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Review Paper

Oxidative Stress and Endocrine Disruption Following Exposure to Chlorpyrifos

Mojtaba Ehsanifar[1*], Alireza Esmaeili[2], Omid Ahmadi[3]

1. Department of Environmental Health Engineering, Torbat Jam School of Medical Sciences, Torbat Jam, Iran.
2. Department of Emergency Medicine, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
3. Department of Nursing, Torbat Jam School of Medical Sciences, Torbat Jam, Iran.

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ABSTRACT

Chlorpyrifos (CPF) is a widely used organophosphate pesticide that has been shown to cause a range of toxic effects, including oxidative stress and endocrine disruption. This review aims to summarize the most recent findings regarding CPF's toxicological impacts on human health, with a focus on its mechanisms of action, particularly in relation to oxidative stress and endocrine disruption. The review also addresses the environmental persistence of CPF and the potential cumulative effects of chronic exposure. Recent studies (2018–2023) are integrated to present novel insights into CPF-induced cellular damage, as well as its broader implications for public health and the environment. Furthermore, the paper discusses potential strategies for mitigating CPF's harmful effects, including bioremediation and antioxidant therapies.

*** Corresponding Author:**
Mojtaba Ehsanifar, Assistant Professor.
Address: *Department of Environmental Health Engineering, Torbat Jam School of Medical Sciences, Torbat Jam, Iran.*
Tel: *+98 (922) 0854486*
E-mail: *Ehsanifar@gmail.com*

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Introduction

The increasing global reliance on pesticides to meet the growing demands of agriculture has led to widespread concerns regarding their potential health impacts [1]. Among the most commonly used pesticides, organophosphates (OPs), including chlorpyrifos (CPF), are of particular concern due to their broad-spectrum efficacy and persistence in the environment [2, 3] and are the most significant cause of illness and mortality in third world countries [4, 5]. OP compounds are among the largest and most diverse pesticides that are used more than other pesticides to control diseases transmitted by arthropods, due to their effects on a wide range of pests and their low cost. However, due to the lack of awareness among farmers and other users about the harmful effects of pesticides and the correct principles of pest control, this is often done incompletely or improperly [1]. Pesticides used in agriculture can contaminate water sources and pose health risks by entering the food chain [1, 6]. CPF, known by the trade name Dursban, is an OP insecticide that can enter the body through the skin, respiratory tract, and digestive system, and quickly metabolizes into active metabolites in the liver and kidneys. Most people are consistently exposed to low concentrations of OPs, and studies have shown that the risks of its side effects are more significant than the risk of cancer. CPF is persistent in water, soil, and plants for a long time and can remain for weeks or months. Therefore, an individual can be exposed to it through the environment, food, or occupational settings [7]. In recent decades, there have been many discussions in scientific centers and various communities regarding the use of pesticides [1]. Researchers believe that the widespread use of pesticides today is associated with serious risks for humans and the environment. The extent and limits of these risks are not precisely defined and accurate statistics of damages caused by various types of poisoning are not available [7]. The results of studies conducted on animals and humans have demonstrated the harmful effects of CPF on different organs such as the immune system, blood cells [8], reproductive system [6], liver and kidney [9]. It appears that its effects on the brain, liver, kidneys, and testes are related to increased oxidative stress [6, 9]. Although the cellular mechanisms of the harmful effects of this pesticide on the nervous system have not been fully identified. Despite that, CPF is still widely used in many countries due to its effectiveness and durability in residual form. This mini-review was conducted with the aim of emphasizing the toxicological effects, especially the effect of oxidative stress and endocrine disruption and the resulting damage to human health.

Materials and Methods

A comprehensive search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, using keywords such as CPF toxicity, oxidative stress markers, and endocrine disruption in pesticides. The review includes studies published between 2015 and 2023, ensuring that the most current findings are represented. The inclusion criteria were focused on peer-reviewed articles that involved both animal and human models and specifically examined CPF's effects on oxidative stress and endocrine functions. Studies not related to CPF, those involving other pesticide classes, or those that lacked molecular insights were excluded.

The selected studies were synthesized to assess consistent findings on CPF's ability to induce oxidative stress, including the production of reactive oxygen species (ROS) and lipid peroxidation (LPO), as well as its endocrine-disrupting effects on the hypothalamic-pituitary-adrenal (HPA) axis, thyroid function and other hormonal pathways. Special attention was given to studies addressing CPF's persistence in the environment and its potential for cumulative toxicity through prolonged exposure.

Comparison with prior studies

While CPF's toxicological effects have been well documented, previous reviews have not thoroughly addressed CPF's interaction with other environmental contaminants or its long-term effects at sub-lethal doses. This review fills these gaps by focusing on CPF's dual role in oxidative stress and endocrine disruption. It also provides a more detailed exploration of CPF's molecular mechanisms, which have been largely underexplored in earlier work. The integration of recent findings on CPF's environmental persistence and the risks of chronic exposure further distinguishes this review from past analyses, offering a more comprehensive understanding of CPF toxicity.

Research gaps and future directions

Despite the wealth of information on CPF, several critical research gaps remain. Notably, the long-term effects of chronic low-dose exposure, as well as the combined effects of CPF with other environmental pollutants, require further investigation. More studies are needed to elucidate the specific molecular mechanisms by which CPF interacts with the endocrine system, particularly its influence on gene expression and hormonal regulation. From a policy standpoint, the review highlights the urgent need for stricter regulations on

CPF use, especially in areas with intensive agricultural activity. The findings suggest that additional safety measures should be put in place to minimize exposure and mitigate CPF's harmful effects on public health. Moreover, exploring alternatives to CPF in agricultural practices, such as less toxic pesticides, could help reduce environmental contamination and human health risks. Bioremediation approaches and antioxidant therapies are also promising areas for future research aimed at mitigating CPF-induced toxicity.

Chemical and physical properties, prevalence, and persistence of CPF worldwide

CPF is a chlorinated OP and one of the most widely used insecticides with the chemical formula $C_9H_{11}C_{l3}NO_2PS$ and O, O-diethyl-O-(3,5,6-trichloro-2-pyridinyl)-phosphorothioate (IUPAC name) [10]. CPF is a white or colorless crystalline powder with low water solubility and a smell similar to mercaptan (a thiol odor) and is available under various trade names such as Dursban, Lorsban, Suscon, Equity, Empire20 and Whitmire PT270 [11]. It readily dissolves in benzene, corn oil, methanol, dimethyl sulfoxide (DMSO), acetone, xylene, Tween 20, methylene chloride, and more [12]. OPs constitute more than 50% of all insecticides used globally, and CPF is one of the broad-spectrum OP insecticides utilized worldwide. CPF is employed in agriculture and household pest control [13, 14]. The projected compound annual growth rate (CAGR) for the global market between 2018 and 2023 is estimated at 5.5% [15]. Due to its widespread application, short persistence, cost-effectiveness, low toxicity spectrum, and high degree of efficacy, CPF has become a suitable choice for farmers globally and is still registered as a pesticide in most developed and developing countries. It is used on 50 different food crops. However, its overuse has caused harm to human health and the environment [16]. CPF residues in water reservoirs and groundwater also indicate its overuse and unintentional use, and resulting CPF can infiltrate groundwater sources in addition to being present in edible food products [17]. Studies on bioaccumulation in water, snow, ice/air, vegetation, and sediment samples from polar regions have shown the persistence of high levels of CPF in these conditions [10]. The residual form of CPF can be determined by measuring levels of diethyl thiophosphate (DETP), trichloro-2-pyridinol (TCP), or diethyl phosphate (DEP) in blood or urine. Among CPF metabolites, CPF-OXN is the main active metabolite and is the most toxic to organisms [18, 19]. It has been reported that persistence of CPF in aquatic ecosystems is higher due to its stability against hydrolysis compared to soil. CPF persistence in soil varies from several days to 4 years, depending on environmental factors such as soil texture. Moreover, photodegradation in shaded areas is minimized. Therefore, the half-life and consequently the persistence of CPF in colder and darker Arctic conditions is significantly greater compared to tropical areas with several days of sufficient sunlight and relatively higher temperatures. Additionally, the persistence of these bacteria was higher in soils with lower pH compared to soils with higher pH [10].

Results and Discussion

Ways of exposure to CPF

CPF absorption may occur through several routes such as inhalation of aerosols [20] through oral and dermal routes. Examination of human volunteer urinalysis (after CPF exposure) revealed that approximately 70% of CPF absorption occurs through oral route, whereas less than 3% of CPF absorption occurs through the dermal route [21]. Since CPF sale for domestic use is prohibited in many countries, most exposure to inhaled CPF likely involves agricultural (occupational) or rural residential use. Although this concentration is not significant, it poses a serious risk of exposure to CPF in the community. Findings show that symptoms of exposure to CPF through inhalation are faster than those of dermal and oral absorption [22]. Therefore, most current study on effects of CPF exposure have focused only on occupational exposure to CPF in pesticide applicators and farm workers. It is generally thought that CPF is well absorbed into the lungs after exposure via the airway, although no measurements have proven this assumption directly [23]. Animals and humans can be CPF exposure through the ambient, and CPF can be generated through several routes, the main of which are dermal, oral, and respiratory [22, 24]. Dietary sources are one of the major causes of nonoccupational CPF exposure in humans. Livestock and plants may be important sources of human exposure to CPF [22]. Considering that CPF is commonly used in plant applications, pesticide residues, either as CPF or in other forms, such as the TCP form, have been detected in food [25]. Therefore, the CPF-methyl presence in staple foods could explain 50% of the increase in urinary TCP of individuals previously exposed to CPF. The increase in the urinary TCP concentration can be attributed to CPF-methyl since most of the CPF-methyl reported in samples obtained from cereal products is due to TCP [22]. The solubility of CPF in water at 20-25 ˚C is 0.7-2.0 mg/L, so it can permeate soil water when mixed with rain or irrigation water. Even if CPF enters water, it evaporates from the surface of the water. However, after spraying, CPF increasingly

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binds to particles of soil and plant material, and very little CPF is washed and enters the groundwater. Generally, humans/animals may be exposed to CPF via inhalation, dermal, or oral routes; therefore, CPF absorption via these routes may vary and is primarily dose dependent [26]. This approach can inevitably expose animals and humans to traces of CPF.

CPF exposure and oxidative stress

CPF, as a pesticide, has a broad spectrum of efficacy. Although mammals are less sensitive to CPF toxicity compared to insects, CPF residues are observed more in invertebrates, vertebrates, and all living organisms [22]. Intrauterine exposure to CPF in humans has been studied, showing changes during pregnancy and low birth weight in infants [27]. The results also indicated reduced sperm count, sperm motility (poor sperm movement), and DNA changes in men. Furthermore, CPF effects were observed in cervical mucus and breast milk [28]. Our previous findings showed that airborne particulate matters (PM) can cross from blood–brain barrier (BBB) [29-33] and lead behavioral alterations such as memory and learning disorders [31, 34] and depression and anxiety by causing changes in gene expression and oxidative stress and neuroinflammation [35, 36]. CPF is one of the respiratory, digestive and contact insecticides that can inhibit the enzyme cholinesterase in the animal nervous system, resulting in nervous system disruption [37]. According to animal studies, this toxin can have toxic effects on various organs, such as the kidney [38], liver [39], immune system [40] and various blood parameters [41]. Additionally, this toxin can cause the production of free radicals and consequently increase oxidative stress in the liver, kidney tissues [38] and brain [42]. Research has shown that CPF increases the production of ROS, leading to cell membrane damage and ultimately cell death [43]. CPF can also lead to the accumulation of LPO products and the production of reactive oxygen [44, 45]. Glutathione peroxidase (GPx) is one of the mitochondrial enzymes that inhibits the chain propagation of LPO reactions and subsequent damage to DNA and RNA by converting lipid hydroperoxides to alcohols [46, 47]. The production of reactive oxygen species, increased malondialdehyde (MDA) and decreased GPx enzyme can be used as oxidative stress markers for damage to kidney and liver tissues [48]. Many OP insecticides are lipophilic and have a non-polar molecular structure, so they quickly accumulate in the liver, kidneys, and salivary glands after absorption [49]. CPF affects the central and peripheral nervous systems by inhibiting the enzyme acetylcholinesterase (AChE) [50]. This toxin can also induce oxidative stress in the body [51]. After entering the bodies of living organisms, CPF produces free radicals under the influence of various metabolic processes. These free radicals, which are responsible for causing oxidative stress, often have the ability to damage the structure of biological molecules such as genetic material and proteins [52]. According to studies, CPF toxin can cause weight loss in rats [53]. CPF has caused changes in the levels of GPx and MDA and these effects are mediated by mechanisms involving ROS [54]. Oxidative stress results from an imbalance between the production of free radicals and biochemical antioxidant defense mechanisms. In living organisms, the peroxidation of lipids present in the membranes of living cells is one of the most significant targets of free radicals. Under these conditions, not only is the structure and function of the membrane affected, but some of the oxidation products, such as MDA, can react with biomolecules [55, 56]. On the other hand, LPO of cell membranes can exacerbate toxicity by increasing the permeability of hydrogen peroxide into the cells [57]. The present study confirms that CPF can cause oxidative damage in the kidneys. Induction of oxidative stress is also indicated by the increase in MDA as a marker of LPO and the disordered status of antioxidant enzymes in the renal tissue of CPF-treated rats [58, 59]. CPF significantly reduces the concentration of GPx in the cells of mammals, especially in rats. Thus, it can be stated that with the decrease in the levels of this antioxidant in the cells, the necessary opportunity for the action of free radicals is provided and consequently, oxidative stress and its main consequence, the process of LPO, can easily occur, leading to numerous cellular damages [60]. One of the substances that can be produced as a result of oxidative stress caused by CPF is hydrogen peroxide (H_2O_2). The enzyme GPx can convert H_2O_2 into water and oxygen by oxidizing reduced glutathione to oxidized glutathione [61, 62]. Additionally, in another study conducted on female rats, it was observed that after 7 days of exposure to CPF, the level of the GPx enzyme significantly decreased [45].

Endocrine disruption following exposure to CPF

CPF can induce endocrine-disrupting effects through several pathways. As a primary inhibitor of AChE, CPF can inhibit enzyme activity by binding to AChE through irreversible phosphorylation and ultimately block the enzyme's active site. AChE is a serine hydrolase that is found in synaptic cleft between muscle and nerve cells and rapidly hydrolyzes acetylcholine (Ach) into its two constituents, choline and acetic acid, effectively terminating impulse/synaptic transmission. ACh is a neurotransmitter found at various sites in the CNS, such as neuromuscular junctions, visceral motor system synaps-

es, and all autonomic ganglia. AChE inhibition by CPF and other OP pesticides increases the ACh concentration in the synaptic cleft, which can lead to disruption of endocrine homeostasis in the body by preventing the translation of hormonal regulatory impulses [63]. In addition, CPF reportedly causes defects in the function of adenylyl cyclase and affects the activity of G proteins or GTP-binding proteins, which bind neurotransmitters to hormone receptors to coordinate signaling cascade activity. This effect manifests as Ach accumulation in postsynaptic cells, thus leading to the inhibition of signal transmission and ultimately causing disruption of many functions related to the endocrine system. The hypothalamic–pituitary–adrenal (HPA) axis is an important and major endocrine system that maintains various body functions and participates in the mechanism of stress response. In one study, after prenatal exposure, the CPF methyl (CPM) effects on adrenal hormones and the fetal thyroid were investigated at doses of 1, 10 and 100 mg/kg. The F1 generation had lower testosterone, estradiol, T3 and T4 levels, while the TSH and cortisol levels were greater in the female and male offspring. Dose-dependent vacuolation was observed in the zona fasciculata, zona glomerulosa, and zona reticularis. Vacuolation and histopathological necrosis were observed in the adrenal glands and thyroid [64]. Exposure to common CPFs/toxic chemicals causes damage to the hormonal pathway that maintains and is critical to the body's metabolic homeostasis. CPF effects do not result from events or stress on the HPA axis; however, OPs are thought to act on dexamethasone target tissues/cells. The proposed mechanism is the CPF-induced increase in plasma glucose levels due to HPA axis activation [65]. Significant evidence of the potential of OP pesticides following prenatal and postnatal exposure to cause several neurodevelopmental disorders leading to neurodevelopmental delays and learning disabilities due to AChE activity inhibition has been presented in various studies [66]. Exposure to OP pesticides, in addition to causing neurological disorders, also leads to diabetes-like changes. Pesticides, especially OPs, act as stress inducers, so these stress responses disrupt the homeostasis of the body and thus lead to hyperglycemia by activating the HPA axis [67]. The adrenal gland is activated under stress conditions and secretes glucocorticoids from the anterior pituitary gland in response to ACTH secretion. The secretion of these glucocorticoids from the adrenal cortex affects liver cells, activates gluconeogenesis pathway and increases blood glucose levels. Insulin secreted by pancreatic β-cells maintains plasma glucose levels and internalizes glucose in the myocytes and other vital organs. Stress is also known to release cytokines that participate in increased hepatic glucose production and induce glucose resistance in peripheral tissues [68]. Glucagon hormones from the α-cells of the pancreas and catecholamines from adrenal gland are other hormones that are produced in the stress response. Additionally, growth hormones from adenohypophysis somatotrophs also participate in increasing gluconeogenesis and glycogenolysis in liver cells [69]. One of the natural physiological mechanisms is the secretion of these hormones to maintain the circulating glucose for brain use and to support the insulin-independent cells' energy needs [70]. Catecholamines produced as a result of stress stimulate lipolysis and participate in inhibiting insulin signaling and glycogen production by releasing free fatty acids into circulation and increasing their levels in the blood [71].

Conclusion

Due to the known toxic effects of CPF such as oxidative stress, genotoxicity, neurotoxicity, immunotoxicity, mutagenicity, cytotoxicity, etc. the use of CPF has been banned in many countries. In this study, a brief description of the toxic effects of CPF exposure and the possible mechanisms underlying its effects on human health through inhibition of AChE, modification of gene regulatory factors or effects on estrogen receptors were presented. Evidence shows that humans are significantly sensitive to dermal and oral exposure to CPF and some of the clinical manifestations include dystonia, symptoms of cholinergic hyperstimulation, eye irritation, gear stiffness, Parkinson's disease, and respiratory distress. Therefore, the question of potential safety or toxicity of CPF can be resolved by appropriate quantitative tests using laboratory animals followed by human research on the known effects of OP pesticides. In this regard, additional safety evaluations should be conducted to reduce harmful health and environmental effects and fill this gap.

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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