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Neurotoxicity Mechanism of Organophosphate Flame Retardants

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Abstract. Organophosphate flame retardants (OPFRs) are the main alternative to bromine-based flame retardants because of their efficient fire-retardant properties, and as a result they are commonly used in industrial and consumer products. However, their widespread detection in the environment and biological samples, as well as their potential neurotoxic risks, have drawn significant attention. Current research has clearly demonstrated that OPFRs can cause multi-target damage to the developing nervous system through mechanisms such as interfering with various neurotransmitter systems (such as dopamine, GABA, and acetylcholine), inducing oxidative stress and mitochondrial damage, and blocking the autophagy-lysosome pathway. In clinical studies, it has been found that they are associated with decreased cognitive development in children and the risk of autism spectrum disorders. Nevertheless, this field still faces many challenges, including insufficient assessment of health risks from low-dose long-term exposure and mixed exposure, unclear sensitivity differences between different developmental stages and genders, and the incomplete establishment of the causal chain between toxicity mechanisms and population epidemiological data. In the future, it is necessary to combine multi-omics technologies, developmental toxicology models, and prospective cohort studies to systematically elucidate the neurotoxic pathways of OPFRs and promote environmental monitoring, exposure prevention and control, and the development of safe alternatives. This article reviews the physicochemical properties and toxicity spectrum of OPFRs, the neurotoxic mechanisms (including neurotransmitter disorders, oxidative stress, autophagy and apoptosis), and human clinical evidence, aiming to provide scientific basis for the risk assessment of neurodevelopment and the formulation of public health strategies.

Keywords: organophosphate flame retardants, neurotoxicity, autophagy, apoptosis.

1. Introduction

OPFRs are important substitutes to traditional bromine-based flame retardants, with their efficient fire-retardant properties and wide applicability. OPFRs have been added to a variety of products to reduce fire risks and ensure the safety of production and life. As their usage and environmental release continue to increase, OPFRs have been widely detected in environmental media such as air, water, and soil, as well as in human blood, urine, and breast milk. Their environmental persistence and bioaccumulation have gradually attracted global attention [1].

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OPEs can cross the placenta and be exposed through breast milk, making pregnant women and children the main sensitive groups. Recent studies have shown that OPEs are not "safe alternatives" but a class of SVOCs with multi-target toxicity, including cytotoxicity, developmental toxicity, endocrine disruption, and genetic and immune toxicity. Among them, developmental neurotoxicity is the most prominent. Currently, research on the neurotoxicity of OPFRs has made certain progress, clarifying the neurotoxic effects of some monomers such as triphenyl phosphate, tri-(2-chloroethyl) phosphate, etc., and finding that they can affect the proliferation and differentiation of nerve cells, interfere with neurotransmitter metabolism, induce oxidative stress and inflammatory responses, and thereby cause cognitive impairment, behavioral abnormalities, and other problems. Mechanism studies show that OPEs can interfere with multiple neurotransmitter systems such as dopamine, GABA, and 5-HT, induce oxidative stress and mitochondrial damage, and cause the blockade of the autophagy-lysosome pathway and neuronal apoptosis. These effects are consistent with the epidemiological results such as decreased cognition and increased autistic-like behaviors in children [2]. Based on this, this article summarizes the physicochemical properties, toxicity spectrum, and neurotoxic mechanism of OPEs, providing a basis for in-depth understanding of their potential impact on children's neurodevelopment and the risk of neurodegenerative diseases.

2. The properties and toxicity of organophosphate esters

OPEs (organophosphate esters, organophosphate flame retardants) are collectively called semi-volatile organic compounds (SVOCs). These compounds always contain a phosphate ester structure at the core and alkyl, aryl or halogenated alkyl groups as side chains. By analyzing their physicochemical properties which determine their migration, persistence and bioavailability in the environment, we will be able to understand their health risks. The core functional group of OPEs is $P(=O)(OR)_3$. According to the substituents, they can be classified as chlorinated OPEs (Chlorinated OPEs), aryl OPEs (Aryl OPEs), and alkyl OPEs (Alkyl OPEs). Most OPEs are moderately to highly hydrophobic compounds. The logKow typically ranging from 2 to 8. They have low vapor pressure and semi-volatility, which means they can be continuously released from materials that contain flame retardants and plasticizers. OPEs are bioaccumulative, have high lipid solubility, strong placental permeability, and can be transferred through breast milk. Blood and urine are common biological samples in the human body.

The toxicity mechanism of OPEs is characterized by multiple targets and multi-system involvement. This characteristic is prominent during the development of the nervous system. The toxicity includes cytotoxicity, developmental toxicity, neurotoxicity, genotoxicity, and endocrine disruption. Neurotoxicity is considered one of the most significant health impacts of OPEs. The neurotoxicity involves multiple interaction mechanisms, such as developmental neurotoxicity (DNT), induced inflammation and oxidative stress, affected secretion and reuptake of neurotransmitters, and dysregulation of autophagy and apoptosis. OPEs cause endocrine toxicity by inhibiting thyroid hormone transport and metabolism (decreased T3/T4), interfering with nuclear receptors such as estrogen receptors (ER) and androgen receptors (AR), and activating the PPAR pathway, leading to metabolic disorders. OPEs also have reproductive and developmental toxicity, which causes a decline in sperm parameters in men, disrupt testosterone levels, alter ovarian hormone levels, affect implantation, and cause delayed embryo development and increased malformation rates. OPEs have immunotoxicity, which can affect the functions of T cells and B cells and alter the secretion of cytokines such as IL-6 and TNF-α. OPEs have genotoxicity, which can induce DNA breaks, chromosomal aberrations, affect DNA repair, and influence signaling pathways.

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3. Neurotoxic mechanisms of organophosphate compounds

3.1. Modulation of neurotransmitter secretion and reuptake

Many in vivo studies and in vitro studies indicate organophosphate flame retardants (OPFRs) can profoundly disrupt various classes of neurotransmitters, including acetylcholine, 5-hydroxytryptamine glutamate, γ-aminobutyric acid and dopamine, in the central nervous system by multi-target mechanisms closely linked to developmental neurotoxicity.

In the study by Ruiwen Li, researchers found out that early-life exposure to TDCPP induces persistent adverse effects on the dopaminergic system, which causes anxiety-like behaviors and other neurobehavioral deficits for adult female zebrafish. The researcher exposed embryos to solution of TDCPP with different concentrations (0 μM as control, 0.01, 0.1, and 1 μM) from 2 hours post-fertilization (hpf) to 10 days post-fertilization (dpf). Brain tissue analysis of larval zebrafish revealed that dopamine content decreased significantly to 1.48-fold in the 1 μM TDCPP group; likewise, DOPAC levels dropped by 1.55-fold in the same group. Upon reaching adulthood, dopamine levels in female zebrafish brain sampling significantly reduced: DA content declined significantly by 1.17-fold and 1.35-fold in the 0.1 μM and 1 μM TDCPP exposure groups, respectively, while DOPAC levels were substantially reduced by 1.26-fold and 1.65-fold in corresponding groups. Conversely, GABA content significantly increased in the brains of adult male zebrafish [3].

In Qipeng Shi's research, aryl-OPFRs were identified as potential acetylcholinesterase (AChE) inhibitors through studies on larval zebrafish. The mechanism is related to direct interaction with the AChE active site. Exposure to aryl-OPFRs (TPHP, TCP, CDP) and chlorpyrifos (CPF) at concentrations from 300 nM to 1500 nM led to significant reduction of hatching and survival rates and increase in malformation rates ($p < 0.05$, $p < 0.01$, $p < 0.001$). These compounds also exhibited concentration-dependent inhibition of AChE activity. IC_{50} values: CPF (56.84 nM), CDP (162.7 nM), TPHP (244.4 nM), and TCP (393.9 nM). Researchers confirmed dose-dependent direct binding between these compounds and AChE through Biolayer interferometry (BLI)-based binding assays. The relation is characterized by distinct association and dissociation profiles. High binding affinity was reflected in their low equilibrium dissociation constants (K_D): CPF (1.70×10^{-5} M), TCP (5.47×10^{-5} M), CDP (1.05×10^{-4} M), and TPHP (2.18×10^{-4} M). Molecular docking simulations illustrated strong binding of aryl-OPFRs and CPF within the AChE active pocket when Glide scores ranged from –7.3 to –8.3. These ligands primarily formed hydrogen bonds with the TYR337 residue in the AChE active site. TCP also engaged TYR124, and water molecules also involved in the binding of some aryl-OPFRs [4].

Kylie's study showed that prenatal exposure to an OPFR mixture disrupts placental function and fetal brain serotonergic signaling by interfering with placental tryptophan metabolism. Pregnant rats exposed to the OPFR mixture were evaluated for placental impacts by collecting and analyzing placental and fetal forebrain tissues. In the 2 mg/kg and 4 mg/kg OPFR exposure groups, expression of Slc6a4 was significantly downregulated. This result indicates that potential impairments in serotonin transport and storage to the fetus. Significant reduction in Slc6a4 was also observed in female placentas at the lowest dose (2 mg/kg). At the 8 mg/kg dose, concentrations of 5-HT and its primary metabolite 5-HIAA increased markedly. To be more specific, in male placentas, 5-HT rose approximately 63-fold and about 20-fold in females. Corresponding 5-HIAA levels were elevated by roughly 13-fold in males and 10-fold in females. Furthermore, tryptophan (Trp) relative abundance was significantly increased in the 8 mg/kg exposure group [5].

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3.2. Inducing oxidative stress

Oxidative stress represents one of the most prevalent and central toxic mechanisms of organophosphate esters (OPEs). This mechanism has been confirmed through cellular models, animal studies, and certain human population investigations. This mechanism is the important factor that causes neurotoxicity. When the overproduction of reactive oxygen species (ROS) or reactive nitrogen species (RNS) exceeds the scavenging capacity of cellular antioxidant systems (GSH, SOD and CAT) the oxidative stress happens. In such situation, the oxidative stress causes biomacromolecule damage, mitochondrial dysfunction, and programmed cell death. Certain OPEs, particularly chlorinated compounds such as TDCIPP, TCEP, and TCPP, as well as aryl-OPEs like TPHP, can induce significant ROS generation even at low exposure levels.

In the study conducted by Jie Gu, zebrafish were used to evaluate the neurotoxic effects of three representative OPEs—TPP, EHDPP, and TCEP—by utilizing multidimensional indicators. The results indicated that exposure to these OPEs can induce neurotoxicity through oxidative stress. The evidence of this conclusion is significant reductions in the enzymatic activities of superoxide dismutase (SOD) and catalase (CAT). The researchers exposed zebrafish larvae to different solution of OPEs. Six days later the fish were collected and placed in the lysis buffer to perform ultrasonic disruption. They were centrifuged and supernatants were taken. Researchers used a kit to detect the activities of SOD and CAT in the homogenate. Researchers used commercial assay kits to evaluate activity levels of SOD and CAT, and protein concentrations were normalized using the BCA method. Compared with the control group, significant decreases ($P < 0.05$) in SOD activity were observed in larvae exposed to TPP (1 $mg \cdot L^{-1}$), EHDPP (0.2 and 2 $mg \cdot L^{-1}$), and TCEP (0.5 and 5 $mg \cdot L^{-1}$). Similarly, CAT activity was significantly reduced ($P < 0.05$) in the TPP (1 $mg \cdot L^{-1}$), EHDPP (0.2 and 2 $mg \cdot L^{-1}$), and TCEP (5 $mg \cdot L^{-1}$) exposure groups [6].

Oxidative stress in the livers of adult zebrafish was triggered by TDCPP in a dose- and sex-dependent manner, according to the research of Hanyan Chen. At low doses, TDCPP activates defense and repair mechanisms, whereas higher exposures appear to cause more severe damages. After a 7-day exposure of zebrafish to TDCPP-contaminated water, liver tissues were collected and analyzed. The study found that ROS levels increased significantly in both female and male zebrafish when TDCPP concentrations rose. For instance, in high-dose males, ROS levels reached 1916.03. This value was prominently higher than 1529.27, which was value of the control group. The GSH content decreased as dose of TDCPP increased for male and female fish. High-dose male zebrafish had GSH levels of 22.91, which was lower than the control value of 72.11. That showed GSH were depleted due to TDCPP-induced oxidative stress. At a low exposure level (45.81 μg/L), female zebrafish showed upregulation in the expression of CuZn-SOD, CAT, and GPx genes, whereas male zebrafish exhibited increased GPx expression. These increasment show an adaptive antioxidant response to elevated ROS. In contrast, high-dose exposure (229.05 μg/L) led to significant downregulation of Mn-SOD and CAT gene expression for male and female. CuZn-SOD and GPx expression were also reduced in males. These findings indicate that high-dose TDCPP impairs the antioxidant system or inhibits its transcriptional regulation. Low-dose females exhibited elevated Mn-SOD and CAT activities, whereas high-dose females showed significantly suppressed Mn-SOD activity, and high-dose males exhibited reduced Cu/Zn-SOD activity. These enzymatic results and gene expression data confirm the conclusion that high-dose TDCPP surpasses cellular antioxidative capacity [7].

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3.3. Dysregulation of autophagy and apoptosis

Autophagy is a critical pathway to maintain cellular homeostasis and clearing damaged proteins and organelles. Numerous studies have demonstrated that various OPFRs, such as TDCIPP, TCEP, TCPP, and TPHP, interfere with the autophagic pathway, and affect neurological health, hepatic metabolism, and developmental processes as a result.

In the study of Chunli Zuo, researchers used the N2a-APPswe cell model. And then TDCIPP exposure was found to disrupt the autophagy–lysosome pathway. Quantitative proteomic analysis combined with Gene Set Enrichment Analysis (GSEA) revealed significant alterations in the expression profiles of proteins associated with autophagy and lysosomal function in TDCIPP-treated N2a-APPswe cells. Specifically, treatment with 15 μM and 45 μM TDCIPP caused enrichment of proteins involved in lysosomal activity, lysosome organization, and lysosomal proteolysis. This result suggests potential disruption of lysosomal function [8].

Immunofluorescence assays further quantified the expression levels of the autophagosome marker Microtubule-Associated Protein 1A/1B-Light Chain 3 (LC3) and ubiquitin-binding protein p62 (SQSTM1). The results showed that, compared to the model group, 45 μM TDCIPP significantly increased LC3 levels ($P < 0.01$) in N2a-APPswe cells. When combined with the lysosomal inhibitor chloroquine (CQ), LC3 levels were further elevated ($P < 0.001$). Additionally, 45 μM TDCIPP treatment significantly increased intracellular accumulation of p62 ($P < 0.001$), which is commonly interpreted as an indication of impaired or inhibited autophagic flux. Detection using the ENZO CYTO-ID® Autophagy Detection Kit confirmed that both 15 μM and 45 μM TDCIPP significantly promoted autophagosome accumulation ($P < 0.05$) compared to the model group, with a more pronounced effect in the presence of chloroquine ($P < 0.001$). These data collectively indicate that TDCIPP exposure impedes autophagic flux and induces lysosomal dysfunction by inhibiting autophagosome-lysosome fusion [8].

Consistent with the in vitro findings, results from the in vivo 3×Tg-AD mouse model showed that TDCIPP exposure led to an upward trend in LC3II protein levels in hippocampal tissues. The LC3II protein levels observed in the 360 mg/kg dose group significantly increase ($P < 0.05$). Similarly, p62 levels were also significantly elevated in the 360 mg/kg group ($P < 0.01$), further validating the inhibitory effect of TDCIPP on autophagy in vivo. Moreover, the lysosomal marker LAMP1 exhibited an increasing trend in TDCIPP-treated groups ($P > 0.05$), while CTSD was significantly upregulated in N2a-APPswe cells ($P < 0.001$), suggesting that lysosomal function is also affected [8].

3.4. Clinical studies on neurotoxicity in humans

Findings from the MABC cohort study indicate that prenatal exposure to OPEs is highly related to a decline in full-scale intelligence quotient (FSIQ) and an elevated risk of autism spectrum disorder (ASD) in children, exhibiting both dose–response relationships and trimester-specific characteristics.

Utilizing the MABC, Lu Mengjuan investigated the influence of OPEs exposure on cognitive development in preschool-aged children. Applying a generalized linear model (GLM) in single-exposure assessments, the study revealed that each logarithmic unit increase in OPEs concentration during each trimester of pregnancy was associated with a reduction in FSIQ scores among preschoolers [9].

Using the same cohort, Zhou Qiong conducted an additional analysis to examine the relationships between prenatal OPE exposure—assessed across all three trimesters—and ASD-related outcomes

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in offspring by applying generalized additive models (GAMs) and generalized linear models. The results demonstrated positive correlations between ASD scores and exposure to certain OPEs: DPHP in the first trimester; DPHP, BEHP, TCEP, and BCIPP in the second trimester; and DPHP, BBOEP, DBP, and BCIPP in the third trimester. Notably, a one log-unit increase in BCIPP during the third trimester was associated with a 0.220-point rise in ASD scores (95% CI: 0.007–0.433). A statistically significant linear relationship was observed between third-trimester BCIPP exposure and ASD (EDF = 1, p = 0.044) [10].

These findings provide clinical evidence in humans for the developmental neurotoxicity of OPEs, underscore the critical importance of the prenatal exposure window, support the use of biomarkers such as BCIPP and DPHP for exposure assessment, and reinforce the public health significance of OPEs in the context of neurodevelopmental disorders in children. From a clinical toxicology perspective, these studies highlight the need to address low-level environmental OPE exposure and advocate for improved prenatal environmental management, early risk assessment, and long-term monitoring of neurobehavioral outcomes.

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5. Conclusion

Current research indicates that organophosphate esters (OPEs) exhibit distinct mechanistic diversity in neurotoxicity. On one hand, representative compounds such as TDCIPP persistently disrupt

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dopaminergic, GABAergic, and serotonin (5-HT) systems, as evidenced by altered neurotransmitter levels and their metabolites, alongside structural and functional impairments in neural networks via acetylcholinesterase inhibition and synaptic protein abnormalities. On the other hand, OPEs including TPP, EHDPP, TCEP, and TDCPP induce significant oxidative stress at low to moderate doses, characterized by increased ROS levels, depletion of GSH, and impairment of key antioxidative defense enzymes such as SOD, CAT, and GPx, ultimately resulting in mitochondrial dysfunction and apoptosis. Furthermore, TDCIPP and other OPEs inhibit autophagosome-lysosome fusion, leading to aberrant accumulation of LC3-II and p62 as well as blockade of autophagic flux, accompanied by dysregulated expression of lysosomal markers such as LAMP1 and protease CTSD —indicating compromised autophagic-lysosomal pathway activity. These alterations not only elucidate OPE-induced neuronal injury and synaptic dysfunction but also provide critical mechanistic insights into their role in promoting Alzheimer's disease-related pathological changes.

Although evidence of OPE-related neurotoxicity continues to accumulate, several key issues remain unresolved. These include the accurate health risk assessment under real-world low-dose, long-term, and mixture exposure scenarios; susceptibility differences across developmental windows and by sex; integration of in vitro and in vivo mechanistic findings with epidemiological evidence to establish causal linkages; and structure–toxicity relationships among different OPEs and their metabolites. Future studies should leverage multi-omics technologies, developmental toxicology models, and prospective birth cohorts to systematically elucidate OPE neurotoxicity mechanisms across molecular, cellular, individual, and population levels, incorporating such findings into environmental risk frameworks for neurodevelopmental disorders and neurodegenerative diseases. From a public health and regulatory perspective, enhancing environmental monitoring and exposure control of OPEs, together with the identification and evaluation of safer alternatives, is of paramount importance for reducing environmental health risks, particularly for vulnerable populations such as pregnant women and children.

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