4 days post ingestion, and becomes apparent with respiration, proximal limb and fascial muscles weakness with some patients requiring ventilator support. To date, there is minimal evidence that we can predict whether a patient will develop these symptoms (Alahakoon et al. 2017; Karalliedde et al. 2006; Yang and Deng 2007).

Acute effects are well known but chronic effects are unclear. Suggested long-term effects include atherosclerosis and cardiovascular disease, especially in young individuals (Hung et al. 2015).

It is well known that Chlorpyrifos produces several effects other than cholinergic and delayed nephropathy, hence some effects should not be regarded as representative for all OPs. Carcinogenesis has also been suggested to be associated with chronic use of OPs since AChE has a tumour suppressor role (Perez-Aguilar et al. 2015), regulating apoptosis (Deng et al. 2006). Tetrachlorvinphos and parathion are classified as “possibly carcinogenic”, whereas malathion and diazinon as “probably carcinogenic” to humans (Guyton et al. 2015). Other factors that influence the toxic effect of OPs include genetic polymorphisms and duration of exposure (Androutsopoulos et al. 2011; Tsatsakis et al. 2011; Tsatsakis et al. 2009).

3. Renal Toxicity of OPs

Although OPs exert their deleterious effect mainly in the nervous system, they can potentially affect other organs too. Respiratory, neurological and cardiac complications are more common, whereas the pathophysiology of nephrological damage has not been extensively investigated. Acute kidney injury (AKI) is a great risk for patients’ health. It is characterized by high morbidity, especially in critically ill patients, and can be easily misdiagnosed especially in cases of massive manifestations
of toxicity from other organs that overshadow the silent but deadly renal injury. The pathogenesis of renal injury is not well established and multiple speculations exist in the limited literature. Some of the suggested mechanisms implicate pseudocholinesterase levels in renal distal convoluted tubule, oxidative stress (Mamoulakis et al. 2017b; Tsarouhas et al. 2018) due to high intratubular OP concentration, rhabdomyolysis and hypovolemia due to dehydration (Agostini and Bianchin 2003). Renal circulation and electrolyte excretion has also been suggested to be partially controlled by cholinergic mechanism, therefore, OP poisoning disrupts renal function (Wedin 1992). Despite the limited knowledge on the pathophysiology, the histopathological damage induced by OPs is slightly more illuminated. Changes observed in renal tissue of rats treated with OPs include: shrunken glomeruli, widened urinary space, inflammatory cells infiltration of the interstitial tissue, pyknotic nuclei, cytoplasm vacuolation of renal tubules, hyaline material in the lumen of some tubules, dilatation and congestion of blood vessels, cytoplasm degeneration of renal tubules, epithelial casts deposition in the lumen of some tubules and rupture of Bowman’s capsule (Zidan Nel 2015).

3.1. Nephrotoxic effects of OPs suggested by animal studies

Administration of chlorpyrifos in mice has been reported to result in body weight reduction, kidney weight gain, significant oxidative stress, decreased serum arginine-methionine-choline concentrations indicating kidney injury/raised serum lactate dehydrogenase activity (Deng et al. 2016). Histological changes include epithelial cell and intratubular edema, focal hemorrhage and inflammatory infiltration. Chlorpyrifos has also been reported to result in functional and structural changes on rat kidneys in a dose and time related manner (Tripathi and Srivastav 2010). Nephrotoxicity with significantly lower pseudocholinesterase levels and raised urea/creatinine but not kidney weight has been reported after exposure of rats to malathion and spinosad (Zidan Nel 2015). Similar results regarding body/organ weight, lipid peroxidation levels and renal histopathological changes have been reported after triazophos administration to rats (Sharma and Sangha 2014). Administration of diazinon has been reported to induce high levels of reactive oxygen
species (ROS) production and oxidization of cellular macro-molecules (lipids, DNA, nucleic acid and proteins) through glutathione reduction in a dose dependent manner as well as depletion of all antioxidant defenses of the kidney in the rat, including NADPH availability (Shah and Iqbal 2010). Similarly, inflammatory cell infiltration, glomerular degeneration and congestion after diazinon exposure has been reported in mice (Cakici and Akat 2013). Uniformly, chronic exposure of diazinon to rabbits, revealed dose dependent renal inflammation and fibrosis as well as induced oxidative stress and DNA damage (Tsitsimpikou et al. 2013).

Potential long-term effects of OP poisoning in combination with other substances have also been reported in the rat (Alfaro-Lira et al. 2012). In this context, malathion amalgamated with estrogen has been reported to exert exponential glomerular hypertrophy, tubular damage and atypical proliferation as well as malignant proliferation in some areas. Another noteworthy observation is the aggressive expression of certain proteins signifying important changes in protein level with the combination of these two agents (Alfaro-Lira et al. 2012). Chlorpyrifos and the fungicide carbendazim is another potential nephrotoxic combination studied in the rat (Abolaji et al. 2017). In line with other studies, raised urea/creatinine levels, decreased anti-oxidant enzymatic activity and non-enzymatic anti-oxidant levels have been reported; with worse outcomes compared to those produced by each substance in single use (Abolaji et al. 2017). Similarly, the combined exposure of rats to chlorpyrifos and abamectin has been reported to result in diminished ACHE activity, raised urea/creatinine, significant reduction of the activity of anti-oxidant enzymes but raised renal lactate dehydrogenase activity (Nasr et al. 2016). Main characteristics of the studies mentioned above are summarized in Table 1.

3.2. Protective effect against OP nephrotoxicity

In a study evaluating the potential nephrotoxic effects of methidathion on rats, the protective effect of vitamin E and ascorbic acid on kidney function was also tested (Sulak 2005). Significantly decreased ACHE activity and increased malondialdehyde levels were detected in those animals.
exposed to OPs without vitamin protection. There was evidence of glomerular sclerosis, vascular congestion/fibrosis, focal tubular necrosis, hydropic degeneration of tubular epithelial cells and severe interstitial mononuclear cell infiltration. Malondialdehyde increase resulted possibly due to lipid peroxidation directly induced by OPs or due to increased ROS production. The vitamins didn’t protect against glomerular sclerosis but restored all other changes. Another beneficial effect these vitamins was the significant decrease of lipid peroxidation and reduction of the renal oxidative stress (Sulak 2005). In another study on mice exposed to several different doses of chlorpyrifos, the protective effect of vitamin E was evaluated as a nephroprotective agent (Ma et al. 2013). Histopathological analysis revealed a large dose-dependent reduction of tubular space and extreme edema of glomerular epithelial cells. Vitamin E prevented tissue damage by reducing chlorpyrifos-induced ROS production OP-promoted lipid peroxidation injury and DNA damage (Ma et al. 2013).

In a similar study on rats exposed to dimethoate, the ameliorating effect of vitamin E and selenium was tested (Ben Amara et al. 2013). Dimethoate induced an increase in lipid peroxidation and hydrogen peroxide production, a decrease in renal ATPase/lactate dehydrogenase activity, GSH and NPSH levels. All these alterations were partially or entirely reversed with the administration of selenium and/or vitamin E (Ben Amara et al. 2013).

Other substances tested on animals as potential nephroprotective agents against OP-induced nephrotoxicity include quercetin (Hou et al. 2014), interleukin-10 (Yurumez et al. 2007), gallic acid (Ajibade et al. 2016), pomegranate seed oil (Boroushaki et al. 2013), caffeic acid phenethyl ester, intralipid (Celik et al. 2015) and lavender essential oils (Selmi et al. 2015). Quercetin, a potent flavonoid antioxidant, was also studied in this respect (Hou et al. 2014). Evaluation of the enzymatic free radical/ROS scavenger complex response (including superoxide dismutase, glutathione peroxidase, and catalase) as well as serum malondialdehyde, urine retinol-binding-protein and 2-microglobulin levels it was shown that quercetin altered favorably the toxic effects of dichlorvos in a dose-dependent manner on rats (Hou et al. 2014). Similarly, it was shown that quercetin provides a nephroprotective defense mechanism in rats even against mixture of OPs, such as dichlorvos and...
dimethoate, by increasing the activity of antioxidative enzymes (catalase, superoxide dismutase) offering protection against DNA damage (Li et al. 2016). Considering that interleukin-10 is one of the few anti-inflammatory cytokines, a study on rats, was conducted in order to investigate the effect of fenthion on liver, kidney and lung, as well as the potential protective effect of interleukin-10 on these organs. Cellular changes and patches of necrosis near the proximal tubules of the kidneys were detected, which were more evident in the group of rats that received the OP and the protective effect of interleukin-10 against OP-induced histological damage was demonstrated (Yurumez et al. 2007).

Gallic acid, a natural phenolic agent, renowned for its antioxidant, anti-inflammatory, anticancer, and free radical scavenging properties, has also been tested against diazinon poisoning in rats (Ajibade et al. 2016). The significant elevation of malondialdehyde and nitric oxide in the kidney tissue, as well as the calculated drop of the enzymatic antioxidant activity got almost neutralized with the administration of gallic acid. On the contrary, the anti-inflammatory effect of gallic acid failed to reduce OP-induced kidney weight gain (Ajibade et al. 2016). In another study on rats, pomegranate seed oil was found to hinder and minimize renal oxidative stress effects and DNA changes induced by diazinon (Boroushaki et al. 2013). Caffeic acid phenethyl ester, a flavonoid, and intralipid were also tested in this respect on rats (Celik et al. 2015). Caffeic acid phenethyl ester is a ROS scavenger by inhibiting xanthine oxidative system, and intralipid binds lipophilic agents. Measuring the total anti-oxidant/oxidant status and performing histopathologic analysis to the experimental renal tissue, it was suggested that both agents are equally adequate in preventing renal injuries caused by dichlorvos. Last but not least, the nephroprotective effect of lavender (Lavandula stoechas) essential oils against malathion-induced oxidative stress was investigated mice and the possible mechanism implicated in such protection (Selmi et al. 2015). It was found that malathion induced a clear nephrotoxicity with kidney weight increase and related hemodynamic parameters deregulation and a considerable perturbation of metabolic parameters. Malathion administration was accompanied by an oxidative stress status assessed by an increase of malondialdehyde and hydrogen peroxide levels as well as a depletion of sulfhydryl group content and antioxidant enzyme activities.
such as catalase and glutathione peroxidase, superoxide dismutase in the kidney. Treatment with lavender essential oils abolished all malathion-induced body weight loss, kidney relative weight increase, hemodynamic and metabolic disorders, as well as renal oxidative stress, exhibiting potential nephroprotective effects against malathion-induced oxidative stress in mice that might be related, in part, to its antioxidant properties. Main characteristics of the studies mentioned above are summarized in Table 1.

3.3. Nephrotoxic effects of OPs suggested by human studies

The nephrotoxic effects of OPs have been evaluated in very few studies on human cells. The effect of chlorpyrifos and trichloropyridinol has been evaluated for example on 293 human embryonic kidney cells (Van Emon et al. 2018). It has been shown that exposure triggers alterations in protein expression, permanent cell damage and death. Loss of viability has been reported to be exponentially increased with increasing dosage. Affected cells develop swelling or shrinkage and exhibit detachment cluster aggregation. It has been suggested that chlorpyrifos induces interleukin-6 and minimal interleukin-1a production contrary to trichloropyridinol, which shows opposite effect. Nevertheless, considering that apoptosis in some cells is initiated prior to production of these cytokines, it seems that apoptosis is driven by an inflammation-independent mechanism (Van Emon et al. 2018).

A limited number on human case reports focusing on OP-induced nephrotoxicity exists in the international literature. Cavari et al and Rubio et al reported on OP poisoning involving four children and one adult, respectively that developed renal failure necessitating conventional renal hemofiltration apart from one case treated with continuous venous-venous hemofiltration (Cavari et al. 2013; Rubio et al. 2012). Similarly, Agostini et al reported on a 41-year-old male with bipolar psychiatric disorder who intentionally ingested methamidophos (Agostini and Bianchin 2003). The patient was admitted to the intensive care unit for 25 days developing acute renal failure despite large volumes of intravenous fluid replacement/adequate atropine and pralidoxime treatment.
Venous-venous hemofiltration was employed for 13 days, and finally the patient was discharged with normal renal function after a total hospitalization of 60 days (Agostini and Bianchin 2003). Another case of a 30-year-old male who sprayed metacid-methyl parathion without appropriate precautions has been reported (Vikrant 2015). Three days later his general condition deteriorated. He was admitted to the hospital with abdominal pain and vomiting due to liver and kidney failure (without evidence of rhabdomyolysis), with a depressed level of plasma cholinesterase, suggesting proximal renal tubular damage. General condition improved with atropine and supportive treatment.

Similarly, the case of a 23-year-old male admitted in a comatose state due to OP poisoning with AKI (Zafar et al. 2017). He was treated with hemodialysis, atropine, pralidoxime and supportive care. Finally, the case of a 75-year-old male, who deliberately performed self-harm with chlorpyrifos and minimal amount of kerosene leading to a unique aspect of OP-induced nephrotoxicity characterized by distal renal tubular acidosis (Narayan et al. 2017).

The potential nephrotoxic effects of OPs have also been evaluated in a few large human studies. To detect the risk of acute renal failure among acute poisoning cases, identify the underlying causes and to analyze the outcome, a prospective study with nested case control was conducted (Sweni et al. 2012). The study included 1,250 cases admitted over a period of 12 consecutive months to the Poison Control, Training and Research Centre of Government General Hospital, Madras Medical College, India. Patients were monitored and evaluated for development of acute renal failure. Thirty-two cases developed ARF. Twenty-four were due to snake bite, the rest due to chemical poisons. None of the 400 patients admitted for OP poisoning presented with evidence of AKI.

Arefi et al, performed a cross-sectional study surveying 1500 poisoned patients referred to the Emergency Department of Baharloo Hospital in Tehran during 2010 (Arefi et al. 2014). They reported that 16.7% of the patients referred presented with OP poisoning developing AKI predominantly due to subsequent rhabdomyolysis. Based on their findings the authors concluded that there is a high probability of renal failure for patients poisoned with various drugs and
substances including OPs that necessitate prompt hospital administration and appropriate treatment to prevent this significant side effect.

Similarly, in order to investigate the association between OP poisoning and the subsequent risk of AKI a National Health Insurance program was launched in Taiwan on March 1, 1995, consisting of detailed healthcare data from >23 million enrollees (>99% of the population of Taiwan). Using the National Health Insurance Research Database, a retrospective cohort study was conducted to study whether patients with OP poisoning are associated with a higher risk of subsequent AKI (Lee et al. 2015). The cohort included 8924 individuals aged ≥20 years with OP poisoning diagnosis of hospitalization during 2000-2011. Each OP poisoning patient was frequency-matched to 4 control patients based on age, sex, index year, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, and stroke (N = 35,696). The overall incidence of AKI was higher in the patients with OP poisoning than in the controls (4.85 vs 3.47/1000 person-years). After age, sex, comorbidity adjustments, patients with OP poisoning were found to be associated with a 6.17-fold higher risk of AKI compared to controls. Main characteristics of the studies mentioned above are summarized in Table 1.

4. Conclusion

Inherently, OPs are widely used in everyday practice, as they remain among the most effective existing pesticides. Nonetheless, their effects pose a threat to human and other mammals’ health which are dose and duration dependent. Within this review article it has become apparent that different OPs exert interchangeable biochemical as well as structural nephrotoxic effects on all studied mammals. Most of the studies that were included in our review incorporated experiments on rats and very few referred to human cells or case reports. Safer outcomes can be acquired from the experiments that were conducted under various but controlled clinical circumstances, e.g. acute, subacute, sub-chronic and chronic exposure to different OPs as well as various dosing protocols. With the limited data that we had in our disposal, it can be assumed that the nephrotoxic effects
become more catastrophic with prolonged exposure or dose escalation. (Refer to Table 1.) We have to be aware of these potential pernicious effects, recognize rapidly their symptoms, treat and provide supportive treatment with special attention to patients developing rare complications. Difficulties may arise due to special properties of OPs, to be stored in the tissue and exhibit low serum levels and slow release, hence their effects might be prolonged. Thus, additional research is required in order to conquer the pathophysiology against OP harmful effects, develop new and health-friendly agents to substitute their use and also counter-act their injurious sequel on our nature as their impact could appear long term even at levels around permitted toxicological values.

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**References**


**Table 1. legend:** Table 1. Organophosphate nephrotoxicity in mammals; review of literature

<table>
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<th>Organophosphate &amp; Dosing</th>
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<th>Duration</th>
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<th>Effects of Organophosphate exposure</th>
</tr>
</thead>
<tbody>
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<td>Orally</td>
<td>Total 28 days</td>
<td>Sample: 28 days</td>
<td><img src="#" alt="Kidney weight" />, <img src="#" alt="LDH activity" />, Methionine, Arginine, Choline levels</td>
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<tr>
<td>Authors</td>
<td>Animals, Treatments, Duration</td>
<td>Treatment Details</td>
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<tr>
<td>Iqbal (2010)</td>
<td>Male, Wistar rats</td>
<td>Chlorpyrifos</td>
<td>5mg/kg, 50mg/kg, 150mg/kg</td>
<td>Orally, Total 8 weeks</td>
<td>Epithelial cell and intertubular space edema, focal hemorrhage and inflammatory cells infiltration</td>
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<td>Shah and Sangha (2014)</td>
<td>Male, Female Albino rats, Sprague-Dawley rats</td>
<td>Diazinon (10mg/kg), (15mg/kg), (30mg/kg)</td>
<td>Orally, Total 8 weeks</td>
<td>Sample: 8th week</td>
<td>GSH levels, GST, antioxidant enzymes, Quinone reductase, c-glutamyl transpeptidase activity, LPO, Urea and Creatinine levels</td>
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<td>Zidan Nel (2015)</td>
<td>Male, Albino (Sprague-Dawley) rats</td>
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<tr>
<td>Sharma and Sangha (2014)</td>
<td>Male rats, Female albino rats</td>
<td>Triazophos, (1/10^9) (1/10^9) (1/40) of LD50 82 mg/kg of body weight</td>
<td>Orally, Total 30 days</td>
<td>Sample: 30 days</td>
<td>Total protein in kidney (1/10^9 and 1/20^9 of LD50), LPO levels of the (1/10^9 and 1/20^9 of LD50), CAT activity (1/10^9 and 1/20^9 of LD50), SOD activity (1/10^9 of LD50), GR, GST, GPx activity in all treated rats, Vascular dilation, dilatation of Bowman’s space with glomerular atrophy, shrunken glomeruli, Bowman’s capsules and associated tubules along with hemorrhage between tubules was observed in 1/10^9 and 1/20^9 of LD50</td>
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<tr>
<td>Shah and Iqbal (2010)</td>
<td>Male, Sprague Dawley male rats</td>
<td>Diazinon (10mg/kg), (15mg/kg), (30mg/kg)</td>
<td>Orally, Total 8 weeks</td>
<td>Sample: 8th week</td>
<td>GSH levels, GST, antioxidant enzymes, Quinone reductase, c-glutamyl transpeptidase activity, LPO, Urea and Creatinine levels, Edema with obliteration of space in Bowman’s capsule, nuclear pyknosis, tubular epithelial cells degeneration</td>
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<tr>
<td>Study/Jurisdiction</td>
<td>Species/Strain</td>
<td>Compound (Concentration)</td>
<td>Route</td>
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<tr>
<td>(Tsitsipikou et al. 2013)</td>
<td>Female, New Zealand white rabbits</td>
<td>Diazinon (2.64mg/kg) (5.28mg/kg)</td>
<td>Orally</td>
<td>1 year (3 months on – 8 months off – 1 month on)</td>
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<td>Telomerase activity, Oxidative DNA damage, Total antioxidant capacity (high dose), GSH (low dose), Focal inflammation and fibrosis</td>
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<td>(Cakici and Akat 2013)</td>
<td>Swiss albino mice</td>
<td>Diazinon (30mg/kg) (60mg/kg) (120mg/kg)</td>
<td>Orally</td>
<td>30 days</td>
<td>Sample: 30th day</td>
<td>Mononuclear cell infiltration, glomerular degeneration and loss, vascular congestion</td>
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<tr>
<td>(Alfaro-Lira et al. 2012)</td>
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<td>Malathion (100µg/100g) 17β-estradiol (22mg/100g)</td>
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<td>Sample: 30th day 124th day 240th day post treatment</td>
<td>Progressive changes: glomerular hypertrophy, tubular damage, atypical proliferation in cortical area and hilum zone. Combination treatment exerted greater histopathological changes.</td>
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<tr>
<td>(Abolaji et al. 2017)</td>
<td>Female, Wistar rats</td>
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<tr>
<td>(Nasr et al. 2016)</td>
<td>Male, Wistar rats</td>
<td>Chlorpyrifos (14.9 mg/kg) Abamectin (30mg/kg)</td>
<td>Orally</td>
<td>Total 30 days</td>
<td>Sample: 30th day</td>
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<td>(Sulak 2005)</td>
<td>Male, Wistar albino rats</td>
<td>Methidathion (5mg/kg)</td>
<td>Orally</td>
<td>Total 4 weeks</td>
<td>Sample: 4th week</td>
<td>AChE activity MDA levels Extensive glomerular sclerosis, vascular congestion, fibrosis, and focal tubular necrosis Hydroptic degeneration of tubular epithelial cells and severe interstitial mononuclear cell infiltration</td>
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<tr>
<td>(Ma et al. 2013)</td>
<td>Male, Kunming mice</td>
<td>Chlorpyrifos (3mg/kg) (6mg/kg) (12mg/kg)</td>
<td>Orally</td>
<td>Total 7 days</td>
<td>Sample: 7th day</td>
<td>Tubular space reduction, glomerular epithelial cell edema ROS MDA levels GSH levels Dose dependent DNA damage due to DNA-protein crosslinks</td>
</tr>
<tr>
<td>(Ben Amara et al. 2013)</td>
<td>Female, Wistar rats</td>
<td>Dimethoate (0.2g/L in their drinking water)</td>
<td>Orally</td>
<td>Total 30 days</td>
<td>Sample: 30th day</td>
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</tr>
<tr>
<td>(Hou et al. 2014)</td>
<td>Male, Wistar rats</td>
<td>Dichlorvos (7.2 mg/kg)</td>
<td>Orally</td>
<td>Total 90 days</td>
<td>Sample: 90th day</td>
<td>SOD, CAT, GPx (activity) MDA levels Urea, Creatinine Urine RBP, β2-MG levels Urine uric acid levels NAG/CR (activity) Extensive cellular vacuolation</td>
</tr>
<tr>
<td>(Yurumez et al. 2007)</td>
<td>Female, Wistar-Albino rats</td>
<td>Fenthion (0.8 g/kg)</td>
<td>Intraperitoneally</td>
<td>Single dose</td>
<td>Sample: 6 hrs post injection</td>
<td>Minimal patchy cellular changes and necrosis around the proximal tubules</td>
</tr>
<tr>
<td>(Abjade et al. 2016)</td>
<td>Male, Wistar rats</td>
<td>Diazinon (3 mg/kg)</td>
<td>Orally</td>
<td>Total 21 days</td>
<td>Sample: 24 hrs post final dose</td>
<td>MDA H2O2 NO LPO GSH GPx GST SOD CAT (activity) Perivascular and interstitial inflammatory infiltration, tubular degenerative changes</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Animal Species</td>
<td>Toxicant</td>
<td>Route</td>
<td>Dose</td>
<td>Duration</td>
<td>Sample</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>----------</td>
<td>-------</td>
<td>------</td>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>(Boroshaki et al. 2013)</td>
<td>Male, Wistar rats</td>
<td>Diazinon (100 mg/kg)</td>
<td>Intraperitoneally</td>
<td>Single dose</td>
<td>24hrs post injection</td>
<td></td>
</tr>
<tr>
<td>(Celik et al. 2015)</td>
<td>Wistar, Albino rats</td>
<td>Dichlorvos (4 mg/kg)</td>
<td>Orally</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Selmi et al. 2015)</td>
<td>Male, Swiss Albino mice</td>
<td>Malathion (200 mg/kg)</td>
<td>Orally</td>
<td>Total 30 days</td>
<td>Sample: 24hrs post dose</td>
<td></td>
</tr>
<tr>
<td>(Li et al. 2016)</td>
<td>Male, Wistar rats</td>
<td>Mixture Dichlorvos (2.4mg/kg) + Dimethoate (0.04 mg/kg) + acephate (0.5 mg/kg) + phorate (0.05mg/kg)</td>
<td>Orally</td>
<td>Total 90 days</td>
<td>Sample: 90th day</td>
<td></td>
</tr>
<tr>
<td>(Van Emon et al. 2018)</td>
<td>HEK 293 cells</td>
<td>Chlorpyrifos (1-100,000 ng/mL)</td>
<td>Culture treatment</td>
<td>Total 24 hours</td>
<td>Sample: 24hrs post exposure</td>
<td></td>
</tr>
<tr>
<td>(Cavari et al. 2013)</td>
<td>4 children</td>
<td>Chlorpyrifos (2 children) Carbamate (1 child) Unidentified (1 child)</td>
<td>Orally</td>
<td>Single dose</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Rubio et al. 2012)</td>
<td>1 adult male</td>
<td>Diazinon</td>
<td>Transdermally and inhalation</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Agostini and Bianchin 2003)</td>
<td>1 adult male</td>
<td>Methamidophos</td>
<td>Orally</td>
<td>Single dose</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Vikrant 2015)</td>
<td>1 adult male</td>
<td>Methyl-parathion</td>
<td>Inhalation Transdermally Ingestion</td>
<td>Two consecutive days for 4 hours</td>
<td>3 days post last exposure</td>
<td></td>
</tr>
<tr>
<td>(Zafar et al. 2017)</td>
<td>1 adult male</td>
<td>Undetermined organophosphate</td>
<td>Ingestion Suicide attempt</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Narayan et al. 2017)</td>
<td>1 adult female</td>
<td>Chlorpyrifos (100ml) + Small amount Kerosene</td>
<td>Ingestion Suicide attempt</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Sweni et al. 2012)</td>
<td>400 patients admitted with organophosphate poisoning</td>
<td>Organophosphate poisoning</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Lee et al. 2015)</td>
<td>8924 individuals</td>
<td>Organophosphate poisoning</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

carbonyl, **ROS**: reactive oxygen species, **SOD**: superoxide dismutase, **TBARS**: thiobarbituric acid-reactive substances, **Zn**: zinc,