A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP9285.

Beyond Cholinesterase Inhibition: Developmental Neurotoxicity of Organophosphate Ester Flame Retardants and Plasticizers

Heather B. Patisaul,[1] Mamta Behl,[2,3] Linda S. Birnbaum,[2,3,4] Arlene Blum,[5,6] Miriam L. Diamond,[7] Seth Rojello Fernández,[5] Helena T. Hogberg,[8] Carol F. Kwiatkowski,[5,9] Jamie D. Page,[10] Anna Soehl,[5] and Heather M. Stapleton[4]

[1]College of Sciences, North Carolina State University, Raleigh, North Carolina, USA
[2]National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA
[3]National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA
[4]Nicholas School of the Environment, Duke University, Durham, North Carolina, USA
[5]Green Science Policy Institute, Berkeley, California, USA
[6]Department of Chemistry, University of California, Berkeley, Berkeley, California, USA
[7]University of Toronto, Toronto, Ontario, Canada
[8]Center for Alternatives to Animal Testing, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[9]Department of Biological Sciences, North Carolina State University, Raleigh, North Carolina, USA
[10]Cancer Prevention & Education Society, Meads House, Leighterton, Tetbury, Gloucestershire, UK

Background: To date, the toxicity of organophosphate esters has primarily been studied regarding their use as pesticides and their effects on the neurotransmitter acetylcholinesterase (AChE). Currently, flame retardants and plasticizers are the two largest market segments for organophosphate esters and they are found in a wide variety of products, including electronics, building materials, vehicles, furniture, car seats, plastics, and textiles. As a result, organophosphate esters and their metabolites are routinely found in human urine, blood, placental tissue, and breast milk across the globe. It has been asserted that their neurological effects are minimal given that they do not act on AChE in precisely the same way as organophosphate ester pesticides.

Objectives: This commentary describes research on the non-AChE neurodevelopmental toxicity of organophosphate esters used as flame retardants and plasticizers (OPEs). Studies in humans, mammalian, nonmammalian, and *in vitro* models are presented, and relevant neurodevelopmental pathways, including adverse outcome pathways, are described. By highlighting this scientific evidence, we hope to elevate the level of concern for widespread human exposure to these OPEs and to provide recommendations for how to better protect public health.

Discussion: Collectively, the findings presented demonstrate that OPEs can alter neurodevelopmental processes by interfering with noncholinergic pathways at environmentally relevant doses. Application of a pathways framework indicates several specific mechanisms of action, including perturbation of glutamate and gamma-aminobutyric acid and disruption of the endocrine system. The effects may have implications for the development of cognitive and social skills in children. Our conclusion is that concern is warranted for the developmental neurotoxicity of OPE exposure. We thus describe important considerations for reducing harm and to provide recommendations for government and industry decision makers. https://doi.org/10.1289/EHP9285

Introduction

Organophosphate esters are a large class of compounds that are increasingly used as flame retardants and plasticizers. Organophosphate esters have the general structure $O=P(OR)_3$, or $S=P(OR)_3$, where the "R" corresponds to various aliphatic and aromatic groups that could be attached to the backbone of the molecule (van der Veen and de Boer 2012). Although some organophosphate esters are used and regulated as nerve agents and pesticides, others are used extensively as flame retardants and plasticizers in a variety of products, including building materials, textiles, electronics, car seats, nail polishes, and furniture (Andresen et al. 2004; Blum et al. 2019; van der Veen and de Boer 2012). Today, most organophosphate pesticides (OPPs) are thiophosphates ($S=P(OR)_3$) (Atwood and Paisley-Jones 2017), whereas most organophosphate flame retardants are not (Liu et al. 2021). Organophosphate esters also occur as oxidation products of organophosphite compounds that are widely used as antioxidants and photoinitiators in polymerization (Liu and Mabury 2019). Hereafter, the acronym OPEs refers to organophosphate esters used as flame retardants and plasticizers and does not refer to organophosphate esters developed and used as pesticides or nerve agents.

Organophosphate esters used as pesticides (i.e., OPPs) are strong inhibitors of the acetylcholine hydrolase, acetylcholinesterase (AChE), whereas OPEs are typically less potent in this respect (COT 2019; Sun et al. 2016). In fact, a 2019 review by the British Committee on the Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) recently concluded that organophosphate flame retardants were at most, only weak inhibitors of AChE and also unlikely to cause neurotoxicity at human exposure levels via other mechanisms of action, such as via gamma-aminobutyric acid (GABA) inhibition. However, recent evidence in zebrafish suggests that some OPEs may be potent AChE inhibitors (Shi et al. 2021). Further, as we briefly summarize here, growing evidence from many studies shows that OPEs are associated with developmental neurotoxicity (DNT) via different modes of action, including endocrine disruption. Thus, we attest that focusing only on AChE activity is insufficient for gauging the potential neurotoxicity of OPEs. Here we show the pressing need to acknowledge and manage the potential risks that OPEs pose to human neurodevelopment given their neurotoxic effects, rapidly increasing use, and environmental ubiquity.

Uses and Exposure

OPEs generally fall into two categories, reflecting their chemical attributes: halogenated [e.g., tris(2-chloroethyl) phosphate (TCEP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP, also known as

Address correspondence to Carol F. Kwiatkowski, Green Science Policy Institute, P.O. Box 9127, Berkeley, CA 94709 USA. Email: carol@greensciencepolicy.org

The authors declare they have no actual or potential competing financial interests.

Received 9 March 2021; Revised 2 July 2021; Accepted 11 August 2021; Published 6 October 2021.

TDCPP), and tris(1-chloro-2-propyl) phosphate (TCIPP, also known as TCPP)], and nonhalogenated, including both aromatic and aliphatic OPEs [e.g., triphenyl phosphate (TPHP, also known as TPP), tributyl phosphate, and tris(2-butoxyethyl) phosphate (TBOEP)] (van der Veen and de Boer 2012).

OPEs have been increasingly used as alternatives to replace brominated flame retardants (BFRs), particularly since the phase-out of the production of polybrominated diphenyl ethers (PBDEs), beginning in 2003 (Stapleton et al. 2012; Blum et al. 2019). Use of OPEs has now reached 18% of the global market share of flame retardants (FlameRetardants-Online 2020). However, OPEs were used extensively before the restrictions of BFRs and have applications beyond flame retardants (e.g., as plasticizers) that contribute to the ubiquity of OPEs in products and materials (Sheldon and Hites 1978; Hartmann et al. 2004; Staaf and Ostman 2005). A recent review estimated that >600,000 tonnes of OPEs were used in 2015 worldwide (Yang et al. 2019a), with usage increasing annually.

The two largest market segments for OPEs are as flame retardants and plasticizers, with the plasticizer applications projected to dominate the global market over the next 5 y (Pulidindi and Pandey 2018). The greatest growth in use is in electronics where some OPEs do double duty as flame retardants and plasticizers, but they are also used in very high volumes in building materials, vehicles, upholstered furniture and mattresses, car seats, plastic and rubber products, and many other use categories (Blum et al. 2019). The vast magnitude of OPE use in construction is illustrated by a study from China that found that the potential total burden of OPEs in wall insulation in completed new buildings in 2017 was estimated to be ∼24,000 tonnes, whereas the total emission of OPEs from those new materials was ∼3 tonnes/y (Wang et al. 2019).

Because of their structure and presumed rapid metabolism (Meeker et al. 2013), OPEs were once considered less persistent in the environment and in human bodies than their brominated predecessors (Blum et al. 2019). However, it is now clear that some have environmental persistence and long-range transport properties similar to the BFRs that they replaced and are accumulating in remote environments (Zhang et al. 2016; Sühring et al. 2016, 2021; Ma et al. 2017a). For example, high concentrations of TCEP, TCIPP, and TPHP have been detected in air and water across the Canadian Arctic (Sühring et al. 2016, 2021). OPEs are also detected in many species of biota around the world (Pantelaki and Voutsa 2020).

Evidence of human exposure to OPEs has been available for over two decades (Doherty et al. 2019a). OPEs and their metabolites are now routinely found in human urine (He et al. 2018; Ospina et al. 2018; Hou et al. 2020), blood (Hou et al. 2020; Ma et al. 2017b), placental tissue (Ding et al. 2016), and breast milk (Chen et al. 2021; Ma et al. 2019; Hammel et al. 2020b) across the globe, with one study documenting high urinary levels in Australian infants and children (He et al. 2018). Air, dust, and food are three known pathways of exposure (Xu et al. 2016; Yu et al. 2021). The semivolatile properties of OPEs ensure their widespread distribution from sources to surfaces and materials indoors with which we come into contact, including dust and clothing, which would allow for dermal uptake (Saini et al. 2016; Yang et al. 2019b; Yu et al. 2021). Household dust is an important exposure pathway (Stapleton et al. 2009; Hoffman et al. 2015a; Larsson, et al. 2018; Khairy and Lohmann 2019; Yang et al. 2019b; Xu et al. 2016), particularly for children, who have higher concentrations than adults owing to hand-to-mouth contact and high levels of OPEs in baby products (Butt et al. 2014, 2016; Hoffman et al. 2015b; Gibson et al. 2019). Diet is another exposure route with a wide variety of foods containing a range of OPEs and their metabolites, some of which may be from food processing and packaging (Xu et al. 2015; Li et al. 2019).

Toxicity

Significant health concerns for OPEs have existed for nearly three decades and some have repeatedly been identified as neurotoxic (Gant et al. 1987; Umezu et al. 1998; van der Veen and de Boer 2012). Despite this evidence, OPEs are commonly found in widely used commercial flame retardant mixtures. For example, Firemaster 550 (FM 550) (Tung et al. 2017), a chemical mixture currently used as an additive flame retardant in commercial products, contains BFRs, TPHP, and several other aromatic OPEs. The commercial mixture V6 contains TCEP [known to be carcinogenic in animals (ECHA 2018)] as an impurity up to 14% by weight (Fang et al. 2013).

Acute toxicity from organophosphate esters used as nerve agents and pesticides has primarily been studied with respect to their inhibitory effects on AChE in nerve cells, resulting in pathological excess of acetylcholine in the body, which can rapidly be fatal (Čolović et al. 2013). OPEs used as flame retardants and plasticizers have subtle structural differences that, by design, make them comparatively less potent inhibitors of AChE (COT 2019). However, there is evidence that these OPEs are developmentally neurotoxic via other effects on neurotransmission pathways that are profoundly important for brain development. Some OPEs are also known to metabolize into more toxic compounds (Casida 2017). A notorious example is the flame retardant tris(2,3-dibromopropyl) phosphate (tris-BP) that is metabolized to the potent mutagen 2-bromoacrolein (Casida 2017). Consequently, the U.S. Consumer Product Safety Commission restricted the use of tris-BP in children's pajamas nearly 50 y ago. Nonetheless, it has been argued by the COT that because OPEs appear less potent via AChE inhibition than OPPs, such as chlorpyrifos, they are less harmful (COT 2019). This rationale fails to consider that AChE inhibition is not the only mechanism of action for developmental toxicity, even for OPPs. OPEs have other known mechanisms of action, particularly during development, including inhibiting GABA, neuropathy target esterase, and voltage-dependent chloride channels (Lotti and Moretto 2005; Casida 2017). Given the common use of OPEs in consumer products with high levels of human exposure (Doherty et al. 2019a), there is a pressing need to acknowledge the potential health and environmental consequences of OPE exposure.

Objectives

This commentary provides an overview of research on the neurodevelopmental toxicity of OPEs used as flame retardants and plasticizers to illustrate the numerous potential mechanisms of action of OPEs, beyond AChE inhibition. It includes research in humans as well as mammalian, nonmammalian, and *in vitro* models. The research is then presented in the context of established pathways, including adverse outcome pathways (AOPs), for DNT. The objective of this commentary is to highlight the need to use the full body of scientific evidence to support decision making that will protect humans and wildlife from harmful exposure to OPEs.

Discussion

Below we summarize three types of evidence demonstrating the developmentally neurotoxic and endocrine disrupting properties of OPEs and depict the relationships between them using AOPs established for DNT. We conclude by describing important regulatory considerations and providing recommendations for reducing harm.

Human Epidemiological Studies

Multiple epidemiological research studies have investigated exposure to OPEs with specific neurodevelopmental outcomes, including cognitive, behavioral, and memory tasks. These studies were recently summarized in reviews by Doherty et al. (2019a) and Vuong et al. (2020). For brevity, we illustrate a few of the most compelling studies.

In the Center for the Health Assessment of Mothers and Children of Salinas birth cohort study, Castorina et al. (2017a, 2017b) measured four urinary OPE metabolites in >300 pregnant women and assessed the neurodevelopment of their children at 7 years of age. Three of the OPE metabolites were detected in >70% of urine samples. The greatest effects were observed with urinary diphenyl phosphate (DPHP), a common metabolite of several different OPEs (Castorina et al. 2017a). Each 10-fold increase in urinary DPHP was associated with a decrease of 2.9 points in Full-Scale Intelligence Quotient (IQ) and a decrease of 3.9 points in Working Memory.

Another study in North Carolina (Doherty et al. 2019b) examined prenatal exposure to the same OPEs with cognitive and motor assessments. Spot urine samples collected from >300 women in the Pregnancy, Infection and Nutrition (PIN) study were analyzed. OPEs were detected in >85% of the samples. Isopropyl-phenyl phenyl phosphate (ip-PPP), a urinary metabolite of isopropyl-phenyl diphenyl phosphate, had the greatest association with cognitive assessments. Specifically, for every interquartile increase in urinary ip-PPP, a 3.08 decrease in the fine motor assessment score was observed. In a separate study, Doherty et al. (2019c) also assessed the same urinary measurements from PIN with behavioral assessment symptoms and found that urinary bis (1,3-dichloro-2-propyl) phosphate (a specific metabolite of TDCIPP) was associated with a higher risk of withdrawal, attention problems, depression, hyperactivity, and aggression.

Postnatal exposure to OPEs and associations with neurobehavioral symptoms have also been studied in children. In a small U.S.-based study (Lipscomb et al. 2017), 72 children 3–5 years of age wore silicone wristbands for a week to evaluate their exposure to OPEs and other organic contaminants. The use of silicone wristbands have been shown to be a reliable way to measure children's exposure to OPEs based on comparisons with urinary biomarkers (Hammel et al. 2016, 2020a). Total OPE levels on the wristbands were significantly associated with less responsible behaviors in children and more externalizing behavioral problems, as rated by teachers using the Social Skills Improvement Rating Scale (Lipscomb et al. 2017).

Evidence of endocrine disruption associated with OPEs has also been found in human studies. Proper functioning of the endocrine system, particularly the thyroid, is critical to neurodevelopment (Demeneix 2019; Gore et al. 2014). A cross-sectional study measured urinary metabolites of five OPEs in 544 children and adolescents 6–19 years of age in the U.S. National Health and Nutrition Examination Survey (2013–2014) (Luo et al. 2020). The authors reported that OPEs could interfere with sex steroids and sex-steroid binding globulins in adolescents, with some effects different in girls than boys. Other studies have shown effects of OPEs on thyroid function (Dishaw et al. 2014b; Yao et al. 2021). For example, Yao et al. (2021) measured metabolites of dibutyl phosphate and DPHP in the urine of 360 pregnant women and found positive associations with both maternal (urinary) and neonatal (heel blood) levels of thyroid-stimulating hormone, particularly in girls. A recent study (Choi et al. 2021) demonstrated that the increased risk of attention deficit hyperactivity disorder among children exposed *in utero* to higher levels of DPHP was mediated by maternal thyroid hormone levels. In addition, evidence from OPPs suggests that the thyroid-disrupting potential of OPEs could be compelling (Campos and Freire 2016; Leemans et al. 2019).

Based on the human data available from these and other studies, we suggest that OPE exposure during development elevates the risk that children will have deficits in social, cognitive, and other skills that play important roles in a child's ability to succeed academically and socially. Limitations of this research include small sample sizes in some studies and a lack of causal specificity for the relationships identified (e.g., due to human exposure to multiple chemicals of concern). Notably, although evidence is accumulating across different exposure measurements and neurodevelopmental assessments, the body of evidence is still relatively small and results have not been confirmed across multiple similarly conducted studies. However, it should be acknowledged that obtaining greater evidence in humans necessitates greater human harm, a situation that can be avoided by more rapidly assessing experimental, nonhuman evidence.

Mammalian Studies

It has been recognized for decades in mammalian studies, mostly in adults, that numerous OPEs are neurotoxic. For example, TCEP was shown over two decades ago to increase ambulatory behavior in adult mice by acting as a GABA antagonist and to interfere with dopamine signaling (Umezu et al. 1998). Even earlier work identified the potential for OPEs to antagonize GABA receptors in rats and to inhibit GABA-regulated chloride channels in the Torpedo electric organ (Gant et al. 1987). A more contemporary study (Yang et al. 2018) exposed 6-wk-old female Sprague–Dawley rats to 50–250 mg/kg per day of TCEP for 60 d and found spatial learning and memory deficits, apoptotic and necrotic lesions in the hippocampus, and disrupted amino acid and neurotransmitter metabolism, energy metabolism, and cell membrane function integrity. Nuclear magnetic resonance metabolomics in rats found that brain concentrations of glutamate, GABA, *N*-acetyl-D-aspartate, creatine, and lactic acid metabolites were also disrupted (Yang et al. 2018). The typically high doses used in these and other historical studies of OPEs is a limitation; nonetheless, the reproducibility of their outcomes clearly demonstrates that OPEs can be neurotoxic despite having little to no cholinergic activity (Gant et al. 1987; Umezu et al. 1998).

More recent studies are finding adverse behavioral and neural effects using lower, environmentally relevant doses administered during brain development. It has been shown, for example, in developmentally exposed Wistar rats, that FM 550 can have endocrine disrupting properties (e.g., increased serum thyroxine) and could produce sex-specific effects on anxiety and other complex behaviors (Patisaul et al. 2013; Baldwin et al. 2017). Further, OPEs accumulate in rat placental tissue, in some cases to a higher degree in male-associated placentas than female (Phillips et al. 2016; Baldwin et al. 2017) and can induce functional changes, including altered neurotransmitter production (Rock et al. 2020). Recent studies in rats exposed *in utero* to FM 550 have demonstrated that forebrain serotonin (5-HT) turnover was reduced, with evidence of endocrine disruption, inflammation, and altered neurotransmitter production found in the placentas (Rock et al. 2018). In addition, serotonergic projections were shown to be significantly longer in the fetal forebrains of exposed males (Rock et al. 2020). This suggests a DNT mechanism that involves the placenta, which is biologically plausible because the placenta coordinates fetal growth and neurodevelopment and is likely the only source of 5-HT and other neurotransmitters for the developing brain at certain developmental time points (Bonnin et al. 2011a; Bonnin and Levitt 2011b; Broad et al. 2016).

Disruption of sexually dimorphic behavior, including socioemotional behaviors, such as anxiety and prosociality, is a common

outcome of developmental OPE exposure. In mice, offspring maternally exposed to an OPE mixture of TDCIPP, TPHP, and tricresyl phosphate [TCP, also known as Tris(4-methylphenyl) phosphate], displayed altered locomotor and anxiety-related behaviors (with some outcomes being sex specific) (Wiersielis et al. 2020) and disrupted hypothalamic gene expression (Adams et al. 2020). Those altered genes included peroxisome proliferator-activated receptor-gamma (PPARγ) and estrogen receptor-alpha (ERα), which supports the hypothesis that a critical route by which OPEs exert detrimental effects on social traits is through endocrine disruption (Gore et al. 2019). Disruption of feeding behavior and metabolic homeostasis via endocrine disruption has also been reported for some OPEs. In mice, perinatal exposure eliminated the sex difference in postnatal neuropeptide Y expression and, in females, increased expression of ERα and other genes critical to the sexual differentiation of reproductive and feeding pathways, including PPARγ, tachykinin 2, and prodynorphin (Adams et al. 2020). Exposed males were also heavier by the second week of life and had higher levels of agouti-related peptide. Similarly, in the liver, numerous genes were sex-specifically disrupted, notably PPARγ and ERα, demonstrating that DNT effects in the hypothalamus can be accompanied by similar disruptions in other organs. Use of ERα-knockout mice has revealed ERα to be a critical part of the hypothalamic disruption mechanism and identified pregnane X receptor (PXR) and constitutive androstane receptor activation in the liver (Krumm et al. 2018). These studies support other work identifying OPEs as metabolic disruptors (Boyle et al. 2019; Farhat et al. 2013; Selmi-Ruby et al. 2020; Vail and Roepke 2020; Walley et al. 2021) and, critically, identify putative, sex-specific mechanisms of action associated with disrupted brain development.

Altered socioemotional behavior has also been reported in prairie voles, which are a unique model for DNT research in that they are spontaneously prosocial, bi-parental, and form monogamous pair bonds (McGraw and Young 2010). Thus, they may be more appropriate models of human social attachment than rats or mice. Exposure of prairie voles to FM 550 during gestation and weaning led to dose–responsive effects that were more pronounced in female than male offspring (Gillera et al. 2020). Exposure-related outcomes in females included elevated anxiety, decreased social interaction, decreased exploratory motivation, and aversion to novelty. Exposed males also had social deficits, with males in all three dose groups failing to show a preference for their mated partner.

Finally, emerging evidence suggests that OPEs are neuroinflammatory in the developing brain. In mice, postnatal TDCPP exposure has dose-dependently provoked microglia-mediating inflammation and neural damage in the hippocampus, including widespread apoptosis (Zhong et al. 2020). Long-term neuroinflammation contributes to neurodevelopmental disorders and can affect memory, cognition and other aspects of brain function (Block et al. 2007; Butovsky and Weiner 2018). Collectively, this research suggests that OPEs can alter neurodevelopment by interfering with noncholinergic pathways at environmentally relevant doses. Although the mechanisms by which these adverse impacts occur are still being elucidated, many of the findings are consistent with the available epidemiological data on OPE-related effects in children.

Nonmammalian and in Vitro Models

Evidence of DNT in zebrafish, including adverse behavioral outcomes (e.g., locomotor behavior, hyperactivity), has been documented for TPHP (Shi et al. 2018), tri-n-butyl phosphate, TBOEP, TCEP (Sun et al. 2016), and numerous other OPEs by multiple laboratories (Jarema et al. 2015, Oliveri et al. 2015, Alzualde et al. 2018, Glazer et al. 2018). Considerable work in zebrafish has also produced concordant evidence that neurotransmitters, such as GABA and dopamine, and endocrine disruption, such as in the thyroid, are involved in the DNT of OPEs (Xia et al. 2021) and are separate from cholinesterase inhibition (Shi et al. 2021). This literature, briefly covered in this short commentary, includes striking examples of endocrine disruption and sex-specific effects. For example, in a study where adult zebrafish were exposed to TDCIPP as embryos, vulnerability to anxiety-like behavior was observed in females but not males (Li et al. 2020). In the female brains, decreased dopamine concentrations and down-regulation of dopaminergic signaling-related genes were also observed. For some key genes [*bdnf* (brain derived neurotrophic factor), *drd4b* (dopamine receptor D4b), *zc4h2* (zinc finger C4H2-type containing), and *th* (tyrosine hydroxylase)] increased methylation of the promoter region accompanied down-regulated transcription, suggesting epigenetic effects. Similarly, it has been shown in zebrafish that TDCIPP can be maternally transferred to the offspring, causing thyroid disruption and DNT, including decreased levels of plasma thyroxine and 3,5,3′-triiodothyronine, dopamine, 5-HT, GABA, and histamine, along with several factors critical for neuronal development, including synaptogenesis (Wang et al. 2015; Li et al. 2020; Sun et al. 2016). Notably, these effects occurred in the absence of effects on AChE. TPHP has also been observed to significantly disrupt thyroid hormones and gene expression in zebrafish (Kim et al. 2015) and TCPP and TDCPP have been shown to alter mRNA expression, thyroid hormone levels, and pipping behavior in chicken embryos (Farhat et al. 2013).

In vitro models have revealed altered neurodifferentiation as a potential mechanism of action for OPEs. One study evaluated the effects of several flame retardants on neurodifferentiation using embryonic rat neural stem cells and rat neuronotypic PC12 cells (Slotkin et al. 2017). In both types of cells, TDCIPP exposure resulted in an increased glia/neuron ratio, a common hallmark of neurotoxicants *in vivo*. Other studies using a battery of cell-based and *in vitro* assays have reported compromised neurodifferentiation, neurite outgrowth, and electrical activity by numerous OPEs (Behl et al. 2015; Hausherr et al. 2014; Shafer et al. 2019), sometimes at concentrations lower than for known neurotoxic OPPs (Dishaw et al. 2014a; Ryan et al. 2016). Furthermore, other key processes involved in neurodevelopment—such as proliferation, migration, and oligodendrocyte differentiation—have been shown to be affected by exposure to OPEs (Klose et al. 2021).

Endocrine disruption by OPEs has also been demonstrated in a wide variety of cell-based *in vitro* systems. This research suggests that several OPEs, particularly TPHP, may have potential endocrine disrupting effects via ERα, ERβ, androgen receptor, glucocorticoid receptor, PPARγ, and PXR (Kojima et al. 2013; Belcher et al. 2014; Pillai et al. 2014; Fang et al. 2015). As an example, a 2012 study assessing the endocrine-disrupting potentials of six OPEs [i.e., TCEP, TCIPP, TDCIPP, tris-(2-butoxyethyl) phosphate, TPHP, and TCP] used both human cell lines and zebrafish (Liu et al. 2012). The results revealed that OPEs could alter sex hormone balance through several mechanisms, including alteration of sex steroidogenesis, ER antagonism, and estrogen metabolism, with some results being sex specific.

Collectively, these nonmammalian and *in vitro* studies demonstrate that OPEs show effects on neurotransmitters, behavior, and endocrine disruption. They also indicate the participation of multiple mechanisms of toxicity.

Potential AOPs

Figures 1–3, from left to right, depict a relational effect of OPEs in increasing order of biological complexity: cellular, organ, and organism. They include perturbations in molecular mechanisms in cell culture systems (e.g., alterations in neurotransmitters, gene

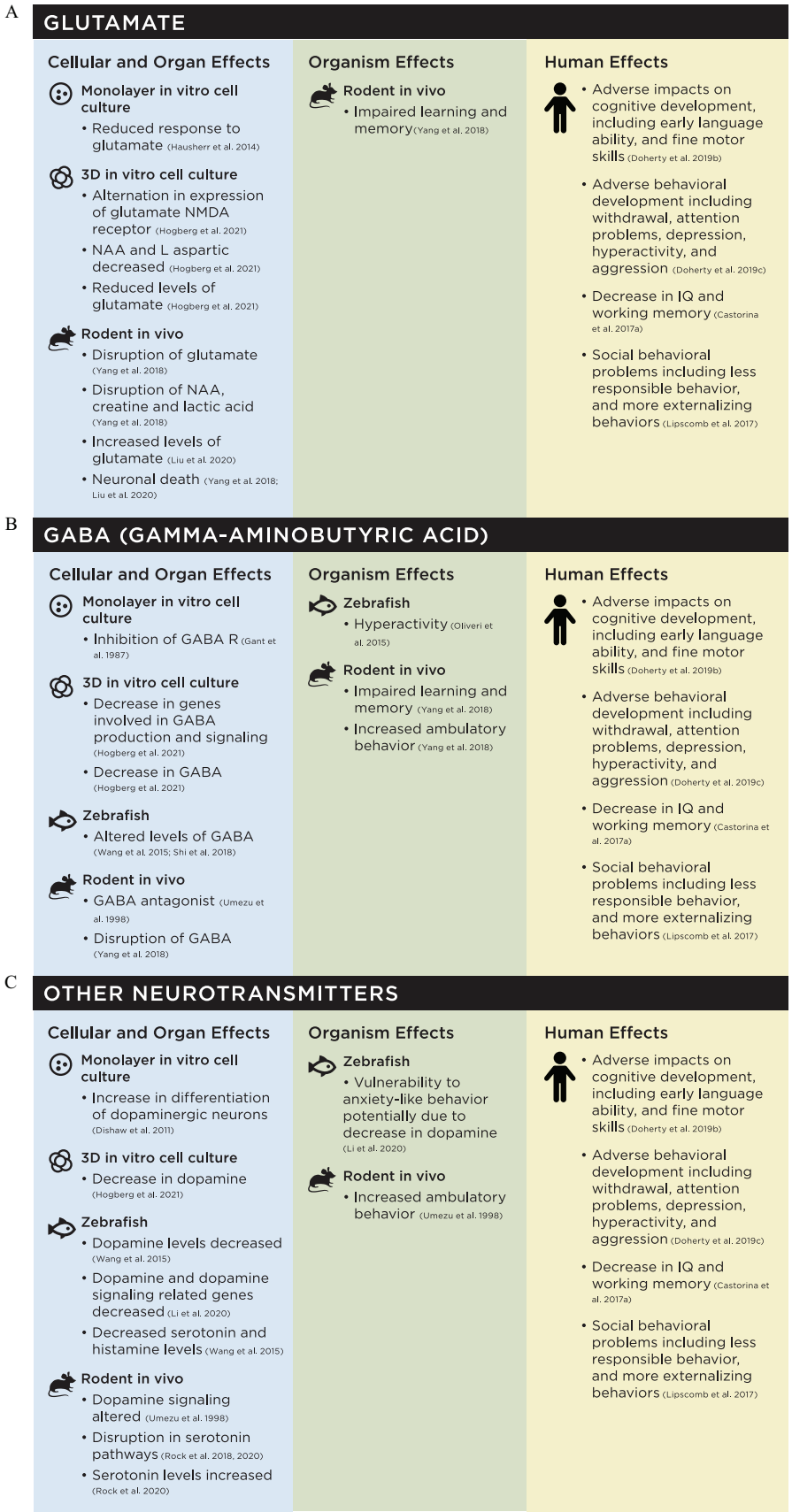

Figure 1. Developmental neurotoxicity: neurotransmitters—(A) glutamate, (B) GABA, and (C) other neurotransmitters. Effects seen in humans may be associated with many different systems and thus are repeated for each outcome category. Note: 3D, three dimensional; GABA, gamma-aminobutyric acid; IQ, intelligence quotient; NAA, n-acetyl aspartate; NMDA, *N*-methyl-D aspartate; R, receptor.

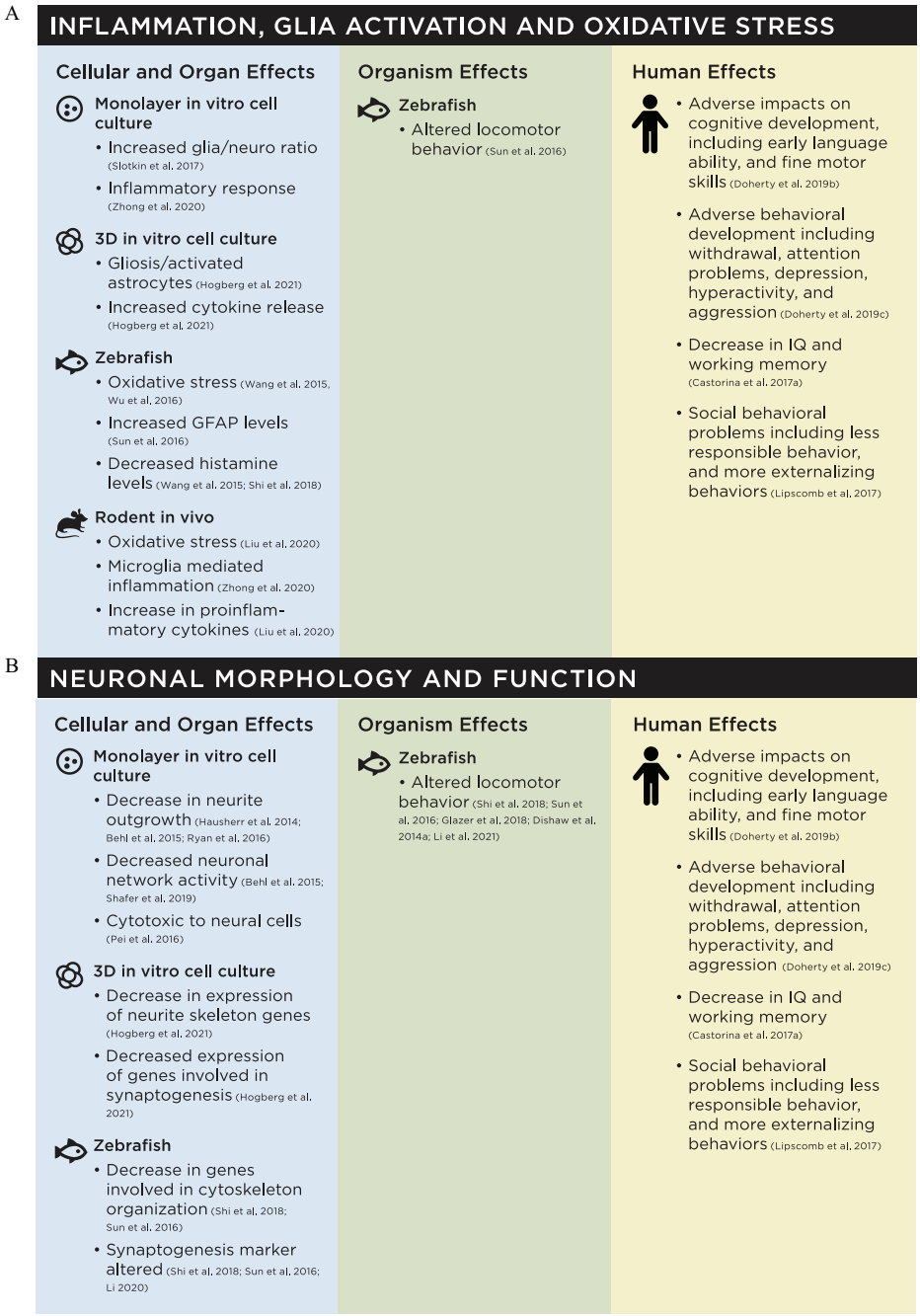

Figure 2. Developmental neurotoxicity: nervous system—(A) inflammation, glia activation, and oxidative stress and (B) neuronal morphology and function. Effects seen in humans may be associated with many different systems and thus are repeated for each outcome category. Note: 3D, three dimensional; GFAP, glial fibrillary acidic protein; IQ, intelligence quotient.

expression, and inflammation), functional changes at the organ level (e.g., altered synaptogenesis, neural network activity, steroidogenesis), and adverse effects in humans, including decreases in IQ, attention deficits, hyperactivity, and cognitive deficits. Based on current existing data displayed in Figures 1–3 and described above, the major pathways perturbed are associated with neurotransmitters and their receptors, particularly glutamate and GABA, and interactions with the endocrine system.

The OPE research findings shown in Figures 1–3 are organized into evidence categories similar to those of AOPs. An AOP is a tool for illustrating relationships between biological events (referred to as key events, often at the cellular or organ level) along a pathway from an initial stressor, such as chemical exposure, to an adverse outcome, such as impaired memory. The Office of Economic Cooperation and Development maintains a website (specifically a Wiki) where AOPs are cataloged and numbered for collaborative development and use by scientists (AOP-Wiki 2021). Although AOPs are not chemical specific, they provide context for plausible biological relationships between chemical exposures and adverse outcomes and, as such, can be used to organize information for decision making on the toxicity of environmental chemicals. Several AOPs (specifically numbers 8, 10, 12, 13, 17, 42, 48, 54, 134, 152, and 300) have been developed for outcomes relevant to DNT (AOP-Wiki 2021).

Many of the effects of OPE exposure shown in Figures 1–3 are key events in AOPs responsible for DNT (Sachana et al.

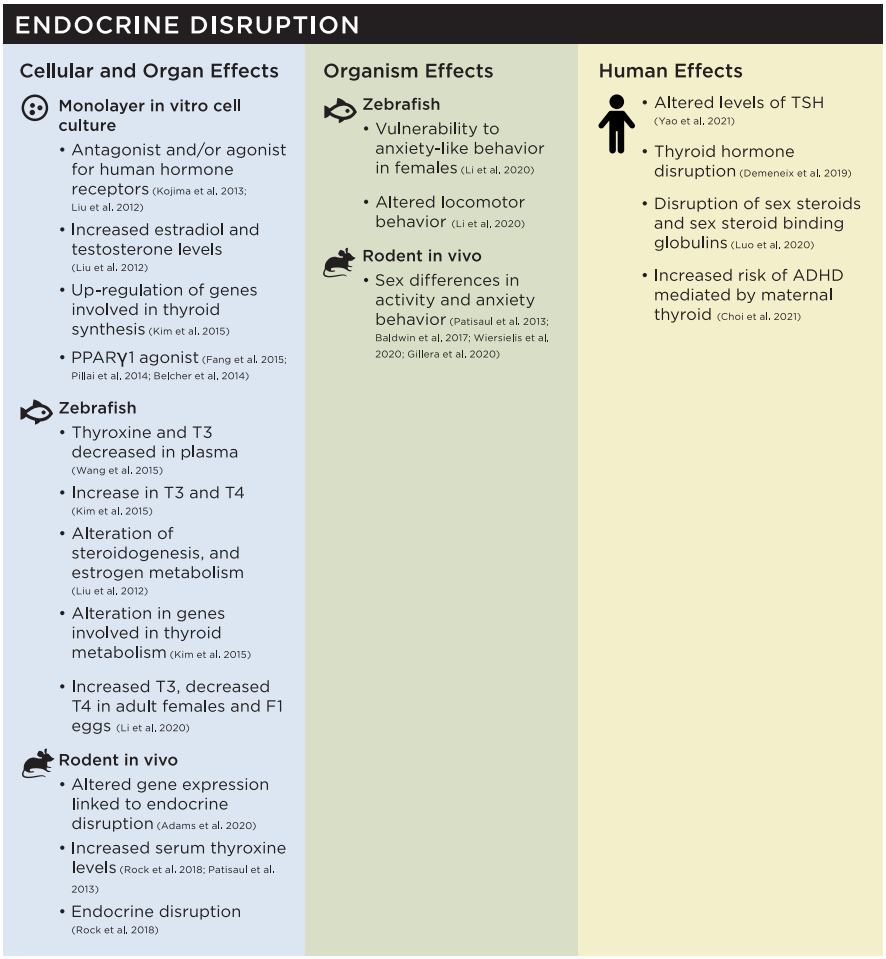

Figure 3. Endocrine Disruption. Note: 3D, three dimensional; ADHD, attention deficit hyperactivity disorder; F1, first filial generation; IQ, intelligence quotient; PPARγ, peroxisome proliferator-activated receptor-gamma; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

2018; Spinu et al. 2019; Wang et al. 2018, 2019; Li et al. 2019). This includes effects on several critical neurotransmitters, as well as endocrine pathways and pathways for oxidative stress, inflammation, and neuronal morphology and function. Application of an AOP framework to OPE effects could help identify potential pathways by which OPEs have DNT of relevance to human risk. In a complete AOP, however, a specific molecular-initiating event must be identified and relationships between key events must be described. To date, this evidence is not available for OPEs, and thus, we did not organize the figures using the precise AOP structural framework. In addition, definitive linkages between cellular effects and adverse outcomes in humans have not yet been established for OPEs. A recent review of organophosphate esters concluded that a single adverse outcome was generally caused by multiple key events (Yan et al. 2021). Therefore, human outcomes in Figures 1 and 2 (e.g., decreases in IQ, attention deficits, hyperactivity, cognitive deficits) were repeated for different effect categories (e.g., glutamate and GABA effects). Despite limitations to our current understanding, the AOP framework serves as a useful organizational tool for the presentation of the OPE effects described herein.

As an example, Figure 1 indicates that several studies observed alteration in neurotransmitters after exposure to OPEs during development. These include altered glutamate levels, expression of the *N*-methyl-D aspartate receptor, neuronal death, and disruption of *N*-acetyl-aspartame, a common biomarker used in patients to diagnose neuronal damage (Alakkas et al. 2019; Baslow et al. 2003). These effects correlate with key events identified in developed DNT AOPs. Another example can be found in Figure 2. Several *in vitro* and *in vivo* studies observed general effects on the nervous system after exposure to OPEs, including inflammation, glia activation, and oxidative stress. These cellular- and organ-level effects are key events in AOPs for DNT. As shown in Figure 3, OPEs also have the potential to induce endocrine disruption in humans and other organisms, as well as in cells. Endocrine disruption is a well-known cause of DNT and several AOPs, especially focusing on thyroid, have been or are being developed to illustrate these relationships. In addition, the key characteristics framework could also be used to help identify and understand the endocrine disrupting properties of OPEs (La Merrill et al. 2020).

Other types of pathway analyses for DNT effects have also been studied and corroborated across species. Analysis of the proteome and metabolome responses in rockfish (*Sebastes schlegelii*) exposed to TCIPP (10 or 100 nM) for 15 d found a total of 143 proteins and 8 metabolites significantly altered. Pathway analysis of the affected end points indicated disruption of pathways and systems related to neurotransmission, neurodevelopment, signal transduction, cellular transport, cholesterol metabolism, bile acid synthesis, and detoxification (Ji et al. 2020). Similarly, transcriptomic and metabolomic analyses in a three-dimensional rat primary brainsphere model after OPE exposure showed perturbation in pathways related to neurotransmission, immune response, and cell cycle and fatty acid metabolism (Hogberg et al. 2021). More in-depth analysis specifically identified glutamate and the subunits

of its receptors as altered. Thus, there is evidence not only for individual effects, but for relationships between the effects, which supports a more comprehensive understanding of how OPEs may affect DNT.

Conclusions

The literature from human, animal, and cell-based studies demonstrates that OPEs can perturb neurodevelopment and behavior via several biological pathways, independent of AChE inhibition. Further, as demonstrated by the framework of AOPs, the different evidence streams converge on several specific mechanisms of action. The most significant of these are perturbation of glutamate and GABA and endocrine disruption. Importantly, many of these effects were shown to occur during development and at environmentally relevant doses, that is, concentrations to which humans and wildlife are exposed. This calls into question the assertion from the COT and others that OPEs are unlikely to cause neurotoxicity at human exposure levels.

In a risk-based regulatory context (in contrast to assessments based on hazard), the issue of dose deserves careful consideration. Of note are that *a*) for some OPEs, points of departure obtained from *in vitro* studies are within the range of human exposure and have proved to be reliable surrogates for minimum risk levels derived from *in vivo* data (Blum et al. 2019); *b*) OPEs have endocrine effects that can be biologically detrimental at extremely low doses, particularly during development (Gore et al. 2015); and *c*) OPE exposures begin early in life, which is a sensitive window of vulnerability, and when disruption of brain development is often irreversible (Dehorter and Del Pino 2020; Gore et al. 2015; McCarthy et al. 2018). Further, a 2018 scientific consensus statement notes that despite the existence of governmental test guidelines, "no routine testing for DNT is carried out in the U.S., in the EU, or elsewhere," which is one reason why so few chemicals have been conclusively identified as developmental neurotoxicants (Fritsche et al. 2018).

Thus, we believe the argument that safety is ensured because typical human exposures are below the reference dose (when known) has not been demonstrated. Also important is that human exposures occur throughout lifetimes to complex mixtures of flame retardants and plasticizers, which may have additive or synergistic effects that are not accounted for in current regulatory assessments (Klose et al. 2021). Such exposures are rapidly increasing on a global scale (Blum et al. 2019). Further, in our experience, assessments often fail to consider risks that occur throughout the life cycle of the chemical and product, and variability in exposures. For example, vulnerable groups at high risk of harm from OPEs but who are not necessarily considered in risk assessments are workers, including people involved in e-waste recycling, and communities living near production sites (Gravel et al. 2020; Wan et al. 2020).

Based on the collective experience of the authors, we propose that reducing the use and harm from OPEs can be achieved by government regulation, by educating consumers to support actions to reduce OPEs, and by educating manufacturers to select safer materials and develop innovative solutions. OPEs have already been recognized as regrettable substitutes for PBDE flame retardants (Blum et al. 2019). Instead of moving from one family of harmful flame retardant chemicals to the next, product manufacturers could instead find innovative ways to reduce both fire hazard and the use of hazardous chemicals (Blum et al. 2019).

Although this commentary focuses on mechanisms of action of OPEs, action by government and manufacturers to reduce exposure and harm for many known hazardous chemicals, such as lead, has been taken in the absence of a clear understanding of how the chemical exerts its effects (Rocha and Trujillo 2019). Regulatory and other actions to reduce exposure to OPEs should be based on the considerable evidence that they are harmful and not be delayed while we seek to better understand the mechanisms of action of each chemical in this large class, or subclasses, as suggested by the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM 2019).

Given the hazards to the developing brain, as detailed in this paper, the goal should be to remove or reduce human exposures to OPEs as quickly as possible. One approach is to remove unnecessary uses of OPEs (e.g., in furniture, building insulation), conduct alternatives assessments for essential uses, and invest in developing innovative solutions without the use of harmful chemicals. Based on scientific research and education, government and business should be able to rapidly reduce new uses of OPEs—for healthier products, people, and ecosystems.

Acknowledgments

The authors thank S. Witchey, National Institutes of Health (NIH)/National Institute of Environmental Health Sciences (NIEHS) Division of the National Toxicology Program, for reviewing this manuscript. The authors gratefully acknowledge the following funding sources: the NIH/NIEHS (ESR01ES028110 to H.B.P. and: R01 ES031419 and P42 ES010356 to H.M.S.); the U.S. Department of Defense (AR160055 to H.B.P.), and charitable contributions to the Green Science Policy Institute (C.F.K., S.R.F., A.B., and A.S.), and the Cancer Prevention and Education Society (J.D.P.).

References

Adams S, Wiersielis K, Yasrebi A, Conde K, Armstrong L, Guo GL, et al. 2020. Sex- and age-dependent effects of maternal organophosphate flame-retardant exposure on neonatal hypothalamic and hepatic gene expression. Reprod Toxicol 94:65–74, PMID: 32360330, https://doi.org/10.1016/j.reprotox.2020.04.001.

Alakkas A, Ellis RJ, Watson CW-M, Umlauf A, Heaton RK, Letendre S, et al. 2019. White matter damage, neuroinflammation, and neuronal integrity in HAND. J Neurovirol 25(1):32–41, PMID: 30291567, https://doi.org/10.1007/s13365-018-0682-9.

Alzualde A, Behl M, Sipes NS, Hsieh J-H, Alday A, Tice RR, et al. 2018. Toxicity profiling of flame retardants in zebrafish embryos using a battery of assays for developmental toxicity, neurotoxicity, cardiotoxicity and hepatotoxicity toward human relevance. Neurotoxicol Teratol 70:40–50, PMID: 30312655, https://doi.org/10.1016/j.ntt.2018.10.002.

Andresen JA, Grundmann A, Bester K. 2004. Organophosphorus flame retardants and plasticisers in surface waters. Sci Total Environ 332(1–3):155–166, PMID: 15336899, https://doi.org/10.1016/j.scitotenv.2004.04.021.

AOP-Wiki. 2021. Collaborative Adverse Outcome Pathway Wiki. https://aopwiki.org/ [accessed 22 June 2021].

Atwood D, Paisley-Jones C. 2017. *Pesticide Industry Sales and Usage: 2008–2012 Market Estimates*. Washington, DC: U.S. Environmental Protection Agency. https://www.epa.gov/sites/default/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf [accessed 30 June 2021].

Baldwin KR, Phillips AL, Horman B, Arambula SE, Rebuli ME, Stapleton HM, et al. 2017. Sex specific placental accumulation and behavioral effects of developmental Firemaster 550 exposure in Wistar rats. Sci Rep 7(1):7118, PMID: 28769031, https://doi.org/10.1038/s41598-017-07216-6.

Baslow MH, Suckow RF, Gaynor K, Bhakoo KK, Marks N, Saito M, et al. 2003. Brain damage results in down-regulation of *N*-acetylaspartate as a neuronal osmolyte. Neuromolecular Med 3(2):95–104, PMID: 12728192, https://doi.org/10.1385/NMM:3:2:95.

Behl M, Hsieh J-H, Shafer TJ, Mundy WR, Rice JR, Boyd WA, et al. 2015. Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity. Neurotoxicol Teratol 52(pt B):181–193, PMID: 26386178, https://doi.org/10.1016/j.ntt.2015.09.003.

Belcher SM, Cookman CJ, Patisaul HB, Stapleton HM. 2014. In vitro assessment of human nuclear hormone receptor activity and cytotoxicity of the flame retardant mixture FM 550 and its triarylphosphate and brominated components. Toxicol Lett 228(2):93–102, PMID: 24786373, https://doi.org/10.1016/j.toxlet.2014.04.017.

Block ML, Zecca L, Hong J-S. 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci 8(1):57–69, PMID: 17180163, https://doi.org/10.1038/nrn2038.

Blum A, Behl M, Birnbaum L, Diamond ML, Phillips A, Singla V, et al. 2019. Organophosphate ester flame retardants: are they a regrettable substitution for polybrominated diphenyl ethers? Environ Sci Technol Lett 6(11):638–649, PMID: 32494578, https://doi.org/10.1021/acs.estlett.9b00582.

Bonnin A, Goeden N, Chen K, Wilson ML, King J, Shih JC, et al. 2011a. A transient placental source of serotonin for the fetal forebrain. Nature 472(7343):347–350, PMID: 21512572, https://doi.org/10.1038/nature09972.

Bonnin A, Levitt P. 2011b. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. Neuroscience 197:1–7, PMID: 22001683, https://doi.org/10.1016/j.neuroscience.2011.10.005.

Boyle M, Buckley JP, Quirós-Alcalá L. 2019. Associations between urinary organophosphate ester metabolites and measures of adiposity among U.S. children and adults: NHANES 2013–2014. Environ Int 127:754–763, PMID: 31003058, https://doi.org/10.1016/j.envint.2019.03.055.

Broad KD, Rocha-Ferreira E, Hristova M. 2016. Placental, matrilineal, and epigenetic mechanisms promoting environmentally adaptive development of the mammalian brain. Neural Plast 2016:6827135, PMID: 27069693, https://doi.org/10.1155/2016/6827135.

Butovsky O, Weiner HW. 2018. Microglial signatures and their role in health and disease. Nat Rev Neurosci 19(10):622–635, PMID: 30206328, https://doi.org/10.1038/s41583-018-0057-5.

Butt CM, Congleton J, Hoffman K, Fang M, Stapleton HM. 2014. Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. Environ Sci Technol 48(17):10432–10438, PMID: 25090580, https://doi.org/10.1021/es5025299.

Butt CM, Hoffman K, Chen A, Lorenzo A, Congleton J, Stapleton HM. 2016. Regional comparison of organophosphate flame retardant (PFR) urinary metabolites and tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey. Environ Int 94:627–634, PMID: 27397928, https://doi.org/10.1016/j.envint.2016.06.029.

Campos É, Freire C. 2016. Exposure to non-persistent pesticides and thyroid function: a systematic review of epidemiological evidence. Int J Hyg Environ Health 219(6):481–497, PMID: 27265299, https://doi.org/10.1016/j.ijheh.2016.05.006.

Casida JE. 2017. Organophosphorus xenobiotic toxicology. Annu Rev Pharmacol Toxicol 57:309–327, PMID: 28061690, https://doi.org/10.1146/annurev-pharmtox-010716-104926.

Castorina R, Bradman A, Stapleton HM, Butt C, Avery D, Harley KG, et al. 2017a. Current-use flame retardants: maternal exposure and neurodevelopment in children of the CHAMACOS cohort. Chemosphere 189:574–580, PMID: 28963974, https://doi.org/10.1016/j.chemosphere.2017.09.037.

Castorina R, Butt C, Stapleton HM, Avery D, Harley KG, Holland N, et al. 2017b. Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort). Chemosphere 179:159–166, PMID: 28365501, https://doi.org/10.1016/j.chemosphere.2017.03.076.

Chen X, Zhao X, Shi Z. 2021. Organophosphorus flame retardants in breast milk from Beijing, China: occurrence, nursing infant's exposure and risk assessment. Sci Total Environ 771:145404, PMID: 33548720, https://doi.org/10.1016/j.scitotenv.2021.145404.

Choi G, Keil AP, Richardson DB, Daniels JL, Hoffman K, Villanger GD, et al. 2021. Pregnancy exposure to organophosphate esters and the risk of attention-deficit hyperactivity disorder in the Norwegian Mother, Father and Child Cohort Study. Environ Int 154:106549, PMID: 33910116, https://doi.org/10.1016/j.envint.2021.106549.

Čolović MB, Krstić DZ, Lazarević-Pašti TD, Bondžic AM, Vasić VM. 2013. Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol 11(3):315–335, PMID: 24179466, https://doi.org/10.2174/1570159X11311030006.

COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment). 2019. Statement on phosphate-based flame retardants and the potential for neurodevelopmental toxicity. https://cot.food.gov.uk/sites/default/files/2020-09/cotphosphatebasedflameretardantsdevelopment.pdf [accessed 8 October 2020].

Dehorter N, Del Pino I. 2020. Shifting developmental trajectories during critical periods of brain formation. Front Cell Neurosci 14:283, PMID: 33132842, https://doi.org/10.3389/fncel.2020.00283.

Demeneix BA. 2019. Evidence for prenatal exposure to thyroid disruptors and adverse effects on brain development. Eur Thyroid J 8(6):283–292, PMID: 31934553, https://doi.org/10.1159/000504668.

Ding J, Xu Z, Huang W, Feng L, Yang F. 2016. Organophosphate ester flame retardants and plasticizers in human placenta in Eastern China. Sci Total Environ 554–555:211–217, PMID: 26950635, https://doi.org/10.1016/j.scitotenv.2016.02.171.

Dishaw LV, Hunter DL, Padnos B, Padilla S, Stapleton HM. 2014a. Developmental exposure to organophosphate flame retardants elicits overt toxicity and alters behavior in early life stage zebrafish (*Danio rerio*). Toxicol Sci 142(2):445–454, PMID: 25239634, https://doi.org/10.1093/toxsci/kfu194.

Dishaw LV, Macaulay LJ, Roberts SC, Stapleton HM. 2014b. Exposures, mechanisms, and impacts of endocrine-active flame retardants. Curr Opin Pharmacol 19:125–133, PMID: 25306433, https://doi.org/10.1016/j.coph.2014.09.018.

Dishaw LV, Powers CM, Ryde IT, Roberts SC, Seidler FJ, Slotkin TA, et al. 2011. Is the PentaBDE replacement, tris (1, 3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. Toxicol Appl Pharmacol 256(3):281–289, PMID: 21255595, https://doi.org/10.1016/j.taap.2011.01.005.

Doherty BT, Hammel SC, Daniels JL, Stapleton HM, Hoffman K. 2019a. Organophosphate esters: are these flame retardants and plasticizers affecting children's health? Curr Environ Health Rep 6(4):201–213, PMID: 31755035, https://doi.org/10.1007/s40572-019-00258-0.

Doherty BT, Hoffman K, Keil AP, Engel SM, Stapleton HM, Goldman BD, et al. 2019b. Prenatal exposure to organophosphate esters and behavioral development in young children in the pregnancy, Infection, and Nutrition Study. Neurotoxicology 73:150–160, PMID: 30951742, https://doi.org/10.1016/j.neuro.2019.03.007.

Doherty BT, Hoffman K, Keil AP, Engel SM, Stapleton HM, Goldman BD, et al. 2019c. Prenatal exposure to organophosphate esters and cognitive development in young children in the Pregnancy, Infection, and Nutrition Study. Environ Res 169:33–40, PMID: 30408751, https://doi.org/10.1016/j.envres.2018.10.033.

ECHA (European Chemicals Agency). 2018. *Screening Report: An Assessment of Whether the Use of TCEP, TCPP, and TDCP in Articles Should Be Restricted*. Version No. 3. https://echa.europa.eu/documents/10162/13641/screening_report_tcep_tcpp_td-cp_en.pdf/e0960aa7-f703-499c-24ff-fba627060698 [accessed 30 August 2021].

Fang M, Webster TF, Gooden D, Cooper EM, McClean MD, Carignan C, et al. 2013. Investigating a novel flame retardant known as V6: measurements in baby products, house dust, and car dust. Environ Sci Technol 47(9):4449–4454, PMID: 23565680, https://doi.org/10.1021/es400032v.

Fang M, Webster TF, Stapleton HM. 2015. Activation of human peroxisome proliferator-activated nuclear receptors (PPARγ1) by semi-volatile compounds (SVOCs) and chemical mixtures in indoor dust. Environ Sci Technol 49(16):10057–10064, PMID: 26172262, https://doi.org/10.1021/acs.est.5b01523.

Farhat A, Crump D, Chiu S, Williams KL, Letcher RJ, Gauthier LT, et al. 2013. *In ovo* effects of two organophosphate flame retardants—TCPP and TDCPP—on pipping success, development, mRNA expression, and thyroid hormone levels in chicken embryos. Toxicol Sci 134(1):92–102, PMID: 23629516, https://doi.org/10.1093/toxsci/kft100.

FlameRetardants-Online. 2020. The flame retardants market. https://www.flameretardants-online.com/flame-retardants/market [accessed 24 November 2020].

Fritsche E, Grandjean P, Crofton KM, Aschner M, Goldberg A, Heinonen T, et al. 2018. Consensus statement on the need for innovation, transition and implementation of developmental neurotoxicity (DNT) testing for regulatory purposes. Toxicol Appl Pharmacol 354:3–6, PMID: 29447839, https://doi.org/10.1016/j.taap.2018.02.004.

Gant DB, Eldefrawi ME, Eldefrawi AT. 1987. Action of organophosphates on GABAA receptor and voltage-dependent chloride channels. Fundam Appl Toxicol 9(4):698–704, PMID: 2446940, https://doi.org/10.1016/0272-0590(87)90176-x.

Gibson EA, Stapleton HM, Calero L, Holmes D, Burke K, Martinez R, et al. 2019. Differential exposure to organophosphate flame retardants in mother-child pairs. Chemosphere 219:567–573, PMID: 30553217, https://doi.org/10.1016/j.chemosphere.2018.12.008.

Gillera SEA, Marinello WP, Horman BM, Phillips AL, Ruis MT, Stapleton HM, et al. 2020. Sex-specific effects of perinatal FireMaster® 550 (FM 550) exposure on socioemotional behavior in prairie voles. Neurotoxicol Teratol 79:106840, PMID: 31730801, https://doi.org/10.1016/j.ntt.2019.106840.

Glazer L, Hawkey AB, Wells CN, Drastal M, Odamah K-A, Behl M, et al. 2018. Developmental exposure to low concentrations of organophosphate flame retardants causes life-long behavioral alterations in zebrafish. Toxicol Sci 165(2):487–498, PMID: 29982741, https://doi.org/10.1093/toxsci/kfy173.

Gore AC, Chappel VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. 2015. EDC-2: the Endocrine Society's second Scientific Statement on endocrine-disrupting chemicals. Endocr Rev 36(6):E1–E150, PMID: 26544531, https://doi.org/10.1210/er.2015-1010.

Gore AC, Krishnan K, Reilly MP. 2019. Endocrine-disrupting chemicals: effects on neuroendocrine systems and the neurobiology of social behavior. Horm Behav 111:7–22, PMID: 30476496, https://doi.org/10.1016/j.yhbeh.2018.11.006.

Gore AC, Martien KM, Gagnidze K, Pfaff D. 2014. Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. Endocr Rev 35(6):961–991, PMID: 25211453, https://doi.org/10.1210/er.2013-1122.

Gravel S, Lavoué J, Bakhiyi B, Lavoie J, Roberge B, Patry L, et al. 2020. Multi-exposures to suspected endocrine disruptors in electronic waste recycling workers: associations with thyroid and reproductive hormones. Int J Hyg Environ Health 225:113445, PMID: 31962273, https://doi.org/10.1016/j.ijheh.2019.113445.

Hammel SC, Hoffman K, Phillips AL, Levasseur JL, Lorenzo AM, Webster TF, et al. 2020a. Comparing the use of silicone wristbands, hand wipes, and dust to evaluate

children's exposure to flame retardants and plasticizers. Environ Sci Technol 54(7):4484–4494, PMID: 32122123, https://doi.org/10.1021/acs.est.9b07909.
Hammel SC, Hoffman K, Webster TF, Anderson KA, Stapleton HM. 2016. Measuring personal exposure to organophosphate flame retardants using silicone wristbands and hand wipes. Environ Sci Technol 50(8):4483–4491, PMID: 26975559, https://doi.org/10.1021/acs.est.6b00030.
Hammel SC, Zhang S, Lorenzo AM, Eichner B, Stapleton HM, Hoffman K. 2020b. Young infants' exposure to organophosphate esters: breast milk as a potential source of exposure. Environ Int 143:106009, PMID: 32771876, https://doi.org/10.1016/j.envint.2020.106009.
Hartmann PC, Bürgi D, Giger W. 2004. Organophosphate flame retardants and plasticizers in indoor air. Chemosphere 57(8):781–787, PMID: 15488569, https://doi.org/10.1016/j.chemosphere.2004.08.051.
Hausherr V, van Thriel C, Krug A, Leist M, Schöbel N. 2014. Impairment of glutamate signaling in mouse central nervous system neurons *in vitro* by tri-ortho-cresyl phosphate at noncytotoxic concentrations. Toxicol Sci 142(1):274–284, PMID: 25199799, https://doi.org/10.1093/toxsci/kfu174.
He C, Toms L-ML, Thai P, Van den Eede N, Wang X, Li Y, et al. 2018. Urinary metabolites of organophosphate esters: concentrations and age trends in Australian children. Environ Int 111:124–130, PMID: 29195135, https://doi.org/10.1016/j.envint.2017.11.019.
Hoffman K, Butt CM, Chen A, Limkakeng AT Jr, Stapleton HM. 2015a. High exposure to organophosphate flame retardants in infants: associations with baby products. Environ Sci Technol 49(24):14554–14559, PMID: 26551726, https://doi.org/10.1021/acs.est.5b03577.
Hoffman K, Garantziotis S, Birnbaum LS, Stapleton HM. 2015b. Monitoring indoor exposure to organophosphate flame retardants: hand wipes and house dust. Environ Health Perspect 123(2):160–165, PMID: 25343780, https://doi.org/10.1289/ehp.1408669.
Hogberg HT, de Cássia da Silveira E Sá R, Kleensang A, Bouhifd M, Cemiloglu Ulker O, Smirnova L, et al. 2021. Organophosphorus flame retardants are developmental neurotoxicants in a rat primary brainsphere in vitro model. Arch Toxicol 95(1):207–228, PMID: 33078273, https://doi.org/10.1007/s00204-020-02903-2.
Hou M, Shi Y, Jin Q, Cai Y. 2020. Organophosphate esters and their metabolites in paired human whole blood, serum, and urine as biomarkers of exposure. Environ Int 139:105698, PMID: 32278199, https://doi.org/10.1016/j.envint.2020.105698.
Jarema KA, Hunter DL, Shaffer RM, Behl M, Padilla S. 2015. Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish. Neurotoxicol Teratol 52(pt B):194–209, PMID: 26348672, https://doi.org/10.1016/j.ntt.2015.08.010.
Ji C, Lu Z, Xu L, Li F, Cong M, Shan X, et al. 2020. Global responses to tris(1-chloro-2-propyl)phosphate (TCPP) in rockfish *Sebastes schlegeli* using integrated proteomic and metabolomic approach. Sci Total Environ 724:138307, PMID: 32272412, https://doi.org/10.1016/j.scitotenv.2020.138307.
Khairy MA, Lohmann R. 2019. Organophosphate flame retardants in the indoor and outdoor dust and gas-phase of Alexandria, Egypt. Chemosphere 220:275–285, PMID: 30590294, https://doi.org/10.1016/j.chemosphere.2018.12.140.
Kim S, Jung J, Lee I, Jung D, Youn H, Choi K. 2015. Thyroid disruption by triphenyl phosphate, an organophosphate flame retardant, in zebrafish (*Danio rerio*) embryos/larvae, and in GH3 and FRTL-5 cell lines. Aquat Toxicol 160:188–196, PMID: 25646720, https://doi.org/10.1016/j.aquatox.2015.01.016.
Klose J, Pahl M, Bartmann K, Bendt F, Blum J, Dolde X, et al. 2021. Neurodevelopmental toxicity assessment of flame retardants using a human DNT in vitro testing battery. Cell Biol Toxicol. Preprint posted online 10 May 2021, PMID: 33969458, https://doi.org/10.1007/s10565-021-09603-2.
Kojima H, Takeuchi S, Itoh T, Iida M, Kobayashi S, Yoshida T. 2013. In vitro endocrine disruption potential of organophosphate flame retardants via human nuclear receptors. Toxicology 314(1):76–83, PMID: 24051214, https://doi.org/10.1016/j.tox.2013.09.004.
Krumm EA, Patel VJ, Tillery TS, Yasrebi A, Shen J, Guo GL, et al. 2018. Organophosphate flame-retardants alter adult mouse homeostasis and gene expression in a sex-dependent manner potentially through interactions with ERα. Toxicol Sci 162(1):212–224, PMID: 29112739, https://doi.org/10.1093/toxsci/kfx238.
La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, et al. 2020. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16(1):45–57, PMID: 31719706, https://doi.org/10.1038/s41574-019-0273-8.
Larsson K, de Wit CA, Sellström U, Sahlström L, Lindh CH, Berglund M. 2018. Brominated flame retardants and organophosphate esters in preschool dust and children's hand wipes. Environ Sci Technol 52(8):4878–4888, PMID: 29569442, https://doi.org/10.1021/acs.est.8b00184.
Leemans M, Couderq S, Demeneix B, Fini J-B. 2019. Pesticides with potential thyroid hormone-disrupting effects: a review of recent data. Front Endocrinol (Lausanne) 10:743, PMID: 31920955, https://doi.org/10.3389/fendo.2019.00743.
Li J, Settivari R, LeBaron MJ, Marty MS. 2019. An industry perspective: a streamlined screening strategy using alternative models for chemical assessment of developmental neurotoxicity. Neurotoxicology 73:17–30, PMID: 30786249, https://doi.org/10.1016/j.neuro.2019.02.010.
Li R, Guo W, Lei L, Zhang L, Liu Y, Han J, et al. 2020. Early-life exposure to the organophosphorus flame-retardant tris (1,3-dichloro-2-propyl) phosphate induces delayed neurotoxicity associated with DNA methylation in adult zebrafish. Environ Int 134:105293, PMID: 31731001, https://doi.org/10.1016/j.envint.2019.105293.
Lipscomb ST, McClelland MM, MacDonald M, Cardenas A, Anderson KA, Kile ML. 2017. Cross-sectional study of social behaviors in preschool children and exposure to flame retardants. Environ Health 16(1):23, PMID: 28274271, https://doi.org/10.1186/s12940-017-0224-6.
Liu R, Mabury S. 2019. Identification of photoinitiators, including novel phosphine oxides, and their transformation products in food packaging materials and indoor dust in Canada. Environ Sci Technol 53(8):4109–4118, PMID: 30942572, https://doi.org/10.1021/acs.est.9b00045.
Liu X, Ji K, Choi K. 2012. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquat Toxicol 114–115:173–181, PMID: 22446829, https://doi.org/10.1016/j.aquatox.2012.02.019.
Liu X, Zeng X, Dong G, Venier M, Xie Q, Yang M, et al. 2021. Plastic additives in ambient fine particulate matter in the Pearl River Delta, China: high-throughput characterization and health implications. Environ Sci Technol 55(8):4474–4482, PMID: 33710877, https://doi.org/10.1021/acs.est.0c08578.
Liu X, Zhao X, Wang Y, Hong J, Shi M, Pfaff D, et al. 2020. Triphenyl phosphate permeates the blood brain barrier and induces neurotoxicity in mouse brain. Chemosphere 252:126470, PMID: 32443258, https://doi.org/10.1016/j.chemosphere.2020.126470.
Lotti M, Moretto A. 2005. Organophosphate-induced delayed polyneuropathy. Toxicol Rev 24(1):37–49, PMID: 16042503, https://doi.org/10.2165/00139709-200524010-00003.
Luo D, Liu W, Tao Y, Wang L, Yu M, Hu L, et al. 2020. Prenatal exposure to organophosphate flame retardants and the risk of low birth weight: a nested case-control study in China. Environ Sci Technol 54(6):3375–3385, PMID: 32106667, https://doi.org/10.1021/acs.est.9b06026.
Ma J, Zhu H, Kannan K. 2019. Organophosphorus flame retardants and plasticizers in breast milk from the United States. Environ Sci Technol Lett 6(9):525–531, PMID: 31534982, https://doi.org/10.1021/acs.estlett.9b00394.
Ma Y, Jin J, Li P, Xu M, Sun Y, Wang Y, et al. 2017a. Organophosphate ester flame retardant concentrations and distributions in serum from inhabitants of Shandong, China, and changes between 2011 and 2015. Environ Toxicol Chem 36(2):414–421, PMID: 27391075, https://doi.org/10.1002/etc.3554.
Ma Y, Xie Z, Lohmann R, Mi W, Gao G. 2017b. Organophosphate ester flame retardants and plasticizers in ocean sediments from the North Pacific to the Arctic Ocean. Environ Sci Technol 51(7):3809–3815, PMID: 28245125, https://doi.org/10.1021/acs.est.7b00755.
McCarthy MM, Herold K, Stockman SL. 2018. Fast, furious and enduring: sensitive versus critical periods in sexual differentiation of the brain. Physiol Behav 187:13–19, PMID: 29101011, https://doi.org/10.1016/j.physbeh.2017.10.030.
McGraw LA, Young LJ. 2010. The prairie vole: an emerging model organism for understanding the social brain. Trends Neurosci 33(2):103–109, PMID: 20005580, https://doi.org/10.1016/j.tins.2009.11.006.
Meeker JC, Cooper EM, Stapleton HM, Hauser R. 2013. Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environ Health Perspect 121(5):580–585, PMID: 23461877, https://doi.org/10.1289/ehp.1205907.
NASEM (National Academies of Sciences, Engineering, and Medicine). 2019. *A Class Approach to Hazard Assessment of Organohalogen Flame Retardants*. Washington, DC: National Academies Press.
Oliveri AN, Bailey JM, Levin ED. 2015. Developmental exposure to organophosphate flame retardants causes behavioral effects in larval and adult zebrafish. Neurotoxicol Teratol 52(pt B):220–227, PMID: 26344674, https://doi.org/10.1016/j.ntt.2015.08.008.
Ospina M, Jayatilaka NK, Wong L-Y, Restrepo P, Calafat AM. 2018. Exposure to organophosphate flame retardant chemicals in the U.S. general population: data from the 2013–2014 National Health and Nutrition Examination Survey. Environ Int 110:32–41, PMID: 29102155, https://doi.org/10.1016/j.envint.2017.10.001.
Pantelaki I, Voutsa D. 2020. Occurrence, analysis and risk assessment of organophosphate esters (OPEs) in biota: a review. Mar Pollut Bull 160:111547, PMID: 32829085, https://doi.org/10.1016/j.marpolbul.2020.111547.
Patisaul HB, Roberts SC, Mabrey N, McCaffrey KA, Gear RB, Braun J, et al. 2013. Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster® 550 in rats: an exploratory assessment. J Biochem Mol Toxicol 27(2):124–136, PMID: 23139171, https://doi.org/10.1002/jbt.21439.
Pei Y, Peng J, Behl M, Sipes NS, Shockley KR, Rao MS, et al. 2016. Comparative neurotoxicity screening in human iPSC-derived neural stem cells, neurons and astrocytes. Brain Res 1638(pt A):57–73, PMID: 26254731, https://doi.org/10.1016/j.brainres.2015.07.048.

Phillips AL, Chen A, Rock KD, Horman B, Patisaul HB, Stapleton HM. 2016. Editor's highlight: transplacental and lactational transfer of Firemaster® 550 components in dosed Wistar rats. Toxicol Sci 153(2):246–257, PMID: 27370412, https://doi.org/10.1093/toxsci/kfw122.

Pillai HK, Fang M, Beglov D, Kozakov D, Vajda S, Stapleton HM, et al. 2014. Ligand binding and activation of PPARγ by Firemaster® 550: effects on adipogenesis and osteogenesis *in vitro*. Environ Health Perspect 122(11):1225–1232, PMID: 25062436, https://doi.org/10.1289/ehp.1408111.

Pulidindi K, Pandey H. 2018. *Phosphate Esters Market Size By Type (Triaryl Phosphate Ester, Trialkyl Phosphate Ester, Alkyl Aryl Phosphate Ester), By Application (Surfactants, Fire Retardants, Lubricants, Agrochemicals, Plasticizers, Hydraulic Fluids), Industry Analysis Report, Regional Outlook, Growth Potential, Price Trends, Competitive Market Share & Forecast, 2018–2025*. Report ID GMI3028. https://www.gminsights.com/industry-analysis/phosphate-esters-market [accessed 15 December 2020].

Rocha A, Trujillo KA. 2019. Neurotoxicity of low-level lead exposure: history, mechanisms of action, and behavioral effects in humans and preclinical models. Neurotoxicology 73:58–80, PMID: 30836127, https://doi.org/10.1016/j.neuro.2019.02.021.

Rock KD, Horman B, Phillips AL, McRitchie SL, Watson S, Deese-Spruill J, et al. 2018. EDC IMPACT: molecular effects of developmental FM 550 exposure in Wistar rat placenta and fetal forebrain. Endocr Connect 7(2):305–324, PMID: 29351906, https://doi.org/10.1530/EC-17-0373.

Rock KD, St Armour G, Horman B, Phillips A, Ruis M, Stewart AK, et al. 2020. Effects of prenatal exposure to a mixture of organophosphate flame retardants on placental gene expression and serotonergic innervation in the fetal rat brain. Toxicol Sci 176(1):203–223, PMID: 32243540, https://doi.org/10.1093/toxsci/kfaa046.

Ryan KR, Sirenko O, Parham F, Hsieh J-H, Cromwell EF, Tice RR, et al. 2016. Neurite outgrowth in human induced pluripotent stem cell-derived neurons as a high-throughput screen for developmental neurotoxicity or neurotoxicity. Neurotoxicology 53:271–281, PMID: 26854185, https://doi.org/10.1016/j.neuro.2016.02.003.

Sachana M, Rolaki A, Bal-Price A. 2018. Development of the Adverse Outcome Pathway (AOP): chronic binding of antagonist to *N*-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities of children. Toxicol Appl Pharmacol 354:153–175, PMID: 29524501, https://doi.org/10.1016/j.taap.2018.02.024.

Saini A, Thaysen C, Jantunen L, McQueen RH, Diamond ML. 2016. From clothing to laundry water: investigating the fate of phthalates, brominated flame retardants, and organophosphate esters. Environ Sci Technol 50(17):9289–9297, PMID: 27507188, https://doi.org/10.1021/acs.est.6b02038.

Selmi-Ruby S, Marín-Sáez J, Fildier A, Buleté A, Abdallah M, Garcia J, et al. 2020. *In vivo* characterization of the toxicological properties of DPhP, one of the main degradation products of aryl phosphate esters. Environ Health Perspect 128(12):127006, PMID: 33296241, https://doi.org/10.1289/EHP6826.

Shafer TJ, Brown JP, Lynch B, Davila-Montero S, Wallace K, Friedman KP. 2019. Evaluation of chemical effects on network formation in cortical neurons grown on microelectrode arrays. Toxicol Sci 169(2):436–455, PMID: 30816951, https://doi.org/10.1093/toxsci/kfz052.

Sheldon LS, Hites RA. 1978. Organic compounds in the Delaware River. Environ Sci Technol 12(10):1188–1194, https://doi.org/10.1021/es60146a006.

Shi Q, Guo W, Shen Q, Han J, Lei L, Chen L, et al. 2021. *In vitro* biolayer interferometry analysis of acetylcholinesterase as a potential target of aryl-organophosphorus flame-retardants. J Hazard Mater 409:124999, PMID: 33454525, https://doi.org/10.1016/j.jhazmat.2020.124999.

Shi Q, Wang M, Shi F, Yang L, Guo Y, Feng C, et al. 2018. Developmental neurotoxicity of triphenyl phosphate in zebrafish larvae. Aquat Toxicol 203:80–87, PMID: 30096480, https://doi.org/10.1016/j.aquatox.2018.08.001.

Slotkin TA, Skavicus S, Stapleton HM, Seidler FJ. 2017. Brominated and organophosphate flame retardants target different neurodevelopmental stages, characterized with embryonic neural stem cells and neuronotypic PC12 cells. Toxicology 390:32–42, PMID: 28851516, https://doi.org/10.1016/j.tox.2017.08.009.

Spinu N, Bal-Price A, Cronin MTD, Enoch SJ, Madden JC, Worth AP. 2019. Development and analysis of an adverse outcome pathway network for human neurotoxicity. Arch Toxicol 93(10):2759–2772, PMID: 31444508, https://doi.org/10.1007/s00204-019-02551-1.

Staaf T, Ostman C. 2005. Organophosphate triesters in indoor environments. J Environ Monit 7(9):883–887, PMID: 16121268, https://doi.org/10.1039/b506631j.

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, et al. 2009. Detection of organophosphate flame retardants in furniture foam and U.S. house dust. Environ Sci Technol 43(19):7490–7495, PMID: 19848166, https://doi.org/10.1021/es9014019.

Stapleton HM, Sharma S, Getzinger G, Ferguson L, Gabriel M, Webster TF, et al. 2012. Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out. Environ Sci Technol 46(24):13432–13439, PMID: 23186002, https://doi.org/10.1021/es303471d.

Sühring R, Diamond ML, Bernstein S, Adams JK, Schuster JK, Fernie K, et al. 2021. Organophosphate esters in the Canadian Arctic Ocean. Environ Sci Technol 55(1):304–312, PMID: 33305563, https://doi.org/10.1021/acs.est.0c04422.

Sühring R, Diamond ML, Scheringer M, Wong F, Pućko M, Stern G, et al. 2016. Organophosphate esters in Canadian Arctic air: occurrence, levels and trends. Environ Sci Technol 50(14):7409–7415, PMID: 27309668, https://doi.org/10.1021/acs.est.6b00365.

Sun L, Xu W, Peng T, Chen H, Ren L, Tan H, et al. 2016. Developmental exposure of zebrafish larvae to organophosphate flame retardants causes neurotoxicity. Neurotoxicol Teratol 55:16–22, PMID: 27018022, https://doi.org/10.1016/j.ntt.2016.03.003.

Tung EWY, Ahmed S, Peshdary V, Atlas E. 2017. Firemaster® 550 and its components isopropylated triphenyl phosphate and triphenyl phosphate enhance adipogenesis and transcriptional activity of peroxisome proliferator activated receptor (PPARγ) on the adipocyte protein 2 (aP2) promoter. PLoS One 12(4):e0175855, PMID: 28437481, https://doi.org/10.1371/journal.pone.0175855.

Umezu T, Yonemoto J, Soma Y, Suzuki T. 1998. Tris(2-chloroethyl)phosphate increases ambulatory activity in mice: pharmacological analyses of its neurochemical mechanism. Toxicol Appl Pharmacol 148(1):109–116, PMID: 9465270, https://doi.org/10.1006/taap.1997.8312.

Vail GM, Roepke TA. 2020. Organophosphate flame retardants excite arcuate melanocortin circuitry and increase neuronal sensitivity to ghrelin in adult mice. Endocrinology 161(11):bqaa168, PMID: 32961558, https://doi.org/10.1210/endocr/bqaa168.

van der Veen I, de Boer J. 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88(10):1119–1153, PMID: 22537891, https://doi.org/10.1016/j.chemosphere.2012.03.067.

Vuong AM, Yolton K, Cecil KM, Braun JM, Lanphear BP, Chen A. 2020. Flame retardants and neurodevelopment: an updated review of epidemiological literature. Curr Epidemiol Rep 7(4):220–236, PMID: 33409120, https://doi.org/10.1007/s40471-020-00256-z.

Walley SN, Krumm EA, Yasrebi A, Wiersielis KR, O'Leary S, Tillery T, et al. 2021. Maternal organophosphate flame-retardant exposure alters offspring feeding, locomotor and exploratory behaviors in a sexually-dimorphic manner in mice. J Appl Toxicol 41(3):442–457, PMID: 33280148, https://doi.org/10.1002/jat.4056.

Wan Y, Diamond ML, Siegel JA. 2020. Elevated concentrations of semivolatile organic compounds in social housing multiunit residential building apartments. Environ Sci Technol Lett 7(3):191–197, https://doi.org/10.1021/acs.estlett.0c00068.

Wang Q, Lai NL-S, Wang X, Guo Y, Lam PK-S, Lam JC-W, et al. 2015. Bioconcentration and transfer of the organophorous flame retardant 1,3-dichloro-2-propyl phosphate causes thyroid endocrine disruption and developmental neurotoxicity in zebrafish larvae. Environ Sci Technol 49(8):5123–5132, PMID: 25826601, https://doi.org/10.1021/acs.est.5b00558.

Wang Y, Tang J-L, Xu X, Zhou X-P, Du J, Wang X, et al. 2018. NMDA receptors inhibit axonal outgrowth by inactivating Akt and activating GSK-3β via calcineurin in cultured immature hippocampal neurons. Exp Cell Res 371(2):389–398, PMID: 30176218, https://doi.org/10.1016/j.yexcr.2018.08.033.

Wang Y, Yang Y, Zhang Y, Tan F, Li Q, Zhao H, et al. 2019. Polyurethane heat preservation materials: the significant sources of organophosphorus flame retardants. Chemosphere 227:409–415, PMID: 31003125, https://doi.org/10.1016/j.chemosphere.2019.04.085.

Wiersielis KR, Adams S, Yasrebi A, Conde K, Roepke TA. 2020. Maternal exposure to organophosphate flame retardants alters locomotor and anxiety-like behavior in male and female adult offspring. Horm Behav 122:104759, PMID: 32320692, https://doi.org/10.1016/j.yhbeh.2020.104759.

Wu S, Ji G, Liu J, Zhang S, Gong Y, Shi L. 2016. TBBPA induces developmental toxicity, oxidative stress, and apoptosis in embryos and zebrafish larvae (Danio rerio). Environ Toxicol 31(10):1241–1249, PMID: 25846749, https://doi.org/10.1002/tox.22131.

Xia M, Wang X, Xu J, Qian Q, Gao M, Wang H. 2021. Tris (1-chloro-2-propyl) phosphate exposure to zebrafish causes neurodevelopmental toxicity and abnormal locomotor behavior. Sci Total Environ 758:143694, PMID: 33267995, https://doi.org/10.1016/j.scitotenv.2020.143694.

Xu F, García-Bermejo Á, Malarvannan G, Gómara B, Neels H, Covaci A. 2015. Multi-contaminant analysis of organophosphate and halogenated flame retardants in food matrices using ultrasonication and vacuum assisted extraction, multi-stage cleanup and gas chromatography–mass spectrometry. J Chromatogr A 1401:33–41, PMID: 25997844, https://doi.org/10.1016/j.chroma.2015.05.001.

Xu F, Giovanoulis G, van Waes S, Padilla-Sanchez JA, Papadopoulou E, Magnér J, et al. 2016. Comprehensive study of human external exposure to organophosphate flame retardants via air, dust, and hand wipes: the importance of sampling and assessment strategy. Environ Sci Technol 50(14):7752–7760, PMID: 27350238, https://doi.org/10.1021/acs.est.6b00246.

Yan Z, Jin X, Liu D, Hong Y, Liao W, Feng C, et al. 2021. The potential connections of adverse outcome pathways with the hazard identifications of typical organophosphate esters based on toxicity mechanisms. Chemisphere 266:128989, PMID: 33228983, https://doi.org/10.1016/j.chemosphere.2020.128989.

Yang C, Harris SA, Jantunen LM, Siddique S, Kubwabo C, Tsirlin D, et al. 2019a. Are cell phones an indicator of personal exposure to organophosphate flame retardants and plasticizers? Environ Int 122:104–116, PMID: 30522823, https://doi.org/10.1016/j.envint.2018.10.021.

Yang J, Zhao Y, Li M, Du M, Li X, Li Y. 2019b. A review of a class of emerging contaminants: the classification, distribution, intensity of consumption, synthesis routes, environmental effects and expectation of pollution abatement to organophosphate flame retardants (OPFRs). Int J Mol Sci 20(12):2874, PMID: 31212857, https://doi.org/10.3390/ijms20122874.

Yang W, Zhao F, Fang Y, Li L, Li C, Ta N. 2018. ^{1}H-nuclear magnetic resonance metabolomics revealing the intrinsic relationships between neurochemical alterations and neurobehavioral and neuropathological abnormalities in rats exposed to tris(2-chloroethyl)phosphate. Chemosphere 200:649–659, PMID: 29518649, https://doi.org/10.1016/j.chemosphere.2018.02.056.

Yao Y, Li M, Pan L, Duan Y, Duan X, Li Y, et al. 2021. Exposure to organophosphate ester flame retardants and plasticizers during pregnancy: thyroid endocrine disruption and mediation role of oxidative stress. Environ Int 146:106215, PMID: 33113466, https://doi.org/10.1016/j.envint.2020.106215.

Yu L, Ru S, Zheng X, Chen S, Guo H, Gao G, et al. 2021. Brominated and phosphate flame retardants from interior and surface dust of personal computers: insights into sources for human dermal exposure. Environ Sci Pollut Res Int 28(10):12566–12575, PMID: 33083952, https://doi.org/10.1007/s11356-020-11132-0.

Zhang X, Sühring R, Serodio D, Bonnell M, Sundin N, Diamond ML. 2016. Novel flame retardants: estimating the physical–chemical properties and environmental fate of 94 halogenated and organophosphate PBDE replacements. Chemosphere 144:2401–2407, PMID: 26613357, https://doi.org/10.1016/j.chemosphere.2015.11.017.

Zhong X, Wu J, Ke W, Yu Y, Ji D, Kang J, et al. 2020. Neonatal exposure to organophosphorus flame retardant TDCPP elicits neurotoxicity in mouse hippocampus via microglia-mediated inflammation in vivo and in vitro. Arch Toxicol 94(2):541–552, PMID: 31894355, https://doi.org/10.1007/s00204-019-02635-y.