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Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish

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ABSTRACT

As polybrominated diphenyl ethers are phased out, numerous compounds are emerging as potential replacement flame retardants for use in consumer and electronic products. Little is known, however, about the neurobehavioral toxicity of these replacements. This study evaluated the neurobehavioral effects of acute or developmental exposure to *t*-butylphenyl diphenyl phosphate (BPDP), 2-ethylhexyl diphenyl phosphate (EHDP), isodecyl diphenyl phosphate (IDDP), isopropylated phenyl phosphate (IPP), tricresyl phosphate (TMPP; also abbreviated TCP), triphenyl phosphate (TPHP; also abbreviated TPP), tetrabromobisphenol A (TBBPA), tris (2-chloroethyl) phosphate (TCEP), tris (1,3-dichloroisopropyl) phosphate (TDCIPP; also abbreviated TDCPP), tri-*o*-cresyl phosphate (TOCP), and 2,2-,4,4′-tetrabromodiphenyl ether (BDE-47) in zebrafish (*Danio rerio*) larvae. Larvae (n ≈ 24 per dose per compound) were exposed to test compounds (0.4–120 μM) at subteratogenic concentrations either developmentally or acutely, and locomotor activity was assessed at 6 days post fertilization. When given developmentally, all chemicals except BPDP, IDDP and TBBPA produced behavioral effects. When given acutely, all chemicals produced behavioral effects, with TPHP, TBBPA, EHDP, IPP, and BPDP eliciting the most effects at the most concentrations. The results indicate that these replacement flame retardants may have developmental or pharmacological effects on the vertebrate nervous system.

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1. Introduction

There is widespread human and wildlife exposure to flame retardants, making these chemicals a priority for both human and ecological health assessments. As some classes of flame retardants (e.g., polybrominated biphenyl ethers PBDEs) are being phased out due to bioaccumulation and toxicity, others have been introduced as replacements for use in furniture, electronics, textiles, automotive products, and construction materials. A recent longitudinal study compared levels of PBDEs and the emerging alternative flame retardants in indoor dust and children's hand wipes; findings suggest that exposure to these alternative flame retardants are predicted to be as high as PBDE exposure (Stapleton et al., 2014). Despite documented human and wildlife exposure to these newer compounds (Segev et al., 2009; Dishaw et al., 2014b; Ezechiáš et al., 2014; Wei et al., 2015; Gao et al., 2014), there is sparse information on the possible human health or ecological toxicity of many of these replacements.

Neurotoxicity is a primary concern associated with emerging alternative flame retardants due to their organophosphorus backbone. Structurally related compounds have previously been shown to affect brain development (Carr et al., 2013, 2014; Dishaw et al., 2011; Slotkin et al., 2006, 2009; Slotkin and Seidler, 2005, 2011). Hence, it is important to deploy a test system for rapid assessment of nervous system perturbations. The zebrafish model is positioned to address these concerns, as there is a basic understanding of nervous system development (reviewed in Blader and Strähle, 2000; Guo, 2009; Young et al., 2011; Guo, 2004), as well as techniques for rapidly evaluating the effects of chemical exposures on the zebrafish nervous system (Bang et al., 2002; Bichara et al., 2014; Ellis and Soanes, 2012; Green et al., 2012). Many investigators concentrate on evaluating behavior, because, to a large extent, behavior integrates nervous system function, making it an appropriate, approachable, and apical endpoint for screening, demonstrating excellent concordance with mammalian neurotoxicity (Kokel et al., 2010; Kokel and Peterson, 2011; Levin et al., 2003, 2004; Sallinen et al., 2009; Selderslaghs et al., 2013, 2010; Anichtchik et al., 2004; Fernandes et al., 2014; Fetcho and Liu, 1998; Nishimura et al., 2015). The developmentally neurotoxic PBDE flame retardants (Costa and Giordano, 2007; Costa et al., 2014) have been phased out and replaced with other halogenated (primarily chlorinated) and organophosphorus based chemicals (see Table 1 for chemicals, abbreviations

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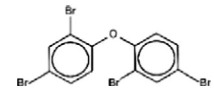
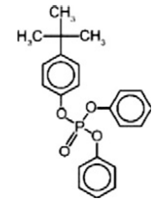
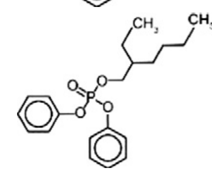
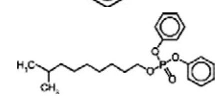
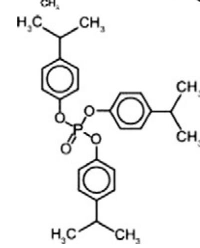
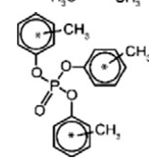
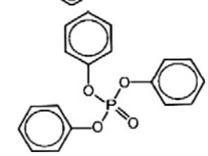
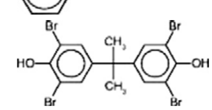
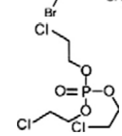
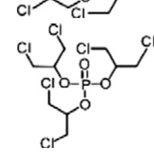
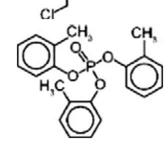
Table 1
Physiochemical Characteristics of the Chemicals Tested.

Chemical Name	Abbreviation	Characteristics	Structure
2,2′4,4′-Tetrabromodiphenyl ether	BDE-47	CAS# 5436–43–1 MW[†] = 485.79 Log P[††] = 6.77	
tert-Butylphenyl diphenyl phosphate	BPDP[*]	CAS# 56,803–37–3 MW = 382.39 Log P = 6.61	
2-Ethylhexyl diphenyl phosphate	EHDP	CAS# 1241–94–7 MW = 362.4 Log P = 6.30	
Isodecyl diphenyl phosphate	IDDP[*]	CAS# 29,761–21–5 MW = 390.45 Log P = 7.28	
Phenol, isopropylated, phosphate (3:1)	IPP	CAS# 68,937–41–7 MW = 390.00 Log P = 9.07	
Tricresyl phosphate	TMPP[*]	CAS# 1330–78–5 MW = 371.39 Log P = 6.34	
Triphenyl phosphate	TPHP	CAS# 115–86–6 MW = 326.28 Log P = 3.065	
3,3′,5,5′-Tetrabromobisphenol A	TBBPA	CAS# 79–94–7 MW = 543.87 Log P = 7.20	
Tris(2-chloroethyl) phosphate	TCEP	CAS# 115–96–8 MW = 285.49 Log P = 1.63	
Tris(1,3-dichloro-2-propyl)phosphate	TDCIPP	CAS# 13,674–87–8 MW = 490.9 Log P = 3.65	
Tri-*o*-cresyl phosphate (this is the ortho isomer of TMPP)	TOCP	CAS# 78–30–8 MW = 368.36 Log P = 6.34	

Both molecular weight and LogP were obtained from EPI SuiteTM (http://www.epa.gov/opptintr/exposure/pubs/episuite.htm).
[*] Mixture.
[†] MW = Molecular Weight.
[††] LogP = Octanol/water Partition Coefficient.

and structures). There is some preliminary evidence that member(s) of both the halogenated and organophosphorus classes (BDE-47, TBBPA, TDCIPP, and TPHP) perturb the thyroid system in developing zebrafish (Chan and Chan, 2012; Kim et al., 2015; Liu et al., 2013). There is also evidence that developmental exposure to either TDCIPP or TCEP produces developmental neurotoxicity as assessed by changes in locomotor