Neurotoxicology and Teratology 52 (2015) 248–269

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Neurotoxicity and risk assessment of brominated and alternative flame retardants

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ARTICLE INFO

Article history:
Received 20 March 2015
Received in revised form 1 September 2015
Accepted 1 September 2015
Available online 10 September 2015

Keywords:
Brominated flame retardants
Alternative flame retardants
Halogenated and halogen-free organophosphorous flame retardants
Inorganic halogen-free flame retardants
Neurotoxicity
Risk assessment

ABSTRACT

Brominated flame retardants (BFRs) are widely used chemicals that prevent or slow the onset and spreading of fire. Unfortunately, many of these compounds pose serious threats for human health and the environment, indicating an urgent need for safe(r) and less persistent alternative flame retardants (AFRs). As previous research identified the nervous system as a sensitive target organ, the neurotoxicity of past and present flame retardants is reviewed.

First, an overview of the neurotoxicity of BFRs in humans and experimental animals is provided, and some common *in vitro* neurotoxic mechanisms of action are discussed. The combined epidemiological and toxicological studies clearly underline the need for replacing BFRs.

Many potentially suitable AFRs are already in use, despite the absence of a full profile of their environmental behavior and toxicological properties. To prioritize the suitability of some selected halogenated and non-halogenated organophosphorous flame retardants and inorganic halogen-free flame retardants, the available neurotoxic data of these AFRs are discussed. The suitability of the AFRs is rank-ordered and combined with human exposure data (serum concentrations, breast milk concentrations and house dust concentrations) and physicochemical properties (useful to predict *e.g.* bioavailability and persistence in the environment) for a first semi-quantitative risk assessment of the AFRs.

As can be concluded from the reviewed data, several BFRs and AFRs share some neurotoxic effects and modes of action. Moreover, the available neurotoxicity data indicate that some AFRs may be suitable substitutes for BFRs. However, proper risk assessment is hampered by an overall scarcity of data, particularly regarding environmental persistence, human exposure levels, and the formation of breakdown products and possible metabolites as well as their toxicity. Until these data gaps in environmental behavioral and toxicological profiles are filled, large scale use of these chemicals should be cautioned.

Abbreviations: AA, arachidonic acid; AChE, acetylcholinesterase; AFRs, alternative flame retardants; ALPI, aluminum diethylphosphinate; APP, ammonium polyphosphate; ATH, aluminum trihydroxide; ATO, antimony trioxide; B35, rat neuroblastoma cells; BBB, blood–brain barrier; BCMP-BCEP, 2,2-bis(chloromethyl)-1,3-propanediol bis[bis(2-chloroethyl)phosphate]; BFRs, brominated flame retardants; BPA-BDPP, bisphenol A bis(diphenyl phosphate); BPDPP, resorcinol bis(diphenyl phosphate); bw, body weight; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; CAMK-II, calcium/calmodulin-dependent protein kinase-II; DCP, diphenylcresylphosphate; DMMP, dimethyl methylphosphonate; DOPO, 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide; dpf, days post fertilization; EC_{50}, half maximal effective concentration; EHDPP, ethylhexyl diphenylphosphate; ER, endoplasmic reticulum; FR, flame retardant; GABA-R, γ-aminobutyric acid receptor; GAP-43, growth associated protein-43; GD, gestational day; GluR, glutamate receptor; HBCDD, hexabromocyclododecane; hpf, hours post fertilization; IC_{50}, half maximal inhibition concentration; IDPP, isodecyl diphenyl phosphate; ip, intraperitoneal; IP_3, inositol-1,4,5-trisphosphate; IPPP, isopropyl phenyl phosphate; LC_{50}, half maximal lethal concentration; LD_{50}, half maximal lethal dose; LOEC, lowest observed effect concentration; Log K_{OW}, octanol–water partition coefficient; LTP, long-term potentiation; lw, lipid weight; mACh-R, muscarinic acetylcholine receptor; MAPK, mitogen-activated protein kinase; MHO, magnesium hydroxide; MPP, melamine polyphosphate; MW, molecular weight; nACh-R, nicotinic acetylcholine receptor; NOAEL, no observed adverse effect level; NOEC, no observed effect concentration; NTE, neuropathy target esterase; OPFRs, organophosphorous flame retardants; PC12, pheochromocytoma cells; PCBs, polychlorinated biphenyls; PBDEs, polybrominated diphenyl ethers; PBDMPP, resorcinol bis[di(2,6-dimethylphenyl) phosphate]; PKC, protein kinase C; PLA, phospholipase A; PND, postnatal day; POPs, persistent organic pollutants; ROS, reactive oxygen species; RyR, ryanodine receptor; $t_{1/2}$, half-life; TBBPA, tetrabromobisphenol-A; TBOEP, tris(2-butoxyethyl) phosphate; TCEP, tris(chloroethyl) phosphate; TCIPP, tris(2-chloroisopropyl) phosphate; TCP, tricresyl phosphate; TDBPP, tris-(2,3-dibromopropyl)phosphate; TDCIPP, tris-(2,3-dichloropropyl)phosphate; TEHP, tris(2-ethylhexyl) phosphate; TEP, tris(ethyl) phosphate; TIBP, tris(isobutyl) phosphate; TMP, tris(methyl) phosphate; TMPP, tris(methylphenyl) phosphate; TNBP, tris(butyl) phosphate; TPHP, tris(phenyl) phosphate; V6, 2,2-bis(chloromethyl)-1,3-propanediol bis[bis(2-chloroethyl)phosphate]; VGCCs, voltage-gated calcium channels; VGSCs, voltage-gated sodium channels; ZHS, zinc hydroxystannate; ZS, zinc stannate.

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http://dx.doi.org/10.1016/j.ntt.2015.09.002
0892-0362/

1. Lessons learned from the brominated flame retardants

1.1. Introduction

Through the centuries, fire has been a major cause of property damage, injuries and death. Modern technologies and legislations of fire safety standards resulted in the development of flame retardant (FR) chemicals to prevent or slow the onset and spreading of fire. Polychlorinated biphenyls (PCBs) were commercially introduced in the 1920s and used as FRs as well as dielectric and coolant fluids in transformers, capacitors and electric motors. Following the discovery of the adverse effects of PCBs, brominated flame retardants (BFRs) were introduced as the main chemical FRs to make polyurethane foam, plastics used in electric and electronic equipment, various textiles, *etc.* more fire-resistant. Most BFRs are persistent organic pollutants (POPs) that are (extremely) persistent, non-combustible, thermostable, lipophilic, subject to long-range geographic transport, and resistant to both biotic and abiotic degradation (de Wit et al., 2010). Consequently, BFRs like polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol-A (TBBPA) and hexabromocyclododecane (HBCDD, also known as HBCD) can be detected in human and environmental samples, which raises concerns for the possible effects on wildlife and human health. Nowadays, BFRs have spread globally *via* air and water and can even be found in abiotic and biotic samples from the polar regions (de Wit et al., 2010). Moreover, BFRs have been suggested to bioaccumulate in aquatic and terrestrial food chains (Boon et al., 2002). The degree of bioaccumulation of BFRs in fatty tissues depends on physicochemical properties like the molecular weight (MW) and octanol–water partition coefficient (Log K_{OW}) that determine the lipophilicity and persistence of BFRs. Besides bioaccumulation, biotransformation is another important biotic process that plays a key role in the toxicity of BFRs. Typically, biotransformation results in inactivation of the toxicant and subsequent elimination from the body. However, in some cases, biotransformation results in the formation of metabolites that are more biologically active than the parent compound (bioactivation), which is among others observed for PBDEs in relation to several (neuro)endocrine and neurodevelopmental effects (Dingemans et al., 2011).

Human exposure is due to the presence of BFRs in house dust (Abb et al., 2011; de Wit et al., 2012; Johnson et al., 2010; Lorber, 2008; Stapleton et al., 2012), fish (Costa and Giordano, 2011; Sjödin et al., 2003) and other animal products, and vegetables (Domingo, 2004, 2012). The estimated average daily intake *via* dust consumption for toddlers was calculated to be 3 ng/kg bw for BDE-209, 1.7 ng/kg bw for HBCDD and 0.2 ng/kg bw for TBBPA (Abb et al., 2011; Fromme et al., 2014a). Due to their lipophilicity, BFRs are also excreted *via* human breast milk resulting in an estimated average daily exposure of infants to 19.3 ng/kg bw for BDE-47, 1.7 ng/kg bw BDE-154 (Abdallah and Harrad, 2014), 1 ng/kg bw TBBPA, and 35 ng/kg bw HBCDD (Abdallah and Harrad, 2011). In addition, high concentrations of PBDEs (*e.g.* up to 70 ng/g lipids for BDE-47; Qiu et al., 2009) and TBBPA (104 ng/g lipids; Cariou et al., 2008) have been detected in cord serum, clearly indicating the transfer of BFRs through the placental barrier. Importantly, serious human adverse effects such as endocrine disruption have been related to BFR exposure (for a recent review of human PBDE exposure and associated health effects, see Linares et al., 2015).

Recently it was shown that high levels of maternal exposure to PBDEs may increase the risk for preterm birth (Peltier et al., 2015). Other epidemiological studies revealed correlations between prenatal exposure and impaired cognitive and motor function, increased attention problems, more anxious behavior, and increased withdrawal (Adgent et al., 2014; Berghuis et al., 2013; Cowell et al., 2015; Eskenazi et al., 2013; Herbstman and Mall, 2014; Lonky et al., 1996; Sagiv et al., 2015; Winneke et al., 2013). Additional associations between PBDE exposure and adverse outcomes in the (developing) nervous system, including reduced psychomotor development index and full scale IQ performances, have been observed in (school)children and adolescents (Chen et al., 2014; Herbstman et al., 2010; Kicinski et al., 2012; Roze et al., 2009).

1.2. In vivo and in vitro neurotoxicity of brominated flame retardants

Effects on behavior and accompanying neurochemical changes following BFR exposure have been extensively studied in rodents (for classification criteria see Table 1; for an overview of *in vivo* and *ex vivo* effects see Table 2). Mice exposed on postnatal day (PND) 10 (*i.e.* the peak of the brain growth spurt) to PBDEs or HBCDD develop permanent aberrations in spontaneous behavior and habituation capability, changes in the development of neuromotor systems, and impairment of long-term potentiation (LTP) (Buratovic et al., 2014; Dingemans et al., 2007; Eriksson et al., 2001, 2002, 2006; Johansson et al., 2008; Maurice et al., 2015; Viberg et al., 2003a,b, 2004; Xing et al., 2009). Additional analyses of brain protein levels of neonatally exposed mice indicate disturbances in cholinergic (nicotinic acetylcholine

Table 1
Threshold values for classification based on neurotoxicity.

Endpoint	Classification	Toxicity
In vitro and zebrafish (developmental) neurotoxicity	High potential (H)	LOEC < 0.1 μM $EC_{50}/IC_{50}/LC_{50}/LD_{50}$ < 0.1 μM
	Moderate potential (M)	0.1 μM ≤ LOEC < 1 μM 0.1 μM ≤ $EC_{50}/IC_{50}/LC_{50}/LD_{50}$ < 1 μM
	Low potential (L)	1 μM ≤ LOEC < 10 μM
	Negligible potential (N)	1 μM ≤ $EC_{50}/IC_{50}/LC_{50}/LD_{50}$ < 10 μM LOEC ≥ 10 μM $EC_{50}/IC_{50}/LC_{50}/LD_{50}$ ≥ 10 μM
In vivo neurotoxicity	High potential (H)	$EC_{50}/LC_{50}/LD_{50}$ ≤ 1 mg/l (or kg) NOEC < 0.1 μM (or μmol/kg bw) LOEC ≤ 0.1 μM (or μmol/kg bw)
	Moderate potential (M)	1 mg/l (or kg) < $EC_{50}/LC_{50}/LD_{50}$ ≤ 10 mg/l (or kg) 0.1 μM < NOEC < 1 μM (or μmol/kg bw) 0.1 μM < LOEC ≤ 1 μM (or μmol/kg bw)
	Low potential (L)	$EC_{50}/LC_{50}/LD_{50}$ > 10 mg/l (or kg) 1 μM < NOEC ≤ 10 μM (or μmol/kg bw) 1 μM < LOEC ≤ 10 μM (or μmol/kg bw)
Physico-chemical properties	Hydrophilic (H)	Log K_{OW} ≤ 2
	Lipophilic (L)	Log K_{OW} > 2
Production volume	Low (LPV)	10–1000 t/year
	High (HPV)	>1000 t/year

LOEC: lowest observed effect concentration; LD_{50}: half maximal lethal dose; EC_{50}: half maximal effective concentration; LC_{50}: half maximal lethal concentration; IC_{50}: half maximal inhibition concentration; NOEC: no observed effect concentration; Log K_{OW}: octanol–water partition coefficient.

Table 2
In vivo and *ex vivo* neurotoxic effects of some brominated flame retardants in rodents and zebrafish.

Compound	Effect	LOEC (μmol/kg bw)	Exposure and species	Classification*	Reference
Behavioral effects					
BDE-47	Altered spontaneous behavior after two months	1.4	Single oral exposure NMRI mice on PND 10	L	Eriksson et al. (2001)
	Altered spontaneous behavior after two months	1.77	Single oral exposure C57BL/6 mice on PND 10	L	Gee and Moser (2008)
BDE-71	Decreased rearing in offspring at PND 110	5.3	Wistar rat dam exposure *via* dosing cookie from GD 1 to PND 21	L	Bowers et al. (2015)
BDE-99	Altered spontaneous behavior after two months	1.4	Single oral exposure NMRI mice on PND 10	L	Eriksson et al. (2001)
	Altered spontaneous behavior after seven days	14	Single oral exposure NMRI mice on PND 3, 10, or 19	L	Eriksson et al. (2002)
	Altered learning and memory functions after four months	1.4	Single oral exposure NMRI mice on PND 10	L	Eriksson et al. (2001)
BDE-153	Altered spontaneous behavior after two months	1.4	Single oral exposure NMRI mice on PND 10	L	Viberg et al. (2003a)
	Altered learning and memory functions after six months	1.4	Single oral exposure NMRI mice on PND 10	L	Viberg et al. (2003a)
BDE-209	Altered spontaneous behavior after two months	21	Single oral exposure NMRI mice on PND 3	L	Viberg et al. (2003b)
	Altered spontaneous behavior after two months	2.3	Single oral exposure NMRI mice on PND 3	L	Johansson et al. (2008)
HBCDD	Altered spontaneous behavior after three months	1.4	Single oral exposure NMRI mice on PND 10	L	Eriksson et al. (2006)
	Altered learning and memory functions after three months	1.4	Neonatal exposed NMRI mice	L	Eriksson et al. (2006)
α-HBCDD	Altered short-term behavioral deficits after four weeks	0.03	Wistar rat dam daily oral exposure from GD 0 to PND 21	H	Maurice et al. (2015)
TBBPA	Altered spontaneous behavior 3 h after exposure	0.18	Acute oral exposed ddY mice	M	Nakajima et al. (2009)
Effects on synaptic plasticity					
BDE-47	Reduced LTP on PND 17–19	14	Single oral exposure C57Bl/6 mice on PND 10	L	Dingemans et al. (2007)
BDE-209	Reduced LTP in offspring on PND 60	20	Dam Wistar rats from PND 1 to weaning	L	Xing et al. (2009)
	Reduced LTP on PND 60	20	Oral exposure Wistar rats from PND 3 to weaning	L	Xing et al. (2009)
	Reduced LTP on PND 60	20	Daily after weaning during 20 days	L	Xing et al. (2009)
	Reduced LTP on PND 60	20	Dam Wistar rats from PND 1 to weaning and pups subsequent daily oral after weaning during 20 days	L	Xing et al. (2009)
TBBPA	Altered synaptic plasticity, not significant on PND 17–19	211	Single exposure C57Bl/6 mice on PND 10	L	Hendriks et al. (2014a)
Effects on neurotransmitter systems					
BDE-71	Decreased GABA-R, increase GluR after five months	53	Daily exposure of four month old C57Bl/6J mice during 30 days	L	Bradner et al. (2013)
BDE-47	Decreased GluR subunits and CAMK-II on PND 17–19	14	Single oral exposure C57Bl/6 mice on PND 10	L	Dingemans et al. (2007)
BDE-99	Decreased nACh-R after four months	21	Single oral exposure NMRI mice on PND 10	L	Viberg et al. (2004)
	Decreased nACh-R after two months	14	Single oral exposure NMRI mice on PND 10	L	Viberg et al. (2002)
BDE-153	Decreased nACh-R after six months	14	Single oral exposure NMRI mice on PND 10	L	Viberg et al. (2003a)
BDE-209	Decreased nACh-R after four months	14	Single oral exposure NMRI mice on PND 3	L	Johansson et al. (2008)
	Increase CAMK-II, increase and decrease GAP-43 on PND 10	21	Single oral exposure NMRI mice on PND 3	L	Viberg et al. (2008)
	Increased synaptophysin on PND 10	21	Single oral exposure NMRI mice on PND 3	L	Viberg (2009)
Effects on zebrafish		**LOEC (μM)**			
6-MeO-BDE-47	Altered spontaneous movement at 72 hpf	10	Zebrafish embryos exposure 4–120 hpf	N	Zheng et al. (2012)
6-OH-BDE-47	Altered spontaneous movement at 72 hpf	2	Zebrafish embryos exposure 4–120 hpf	L	Zheng et al. (2012)
	Decreased locomotor activity at 6 dpf	0.05	Zebrafish embryos and larvae exposure 0–6 dpf	H	Macaulay et al. (2015)
	Increased fear or anxiety at 45 dpf	0.001	Zebrafish juvenile exposure 0–6 dpf	H	Macaulay et al. (2015)
	Increased swimming activity at 6 dpf	0.05	Zebrafish larvae exposure 0–6 dpf	H	Macaulay et al. (2015)
BDE-47	Altered cerebrospinal fluid movement at 96 hpf	10	Zebrafish larvae exposure 3–5 hpf	N	Lema et al. (2007)
	Hypoactivity at 5 dpf	1	Zebrafish embryos exposure 3–5 hpf	L	Zhao et al. (2014)
	Altered spontaneous movement at 27 hpf	1	Zebrafish embryos exposure 6–27 hpf	L	Chen et al. (2012)
	Decreased locomotor activity at 6 dpf	4	Zebrafish larvae 0.5–2.5 h after exposure	L	Jarema et al. (2015)
	Developmental toxicity at 6 dpf	28	Zebrafish larvae exposure 1–5 dpf	N	Behl et al. (2015)
	Decreased locomotor activity at 6 dpf	4	Zebrafish larvae exposure 1–5 dpf	L	Jarema et al. (2015)
BDE-209	Altered neurologic pathways at 8 dpf	Spiked 12.5 mg/kg sediment	Zebrafish larvae exposure 4 hpf–8 dpf		Garcia-Reyero et al. (2014)
HBCDD	Malformations at 120 hpf	0.02	Zebrafish larvae exposure 4–120 hpf	H	Du et al. (2012)
TBBPA	Altered locomotor activity at 6 dpf	1.2	Zebrafish larvae 0.5–2.5 h after exposure	L	Jarema et al. (2015)
	Developmental toxicity at 6 dpf	4.6	Zebrafish larvae exposure 1–5 dpf	L	Behl et al. (2015)
	Malformations at 8 dpf	0.7	Zebrafish embryos and larvae exposure for eight days	M	Wu et al. (2015)

LOEC: lowest observed effect concentration; PND: postnatal day; GD: gestational day; hpf: hours post fertilization; dpf: days post fertilization. Note: studies showing negative effects are in general not included in this overview.

* Classification follows the classification criteria shown in Table 1.

receptor (nACh-R) and muscarinic acetylcholine receptor (mACh-R)), GABAergic (γ-aminobutyric acid receptor; GABA-R) and glutamatergic (glutamate receptor, GluR) neurotransmitter systems (Bradner et al., 2013; Buratovic et al., 2014; Dingemans et al., 2007; Johansson et al., 2008; Viberg et al., 2002, 2003a, 2008; Viberg, 2009). On the other hand, exposure of mice to TBBPA on PND 10 does not cause significant changes in the studied behavioral parameters (Eriksson et al., 2001) or synaptic protein levels (Hendriks et al., 2014a), and exerts only minor effects on LTP in mice (Hendriks et al., 2014a). A reproductive, developmental and neurobehavioral study also did not reveal

(neuro)developmental effects at exposure doses up to 1000 mg/kg bw/day (Cope et al., 2015). However, TBBPA exerts numerous cellular effects (see below) as well as behavioral effects in mice following acute TBBPA exposure (Nakajima et al., 2009), leaving the debate regarding the (developmental) neurotoxicity of TBBPA unresolved.

In recent years, the zebrafish (*Danio rerio*) has become an increasingly popular vertebrate animal model for investigating (developmental) neurotoxicity due to the similarities in genetic properties and fundamental processes of neurodevelopment compared with mammals (Bailey et al., 2013; Tropepe and Sive, 2003). Consequently, developmental neurotoxicity research using zebrafish is becoming increasingly common in behavioral neuroscience and behavioral neurotoxicology. For example, it has been shown that BDE-209 affects expression of neurological pathways and alters behavior of larvae (Garcia-Reyero et al., 2014), whereas parental chronic low dose exposure affects growth and reproduction, and elicits neurobehavioral alternations in offspring (He et al., 2011). Exposure to BDE-47 and its metabolite 6-OH-BDE-47 also affects the locomotion behavior of zebrafish (both larval and juvenile) (Chen et al., 2012; Chou et al., 2010; Jarema et al., 2015; Lema et al., 2007; Macaulay et al., 2015; Zhao et al., 2014; Zheng et al., 2012). An overview of neurotoxic effects of BFRs on zebrafish is shown in Table 2.

Mechanisms underlying the developmental and behavioral effects associated with BFR exposure have been further unraveled using *in vitro* studies (for a detailed review see Costa et al., 2013). As shown in Table 3, several studies reported BFR-induced cytotoxicity in neuronal cells as a result of disruption of (mitochondrial) Ca^{2+}-homeostasis and increased formation of reactive oxygen species (ROS) resulting in damage of DNA, proteins and membrane lipids, and ultimately apoptosis (Al-Mousa and Michelangeli, 2012; He et al., 2009; Hendriks et al., 2014b; Huang et al., 2010; Jiang et al., 2012; Xing et al., 2010; Zhang et al., 2010, 2013). Since Ca^{2+} is essential for neuronal function and survival, effects of BFRs on Ca^{2+}-homeostasis are well-studied. For example, BFRs have been shown to inhibit voltage-gated calcium channels (VGCCs) resulting in decreased Ca^{2+} influx into the cell and reduced neurotransmitter secretion (Dingemans et al., 2008, 2009, 2010; Hendriks et al., 2012a, 2014b). Additionally, BFR-induced inhibition of voltage-gated sodium channels (VGSCs), which play a pivotal role in depolarization of the membrane, may contribute to attenuation of action potential generation in neurons (Xing et al., 2010). In line with these studies, it was recently shown using multi-well microelectrode array (MEA) recordings that BDE-47 reduces the mean firing rate of a rat neuronal (cortical) network (Behl et al., 2015).

On the other hand, BFRs can increase the intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) *via* the release of Ca^{2+} from intracellular stores (*e.g.* from the endoplasmic reticulum (ER) and mitochondria) (Costa and Giordano, 2007; Dingemans et al., 2009, 2011; Fonnum and Mariussen, 2009; Hendriks et al., 2012a), potentially resulting in the release of cytochrome *c* and activation of caspases ultimately resulting in cell death (Hendriks et al., 2012a; Yu et al., 2008; Zhang et al., 2013). The BFR-induced release of Ca^{2+} from intracellular stores appears mediated by direct activation of inositol-1,4,5-trisphosphate (IP_3) receptors (Gassmann et al., 2014) as well as activation of ryanodine receptors (RyR) on the ER (Kim et al., 2011). Other studies also showed BFR-induced translocation of the second messenger protein kinase C (PKC), stimulation of mitogen-activated protein kinase (MAPK) pathways, and activation of phospholipase A (PLA), which results in arachidonic acid (AA) release (Fan et al., 2010; Kodavanti and Derr-Yellin, 2002; Kodavanti and Ward, 2005; Madia et al., 2004). AA can subsequently be oxidized and modified into eicosanoids ('messenger molecules') or diffuse into the nucleus and interact with transcription factors to control DNA transcription (Striggow and Ehrlich, 1997).

Though (post)synaptic neurotransmitter receptor function is also essential for proper neurotransmission, effects of BFRs on these systems are less studied. Few studies have shown that TBBPA acts as full and partial agonist on the inhibitory $GABA_A$-R, while it also acts as antagonist on the excitatory $\alpha_4\beta_2$ nACh-R (Hendriks et al., 2012a,b). These opposite effects on $GABA_A$-R and $\alpha_4\beta_2$ nACh-R may add up *in vivo*, resulting in disequilibrium between excitatory and inhibitory systems. Since both $GABA_A$-R and $\alpha_4\beta_2$ nACh-R play an important role in LTP and other forms of synaptic plasticity, these mechanisms may also (partly) underlie the observed neurobehavioral and neurodevelopmental effects. Moreover, during early brain development (but not at other developmental stages), the $GABA_A$-R acts as an excitatory receptor (D'Hulst et al., 2009), potentially resulting in different effects at different life stages.

Importantly, several studies indicate that oxidative metabolism can increase the neurotoxic potential of PBDEs. For example, several neuronal cell lines exposed to the hydroxylated PBDE metabolite 6-OH-BDE-47 show alterations in cytotoxicity, Ca^{2+}-homeostasis, neurotransmitter release, and RyR activation at much lower concentration than the parent compound (Dingemans et al., 2008, 2010; Gassmann et al., 2014; Kim et al., 2011; Li et al., 2013). The increased neurotoxic potential of OH-PBDEs is also evident for neurotransmitter receptors; 6-OH-BDE-47 is able to act as full and partial agonist on the $GABA_A$-R and as antagonist on the $\alpha_4\beta_2$ nACh receptor, whereas BDE-47 is not effective (Hendriks et al., 2010). From these studies it is clear that bioactivation should be included in (human) risk assessment of (alternative) flame retardants.

1.3. Risk assessment and conclusions

For risk assessment purposes, chemicals can be classified according to the potential harm that they may cause, for example using the Toxic Equivalency Factor concept for PCBs, polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) (Van den Berg et al., 1998). However, several *in vitro* neurotoxicity endpoints cannot be classified using one of the existing classification schemes because the lack of complete concentration–response curves obviates the determination of *e.g.* half maximal effective concentration (EC_{50}) values to determine relative potencies for a given (*in vitro*) neurotoxic effect. In order to still provide potencies for both BFRs and alternative flame retardants (AFRs, see Section 2), we defined threshold values for classification of neurotoxicity data based on the classification criteria of Hamers et al. (2006), and the European Union REACH regulations (European Union, 2006; European Union, 2008) (Table 1). Following our classification criteria, the available data on the selected endpoints (*in vivo* neurotoxicity, zebrafish neurotoxicity, *in vitro* neurotoxicity, effects on acetylcholinesterase (AChE), and/or effects on neuropathy target esterase (NTE)) were ranked as having a high, moderate, low or negligible neurotoxic potential (the latter applies only for *in vitro* and zebrafish neurotoxicity) and combined to derive the final neurotoxic potential. As a result, our classification is also applicable for studies presenting lowest observed effect concentrations (LOECs), no observed effects concentrations (NOECs), half maximal lethal concentration (LC_{50}), half maximal inhibition concentration (IC_{50}), and half maximal lethal dose (LD_{50}) values. Recently, comparable classifications to rank the neurotoxicity of AFRs compared to BFRs in an objective and uniform manner have also been used in zebrafish studies (Behl et al., 2015; Jarema et al., 2015).

As can be concluded from the mentioned *in vivo* studies, BFRs exert several neurotoxic effects including altered spontaneous behavior and habituation capability, changed neuromotor system development, disturbed neurotransmitter systems, and impairment of LTP. As summarized in Fig. 1, mechanisms of action as observed in *in vitro* studies include decreased cell viability, increased ROS formation, disturbed Ca^{2+}-homeostasis and differential effects on neurotransmitter receptor function. A possible net result of the differential effects on neurotransmitter receptor function is reduced neuronal activity and neurotransmitter secretion (also see Behl et al., 2015). On the other hand, Ca^{2+} release from intracellular stores may result in a temporary increase in neurotransmitter secretion as well as increased ROS formation and activation of apoptosis. These modes of action may (partly) underlie the

reported *ex vivo* reduction in LTP and *in vivo* behavioral effects as well as the observed correlations between BFRs and impaired cognitive and motor functioning in children and adolescents. Based on the classification as shown in Tables 2 and 3, the neurotoxicity of BFRs is frequently classified as low or even negligible. However, it should be noted that for a full toxicological profile these data have to be combined with other (toxicity) studies, including for example the earlier mentioned potent effects on the endocrine system. Additionally, for many BFRs, environmental fate and/or bioaccumulation are also factors of concern that argue for replacing BFRs with less persistent AFRs.

BFRs are widely used to reduce the likelihood of ignition of materials and/or decrease the rate of combustion, thereby increasing consumer safety. However, several significant disadvantages for human health are recognized and it remains therefore debated whether the fire safety benefits justify the environmental and human health risks (see *e.g.* Jinhui et al., 2015; Shaw et al., 2010). Whether a BFR is of concern for human health and the environment depends on several factors, including the abundance in the environment, the physicochemical properties of the compound, human plasma concentrations, toxicokinetics, extrapolation of experimental *in vitro* and *in vivo* data to the human situation, *etc.* In the case of infants and toddlers, the possible risks for their developing brain is evident as a result of high exposure *via* dust and breast milk, which is also confirmed by the high concentrations in cord serum. The combined experimental and epidemiological studies clearly underline the need for replacing (some) BFRs by less toxic and less persistent AFRs. In addition, the lessons learned from the adverse effects of BFRs and factors involved in risk assessment indicate the need for a full (eco)toxicological risk assessment before new AFRs are commercially introduced on the market.

2. Neurotoxicity and risk assessment of alternative flame retardants

Considering the toxicological and ecological concerns associated with the wide application of PCBs and BFRs, there is a clear need to replace these compounds by safe(r) and less persistent alternatives. Depending on their application and molecular constituents, alternative flame retardants (AFRs) can be divided into several categories, including inorganic FRs and synergists (chemicals incorporated together with *e.g.* an inorganic FR to obtain efficient FR systems) as well as halogenated and non-halogenated organophosphorous FRs (OPFRs) and their salts (see Table 4). The selection of AFRs discussed in this review that may be suitable as alternatives for the commonly used BFRs is based on their application (mainly electrical appliances, furniture and textiles) and suggestion by the industry. Mixtures like FireMaster© (a mixture of brominated and organophosphate flame retardants, see *e.g.* the recent studies by Bailey and Levin, 2015; Dishaw et al., 2014) are not included. For uniformity with other studies, we used abbreviations following the standards of Bergman et al. (2012).

Despite regulations like REACH (Registration, Evaluation, Authorization, and Restriction of Chemical substances), several AFRs have already been marketed without having a full profile of their environmental behavior and toxicological properties. The available data on the physical–chemical properties, production volumes, persistence, bioaccumulation, and toxicity of a subset of AFRs have recently been reviewed and illustrates big data gaps (Bergman et al., 2012; van der Veen and de Boer, 2012; Waaijers et al., 2013). Considering the general lack of data regarding the toxicity of AFRs and that the nervous system is a sensitive target organ for BFRs, it is essential to assess the (neuro)toxic potential of AFRs for a number of critical, established toxicological and biological endpoints before large scale use. Available neurotoxicity data of the selected AFRs (Table 4) are summarized and discussed below, with strong emphasis on studies that did show adverse effects and largely excluding studies with negative results. For most AFRs discussed in this review, available data on eco- and *in vivo* toxicity, environmental occurrence, persistence, and bioaccumulation have been reviewed elsewhere (Bergman et al., 2012; van der Veen and de Boer, 2012; Waaijers et al., 2013; Wei et al., 2015) and is not specifically addressed in this review.

2.1. Neurotoxicity of halogen-free organophosphorous flame retardants

An overview of the (neuro)toxicity and exposure data as discussed below is presented in Tables 5 and 6. The last column of Table 5 presents the overall neurotoxic potential, which is derived from the highest *in vitro*, zebrafish and/or *in vivo* neurotoxic potential and findings on acetylcholinesterase (AChE) and neuropathy target esterase (NTE, both major targets for organophosphates). Threshold values for classification of the data are based on the criteria as shown in Table 1.

2.1.1. Aluminum diethylphosphinate (ALPI, CAS nr 225789-38-8)

Data on ALPI levels in dust, breast milk or human serum concentrations are currently not available. The hydrophilicity of ALPI (Log K_{OW} of −0.4, see Table 1) hampers absorption in the gut as well as passage across blood–brain- and placental barriers, likely resulting in a very low bioavailability. A recent toxicokinetic study confirms that only a small amount of the administered ALPI dose is absorbed by the gastrointestinal tract, and that the major part is excreted *via* feces (European Chemicals Agency, 2015). Though half-lives ($t_{1/2}$) were not reported, ALPI is no longer detected in feces and/or urine after 36 h. One *in vivo* study reported a low toxicity based on lethal doses (LD) for oral, dermal or inhalation exposure of rats (oral LD_{50} > 2000 mg/kg; U.S. Environmental Protection Agency (EPA), 2008). In a recent *ex vivo* case study, no effects on long-term potentiation (LTP) and synaptic protein levels in mouse hippocampus have been observed in mice receiving a single ALPI exposure (211 μmol (82 mg)/kg bw) on PND 10 (Hendriks et al., 2014a). Also in *in vitro* neurotoxicity tests ALPI is classified as having a negligible neurotoxic potential on cytotoxicity (LOEC > 279 μM), ROS formation (LOEC 140 μM) and Ca^{2+}-homeostasis (LOEC 279 μM) in PC12 and B35 cells, and nACh-R modulation (LOEC 27.9 μM) (Hendriks et al., 2012b, 2014b). It should be noted that a metal-based phosphorous flame retardant may dissociate into its ion constituents under some conditions, although it is unlikely that the levels of aluminum become high enough to cause serious health concerns. Although additional data, in particular regarding human exposure levels, breakdown products and possible metabolites, the persistence in the environment, *etc.*, are required to determine the human risk associated with the use of ALPI, the (very) low observed *in vitro* and *in vivo* toxicity indicate an overall low neurotoxic potential and suggests ALPI could be a suitable alternative FR.

2.1.2. Bisphenol A bis(diphenyl phosphate) (BPA-BDPP, CAS nr 5945-33-5)

BPA-BDPP is relatively ubiquitous in house dust samples as well as dust samples from cars and electronic stores (see Table 6; Ballesteros-Gómez et al., 2014; Brandsma et al., 2013). Though toxicological data on BPA-BDPP are limited, *in vivo* toxicity in rats has been classified as low (LD_{50} > 2000 mg/kg) (reviewed in Waaijers et al., 2013). Due to its lipophilicity (Log K_{OW} < 6, see Table 1), BPA-BDPP is expected to bind to serum proteins, likely resulting in a low free concentration and poor excretion from the human body. One of the degradation products of BPA-BDPP appears to be bisphenol-A, which is a low potency endocrine disruptor that affects multiple reproductive endpoints as well as (indirectly) immune function and brain development (Maine, 2007). It has also been suggested that tris(phenyl) phosphate (TPHP)-like compounds may be formed as breakdown products and that the commercial product may contain up to 5% TPHP as impurity (Clean Production Action et al., 2007; Umwelt Bundes Amt, 2001). As mentioned for BFRs, degradation and metabolism are important factors to include in the risk assessment of FRs as it is well known that metabolites can be more toxic than the parent compound. The *in vitro* neurotoxicity of BPA-BDPP is classified as negligible as it induces only minor cytotoxicity in PC12 and B35 cells (LOEC 100 μM), minor effects on the depolarization-evoked increase in $[Ca^{2+}]_i$ in PC12 cells (LOEC 10 μM)

Table 3
In vitro neurotoxic effects of brominated flame retardants.

Compound	Effect	Effect concentration (μM)	Test system	Classification*	Reference
Cytotoxicity					
BDE-47	Decreased cell viability	5	MTT, SH-SY5Y cells	L	He et al. (2009)
	Decreased cell viability	11 (IC_{50})	MTT, mouse cerebellar granule neurons	N	Huang et al. (2010)
	Decreased cell viability	12.1 (IC_{50})	MTT, SK-N-MC cells	N	Pellacani et al. (2012)
	Decreased cell viability	5.7	Counted total cell number, human neuroprogenitor cells	L	Behl et al. (2015)
BDE-99	Decreased cell viability	15.7 (IC_{50})	MTT, mouse cerebellar granule neurons	N	Huang et al. (2010)
	Decreased cell viability	30.8 (IC_{50})	MTT, SK-N-MC cells	N	Pellacani et al. (2012)
BDE-100	Decreased cell viability	4.5 (IC_{50})	MTT, mouse cerebellar granule neurons	L	Huang et al. (2010)
BDE-153	Decreased cell viability	19.9 (IC_{50})	MTT, mouse cerebellar granule neurons	N	Huang et al. (2010)
BDE-209	Decreased cell viability	28 (LC_{50})	MTT, SH-SY5Y cells	N	Al-Mousa and Michelangeli (2012)
	Decreased cell viability	10.4	MTT, neonatal rat hippocampal neurons	N	Chen et al. (2010)
	Decreased cell viability	>50 (IC_{50})	MTT, mouse cerebellar granule neurons	N	Huang et al. (2010)
	Decreased cell viability	10	MTT, rat hippocampal neurons	N	Zhang et al. (2010)
TBBPA	Decreased cell viability	15 (LC_{50})	MTT, SH-SY5Y cells	N	Al-Mousa and Michelangeli (2012)
	Decreased cell viability	100	NR, B35 cells	N	Hendriks et al. (2012a)
	Decreased cell viability	100	AB and NR, PC12 cells	N	Hendriks et al. (2012a)
	Decreased cell viability	47	In-cell Western analysis, mouse embryonic stem cells	N	Behl et al. (2015)
	Decreased cell viability	15.3	Counted total cell number, human neuroprogenitor cells	N	Behl et al. (2015)
HBCDD	Decreased cell viability	2.7 (LC_{50})	MTT, SH-SY5Y cells	L	Al-Mousa and Michelangeli (2012)
	Decreased cell viability	20	MTT, PC12 cells	N	Dingemans et al. (2009)
	Decreased cell viability	10	WST-1, SK-N-SH cells	N	Genskow et al. (2015)
ROS production					
BDE-47	Increase ROS	1	H_2-DCFDA, mouse cerebellar granule neurons	L	Huang et al. (2010)
	Increase ROS	5	DCFH-DA, SH-SY5Y cells	L	Jiang et al. (2012)
BDE-99	Increase ROS	1.5	H_2-DCFDA, mouse cerebellar granule neurons	L	Huang et al. (2010)
BDE-100	Increase ROS	0.5	H_2-DCFDA mouse cerebellar granule neurons	M	Huang et al. (2010)
BDE-153	Increase ROS	2.5	H_2-DCFDA mouse cerebellar granule neurons	L	Huang et al. (2010)
BDE-209	Increase ROS	10.4	Immunofluorescent staining, neonatal rat hippocampal neurons	N	Chen et al. (2010)
	Increase ROS	1	H_2-DCFDA, PC12 cells	L	Hendriks et al. (2014b)
	Increase ROS	50	H_2-DCFDA, mouse cerebellar granule neurons	N	Huang et al. (2010)
	Increase ROS	10	H_2-DCFDA, rat hippocampal neurons	N	Zhang et al. (2010)
TBBPA	Increase ROS	5	DCFH-DA, SH-SY5Y cells	L	Al-Mousa and Michelangeli (2012)
	Increase ROS	10	H_2-DCFDA, B35 cells	N	Hendriks et al. (2012a)
	Increase ROS	10	H_2-DCFDA, PC12 cells	N	Hendriks et al. (2012a)
HBCDD	Increase ROS	3	DCFH-DA, SH-SY5Y cells	L	Al-Mousa and Michelangeli (2012)
Ca^{2+}-homeostasis					
6-OH-BDE-47	Increase $[Ca^{2+}]_i$, originating from intracellular stores	1	Single-cell fluorescent microscopy, PC12 cells	L	Dingemans et al. (2008)
BDE-209	Increase $[Ca^{2+}]_i$, originating from intracellular stores	20	Single-cell fluorescent microscopy, SH-SY5Y cells	N	Al-Mousa and Michelangeli (2012)
TBBPA	Increase $[Ca^{2+}]_i$, originating from intracellular stores	20	Single-cell fluorescent microscopy, SH-SY5Y cells	N	Al-Mousa and Michelangeli (2012)
	Increase $[Ca^{2+}]_i$, originating from intracellular stores	10	Single-cell fluorescent microscopy, B35 cells	N	Hendriks et al. (2012a)
	Increase $[Ca^{2+}]_i$, originating from intracellular stores	10	Single-cell fluorescent microscopy, PC12 cells	N	Hendriks et al. (2012a)
HBCDD	Increase $[Ca^{2+}]_i$, originating from intracellular stores	10	Single-cell fluorescent microscopy, SH-SY5Y cells	N	Al-Mousa and Michelangeli (2012)
Other intracellular signaling pathways					
6-OH-BDE-47	Activation IP_3 receptor	0.2	Primary fetal human neural progenitor cells	M	Gassmann et al. (2014)
BDE-47	Increase p53 mRNA levels	1	mRNA levels in SH-SY5Y cells	L	Zhang et al. (2013)
	Increase cytochrome *c* mRNA levels	10	mRNA levels in SH-SY5Y cells	N	Zhang et al. (2013)
	Increase caspase-3 mRNA levels	5	mRNA levels in SH-SY5Y cells	L	Zhang et al. (2013)
BDE-71	Arachidonic acid release by activating PLA_2 pathway	18	[^{3}H]AA labeled rat cerebellar granule neurons	N	Kodavanti and Derr-Yellin (2002)
	PKC translocation	5	^{3}H-PDBu binding, rat cerebellar granule neurons	L	Kodavanti and Ward (2005)
	Inhibited Ca^{2+} uptake by microsomes and mitochondria	5	$^{45}Ca^{2+}$ uptake by microsomes and mitochondria isolated from rat brain	L	Kodavanti and Ward (2005)
	Increase caspase-3, -8 and -9 activity	25.6	Caspase assay kit from Keygen, SK-N-SH cells	N	Yu et al. (2008)
BDE-77	MAPK activation	3	Adult male rat brain	L	Fan et al. (2010)
BDE-95	Activation RyR	10	[^{3}H]ryanodine binding, HEK293 cells	N	Kim et al. (2011)
BDE-99	MAPK activation	10	Western blot, rat cerebellar granule neuronal cells	N	Fan et al. (2010)
	PKC translocation	100	Western blot, 132-1N1 human astrocytoma cells	N	Madia et al. (2004)

(continued on next page)

Table 3 (*continued*)

Compound	Effect	Effect concentration (μM)	Test system	Classification*	Reference
Other intracellular signaling pathways					
BDE-153	MAPK activation	1	Western blot, rat cerebellar granule neuronal cells	L	Fan et al. (2010)
TBBPA	Increase caspase-3 activity	10	Casp3F kit from Sigma-Aldrich, PC12 cells	N	Hendriks et al. (2012a)
VGCCs and VGSCs					
BDE-209	Inhibition VGSCs	0.1	Electrophysiology, rat hippocampal neurons	M	Xing et al. (2010)
TBBPA	Inhibition VGCCs	1	Single-cell fluorescent microscopy, B35 cells	L	Hendriks et al. (2012a)
	Inhibition VGCCs	1	Single-cell fluorescent microscopy, PC12 cells	L	Hendriks et al. (2012a)
HBCDD	Inhibition VGCCs	2	Single-cell fluorescent microscopy, PC12 cells	L	Dingemans et al. (2009)
Neurotransmitter receptors					
6-OH-BDE-47	Full and partial agonist $GABA_A$-R	1	Neurotransmitter receptors expressed in *Xenopus* oocytes	L	Hendriks et al. (2010)
	Antagonist nACh-R	1	Neurotransmitter receptors expressed in *Xenopus* oocytes	L	Hendriks et al. (2010)
BDE-209	Antagonist nACh-R	10	Neurotransmitter receptors expressed in *Xenopus* oocytes	N	Hendriks et al. (2012b)
TBBPA	Full and partial agonist $GABA_A$-R	0.1 (partial) and 10 (full)	Neurotransmitter receptors expressed in *Xenopus* oocytes	M/N	Hendriks et al. (2012a)
	Antagonist nACh-R	10	Neurotransmitter receptors expressed in *Xenopus* oocytes	N	Hendriks et al. (2012a)

AB: Alamar Blue; B35 cells: rat neuroblastoma cells; H_2-DCFDA: 2′,7′-dichlorofluorescin diacetate; HEK cells: human embryonic kidney cells; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NR: neutral red; WST-1: cytotoxicity assay kit; p53: tumor suppressor p53; PC12 cells: pheochromocytoma cells; ^{3}H-PDBu: 4-β-^{3}H-phorbol 12,13-dibutyrate; SH-SY5Y cells: human neuroblastoma cells; SK-N-MC cells: human neuronal epithelioma cells; SK-N-SH cells: human neuroblastoma cells. Note: studies showing negative effects are in general not included in this overview.

* Classification follows the classification criteria shown in Table 1.

and does not affect the nACh-R (Hendriks et al., 2014b). Due to the limited available studies, there is not enough data to classify the neurotoxic potential of BPA-BDPP. Considering the breakdown products, impurity and presence in (house) dust, additional data including information on bioavailability, toxicokinetics and human exposure are clearly needed to obtain a full toxicological profile for proper risk assessment.

2.1.3. Resorcinol bis(diphenyl phosphate) (BPDPP, CAS nr 57583-54-7)

BPDPP is widely present in dust samples from houses, cars and electronic stores (Brandsma et al., 2013; Fan et al., 2014; Yang et al., 2014). *In vivo* studies report that BPDPP induces no adverse teratogenic and developmental effects (at concentrations up to 20,000 mg/kg diet) (Henrich et al., 2000; Ryan et al., 2000) and does not exert effects on the activity of NTE (chronic exposed hens, 2000 mg/kg bw) (European Chemicals Agency, 2015). There are however some contradictory effects reported on inhibition of monocyte non-specific esterase activity (European Chemicals Agency, 2015). Only one study reports the metabolism and toxicokinetics of BPDPP in rats and monkeys, which correspondents with a $t_{1/2}$ of 2.4 days in rats and 5.2 days in monkeys following intravenous administration (Freudenthal et al., 2000). Comparable to BPA-BDPP, BPDPP is lipophilic (Log K_{OW} 4.9) and is consequently expected to bind to serum proteins. *In vitro*, BPDPP inhibits $\alpha_4\beta_2$ nACh receptors (LOEC 100 μM) (Hendriks et al., 2012b) and depolarization-evoked Ca^{2+} in PC12 cells (LOEC 1 μM), though it is classified as having a low neurotoxic potential (Hendriks et al., 2014b). BPDPP may also contain up to 5% TPHP as impurity (Clean Production Action et al., 2007; Umwelt Bundes Amt, 2001) and TPHP-like products may be formed as a breakdown product, which may explain the observed small antagonistic effects on $\alpha_4\beta_2$ nACh receptors (Hendriks et al., 2012b). Based on the available data, BPDPP is classified as having a low neurotoxic potential and could be a suitable alternative.

2.1.4. Diphenylcresylphosphate (DCP, CAS nr 26444-49-5)

Data on DCP levels in dust, breast milk or human serum concentrations are currently not available. Repeated oral dosing of hens (2.5 mg/kg/day during three to ten weeks) does not result in clinical or clear histological signs of neuropathy (Bayer Material Science, 2010; Johnson and Lotti, 1980; Lotti and Johnson, 1980). In rats intraperitoneal exposed to a commercial DCP preparation (300 mg/kg), no effects on the activities of cerebral and muscle acetylcholine esterase are observed after 24 h (Vainiotalo et al., 1987). However, following a two-week observation period, brain 2′,3′-cyclic nucleotide 3′-phosphohydrolase (CNPase, a myelin-associated enzyme) is inhibited and associated with peripheral nerve demyelination (Vainiotalo et al., 1987). In the study by Sprague and Castles (1985), DCP does not inhibit hen brain NTE activity *in vitro* in the absence of metabolic activation up to 100 μM. However, NTE activity is markedly inhibited after metabolism with rat liver microsomes (IC_{50} 6.2 μM). This adverse effect has been confirmed in adult hens exposed to 10 mg/kg DCP, which show inhibited brain NTE 24 h after exposure. Overall, DCP has a low neurotoxic potential and could be a suitable alternative. However, inhalation toxicity in sheep is relatively high ($LC_{50} > 0.37$ mg/m^3/h), DCP exerts reproductive and developmental toxicity (for review see van der Veen and de Boer, 2012) and human exposure data or data on environmental levels are unknown, warranting additional research.

2.1.5. Dimethyl methylphosphonate (DMMP, CAS nr 756-79-6)

Although DMMP is used as a FR and also as a nerve gas simulant to mimic the physical and spectroscopic properties of anticholinesterase agents (National Toxicology Program, 1987), data on human internal concentrations are lacking. The *in vivo* neurotoxicity of DMMP is low; no delayed neurotoxicity is observed in adult hens after 45 daily intraperitoneal injections (Hollingshaus et al., 1981), though delayed toxicity (including loss of weight) is observed in rats after chronic exposure (LD_{50} 3 mg/kg) (Hollingshaus et al., 1981; National Toxicology Program, 1987). Based on the Log K_{OW} value (−0.61), a low bioavailability is expected. In addition, rapid absorption and excretion of DMMP has been measured in rats and mice (Blumbach et al., 2000). DMMP is classified as "not enough data to classify" due to the lack of neurotoxicity studies. The observed adverse effects following long-term exposure in rats also indicate that more studies on human exposure and effects on the environment are necessary to evaluate the suitability of DMMP as an alternative FR.

2.1.6. 9,10-Dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO, CAS nr 35948-25-5)

Limited information is available for DOPO (for an overview see Waaijers et al., 2013). DOPO showed only minor effects on

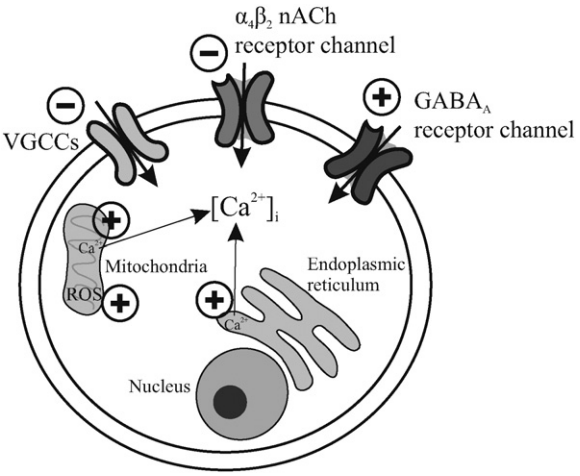


Fig. 1. Summarizing figure of some *in vitro* neuronal targets of BFRs as described in this review. Voltage-gated calcium channels (VGCCs) and $\alpha_4\beta_2$ nicotinic acetylcholine (nACh) receptors are inhibited, while $GABA_A$ receptors are activated or potentiated. Several intracellular pathways are involved in disturbance of Ca^{2+}-homeostasis, including activation of IP_3 and RyR receptors, resulting in Ca^{2+} release from intracellular stores and increased ROS formation.

depolarization-evoked increase in $[Ca^{2+}]_i$ (LOEC 1 μM) in recent *in vitro* neurotoxicity studies (Hendriks et al., 2014b). Clearly, additional data on environmental levels, human exposure, and *in vivo* and *in vitro* toxicity are required to evaluate the suitability of DOPO as an alternative FR which is now classified as "not enough data to classify".

2.1.7. Ethylhexyl diphenyl phosphate (EHDPP, CAS nr 1241-94-7)

No information on human toxicity or internal concentrations for EHDPP is available. The *in vivo* toxicity is low (European Chemicals Agency, 2015). Absorption and excretion of EHDPP in rats are fast (Nishimaki-Mogami et al., 1988), although binding to serum proteins and poor excretion is to be expected based on its lipophilicity. No indications of neuropathy or other neurotoxic symptoms have been reported in repeated-dose studies in adult hens, suggesting a low neurotoxic potential (Johannsen et al., 1977). Recently, extensive behavioral changes have been observed in zebrafish larvae on 6 days post fertilization (dpf) after acute (LOEC 1.2 μM, measured 0.5–2.5 h after exposure) and developmental exposure (LOEC 2.1 μM, exposure 1–5 dpf) (Jarema et al., 2015). In addition, Behl et al. (2015) recently investigated the neurotoxicity of EHDPP using several endpoints: mouse (LOEC 20.9 μM) and human (LOEC 13.4 μM) (neuronal) stem cell viability is decreased, the mean firing rate (LOEC 5.3 μM) in rat cortical neuronal networks is decreased, and larval development of *Caenorhabditis elegans* (LOEC 2.3 μM) is decreased. Based on these studies, the neurotoxic potential of EHDPP is classified as low. Although additional research is required to determine the human risk associated with the use of EHDPP, the low neurotoxic potential suggests EHDPP could be a suitable alternative FR.

2.1.8. Isodecyl diphenyl phosphate (IDDP, CAS nr 29761-21-5)

Data on IDDP are generally lacking, though some studies using hens indicate low *in vivo* (neuro)toxicity, and recent zebrafish studies indicate decreased activity of larvae following acute exposure (LOEC 12 μM measured on 6 dpf, 0.5–2.5 h after exposure) (Jarema et al., 2015). In another recent study, the neurotoxicity of IDDP was confirmed with several endpoints (Behl et al., 2015), including decrease in mouse (LOEC 87.2 μM) and human (LOEC 13.8 μM) (neuronal) stem cell viability, a reduced mean firing rate (LOEC 15 μM) in rat cortical neuronal network, and a decrease of larval development of *C. elegans* (LOEC 3.9 μM). Overall, IDDP has a low neurotoxic potential. Although additional data on eco-, *in vivo*-, and *in vitro* toxicity, and human exposure are required, IDDP could be a suitable alternative FR.

2.1.9. Isopropyl phenyl phosphate (IPPP, CAS nr 46355-07-1)

No information on production volumes, persistence, bioaccumulation and (neuro)toxicity is available for IPPP. Only one study reported acute toxicity in rats indicating a low toxicity (oral LD_{50} > 20,000 mg/kg, inhalation LC_{50} > 200 g/m^3 and skin > 10,000 mg/kg; Cascieri and MacKellar, 1978). Clearly, the lack of (neurotoxic) information is hampering a proper evaluation of the suitability of IPPP as an alternative FR.

2.1.10. Melamine polyphosphate (MPP, CAS nr 218768-84-4)

Information on MPP is scarce and data on human exposure are lacking. Recent *in vitro* studies demonstrated that MPP inhibits nACh receptors (LOEC 70 μM), affects the depolarization-evoked increase in $[Ca^{2+}]_i$ (LOEC 70 μM) and increases ROS production (LOEC 0.35 μM). It is therefore classified as having a moderate *in vitro* neurotoxic potency (Hendriks et al., 2014b). However, in water MPP will dissociate into the monomers melamine and phosphoric acid. It is therefore a subject of discussion whether the observed effects are realistic and useful for human exposure, and whether they are induced by the polymer or by melamine and/or phosphoric acid, since it is known that at least melamine affects voltage-gated sodium channels (Yang et al., 2010). The scarce data indicate a low bioaccumulation potential in *in vivo* (eco)toxicity studies (Waaijers et al., 2013). As there is not enough data to classify MPP, additional *in vivo* toxicity and human exposure data are required before MPP can be considered as a suitable alternative FR.

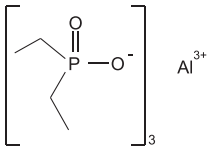
2.1.11. Tris(methylphenyl) phosphate (TMPP, CAS nr 1330-78-5)

TMPP (also known as tricresyl phosphate, TCP) is a mixture of different *ortho*- and non-*ortho* tricresyl phosphates, including tri-*ortho*-cresyl phosphate (*o*-TCP, CAS nr 78-30-8), tri-*meta*-cresyl phosphate (*m*-TCP, CAS nr 563-04-2) and tri-*para*-cresyl phosphate (*p*-TCP, CAS nr 78-32-0). Besides its use as a flame retardant, TMPP is also a frequently used engine oil additive, potentially resulting in occupational exposure. The toxicity of TMPP differs per isomer, in particular exposure to *o*-TCP is associated with (*in vivo*) neurotoxicity, including the so-called organophosphate-induced delayed neuropathy (OPIDN, LOEC 2.7 μM; Abou-Donia, 1981; Craig, 1999; Henschler, 1958), and dose-dependent reduction of AChE and NTE activities in the hippocampus of chronic (63 days, 150 mg/kg in 14 gavages) exposed rats (Jortner et al., 2005). Since the neurotoxicity of *o*-TCP appears largely due to its reactive metabolite (Eto et al., 1962), the involvement of bioactivation in human exposure settings should be taken into account for risk assessment. Because of rapid metabolism, human serum or blood concentrations of *o*-TCP half-lives are difficult to establish and are variable. In zebrafish larvae, extensive behavioral changes were observed 6 dpf after acute (LOEC 4 μM, measured 0.5–2.5 h after exposure (Jarema et al., 2015), and developmental TMPP exposure (LOEC 4 μM, exposure 1–5 dpf) (Jarema et al., 2015). These authors also indicate that developmental and acute behavioral effects of TMPP are distinct from those of *o*-TCP (LOEC acute effects 1.2 μM, developmental effects 4 μM). In a recent *in ovo* study, no definitive behavioral or neurochemical changes in TMPP-treated chicks (air cell egg injections up to 1000 ng/g per egg) were observed (Bradley et al., 2015). *In vitro*, it has been shown that *o*-TCP can inhibit neurite outgrowth in neuroblastoma cells (LOECs ≥ 2 μM) (Flaskos et al., 1998; Henschler et al., 1992; Li and Casida, 1998) and primary cultured mouse embryonic cortical neurons (LOEC 10 μM) (Hausherr et al., 2014). In both mouse and human neuroblastoma cells, it has been demonstrated that the loss of cytoskeletal components is one of the early events in the neurotoxic effects of *o*-TCP (LOEC ≥ 100 μM) (Carlson and Ehrich, 2001; Chang and Wu, 2006; Chen et al., 2013; Fowler et al., 2001). Recently, *o*-TCP was also shown to reduce the response to glutamatergic signaling in cortical neurons following subchronic exposure at submicromolar concentrations (LOEC 0.1 μM) (Hausherr et al., 2014). In human embryonic stem cell-derived neurons, neurite outgrowth is decreased in both TMPP (LOEC 9.2 μM) and *o*-TCP (LOEC 6.1 μM) cells (Behl et al., 2015). The mean firing rate in rat cortical neuronal networks is reduced following 1 h

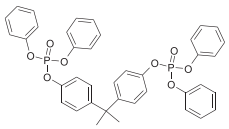
Table 4
Flame retardants discussed in this review and some of their physicochemical properties.

Halogen-free organophosphorousflameretardants

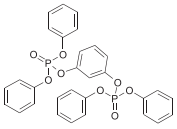
Aluminiumdiethylphosphinate
ALPI
$[C_4H_{10}P0_2]_3Al$
225789-38-8
390 g/mol
Log K_{OW} -0.4[1] (H)



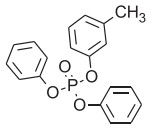
Bisphenol A bis(diphenyl phosphate)
BPA-BDPP
$C_{39}H_{34}O_8P_2$
5945-33-5
693 g/mol
Log K_{OW}< 6[1] (L)



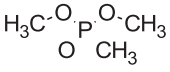
Resorcinol bis(diphenyl phosphate)
BPDPP
$C_{30}H_{24}O_8P_2$
57583-54-7
574 g/mol
Log K_{OW} 4.9[1] (L)



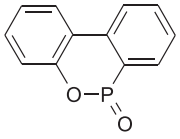
Diphenylcresylphosphate
DCP
$C_{19}H_{17}O_4P$
26444-49-5
340 g/mol
Log K_{OW} 4.5[2] (L)



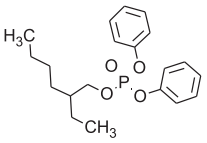
Dimethyl methylphosphonate
DMMP
$C_3H_9O_3P$
756-79-6
124 g/mol
Log K_{OW} -0.61[3] (H)



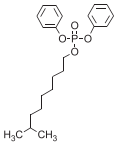
9,10-Dihydro-9-oxa-10-phosphaphenanthrene-10-oxide
DOPO
$C_{12}H_9O_2P$
35948-25-5
216 g/mol
Log K_{OW} ~2[2] (H)



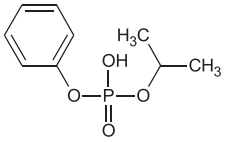
Ethylhexyldiphenylphosphate
EHDPP
$C_{20}H_{27}O_4P$
1241-94-7
362 g/mol
Log K_{OW} 5.73[4] (L)



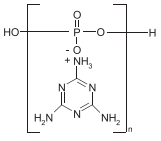
Isodecyl diphenyl phosphate
IDPP
$C_{22}H_{31}O_4P$
29761-21-5
391 g/mol
Log K_{OW} 5.44[5] (L)



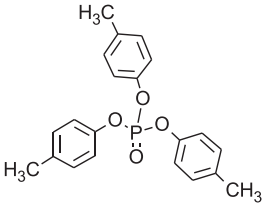
Isopropyl phenyl phosphate
IPPP
$C_{19}H_{17}O_4P$
46355-07-1
216 g/mol
Log K_{OW} 1.76 (H)



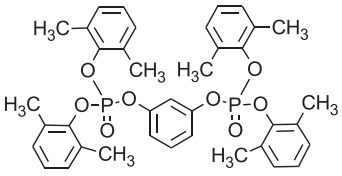
Melamine polyphosphate
MPP
$C_3H_6N_6 \cdot (H_3PO_4)_n$
218768-84-4
>10,000 g/mol
Log K_{OW} -2.3[1] (H)



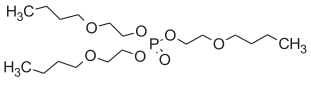
Tris(methylphenyl) phosphate, mixture of *ortho*-, *meta*- and *para*-tricresylphosphate
TMPP (or TCP)
$C_{21}H_{21}O_4P$
1330-78-5
368 g/mol
Log K_{OW} 5.0[2,6] (L)



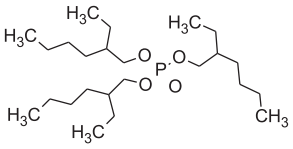
Resorcinol bis[di(2,6-dimethylphenyl) phosphate]
PBDMPP
$C_{38}H_{40}O_8P_2$
139189-30-3
687 g/mol
Log K_{OW} 10.3[6] (L)



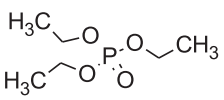
Tris(2-butoxyethyl) phosphate
TBOEP
$C_{18}H_{39}O_7P$
78-51-3
398 g/mol
Log K_{OW} 3.7[2,6] (L)



Tris(2-ethylhexyl) phosphate
TEHP
$C_{24}H_{51}O_4P$
78-42-2
435 g/mol
Log K_{OW} 4.2[2] (L)



Tris(ethyl) phosphate
TEP
$C_6H_{15}O_4P$
78-40-0
182 g/mol
Log K_{OW} 0.8[2,6] (H)



Tris(isobutyl) phosphate
TIBP
$C_{12}H_{27}O_4P$
126-71-6
266 g/mol
Log K_{OW} 3.6[2,6] (L)

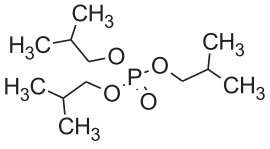
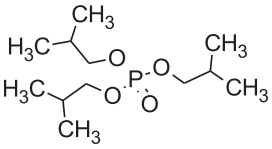
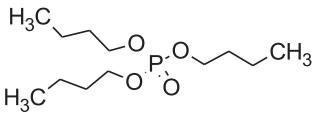


Table 4 (*continued*)

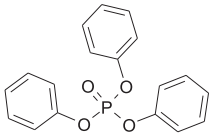
Tris(methyl) phosphate
TMP
$C_3H_9O_4P$
512-56-1
140 g/mol
Log K_{OW} -0.65[2,6] (H)



Tris(butyl) phosphate
TNBP
$C_{12}H_{27}O_4P$
126-73-8
266 g/mol
Log K_{OW} 4.0[2,6] (L)

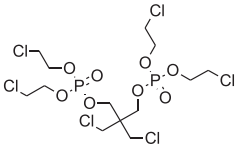


Tris(phenyl) phosphate
TPHP
$C_{18}H_{15}O_4P$
115-86-6
326 g/mol
Log K_{OW} 4.6[1] (L)

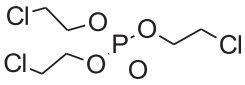


Halogenated organophosphorous flame retardants

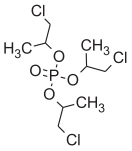
2,2-Bis(chloromethyl)-1,3-propanediol bis[bis(2-chloroethyl)-phosphate]
BCMP-BCEP (or V6)
$C_{13}H_{24}Cl_6O_8P_2$
38051-10-4
583 g/mol
Log K_{OW}1.9[2] (H)



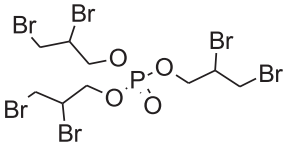
Tris(chloroethyl) phosphate
TCEP
$C_6H_{12}Cl_3O_4P$
115-96-8
285 g/mol
Log K_{OW}1.4[2] (H)



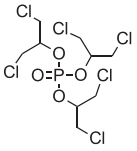
Tris(2-chloroisopropyl) phosphate
TCIPP
$C_9H_{18}Cl_3O_4P$
13674-84-5
328 g/mol
Log K_{OW}2.6[2] (L)



Tris-(2,3-dibromopropyl)phosphate
TDBPP
$C_9H_{15}Br_6O_4P$
126-72-7
698 g/mol
Log K_{OW}3.7[6] (L)

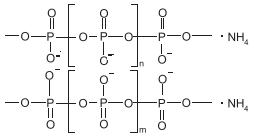


Tris-(2,3-dichloropropyl)phosphate
TDCIPP
$C_9H_{15}Cl_6O_4P$
13674-87-8
431 g/mol
Log K_{OW}3.3[6] (L)

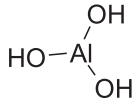


Inorganic halogen-free flame retardants

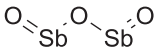
Ammonium polyphosphate
APP
$(NH_4PO_3)_n$
68333-79-9
~100,000 g/mol
Log K_{OW}-2.2[1] (H)



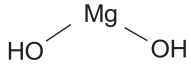
Aluminiumtrihydroxide
ATH
$Al(OH)_3$
21645-51-2
78 g/mol
Log K_{OW}n/a



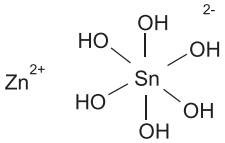
Antimony trioxide
ATO
Sb_2O_3
1309-64-4
292 g/mol
Log K_{OW}n/a



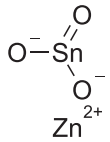
Magnesium hydroxide
MHO
H_2MgO_2
1309-42-8
58 g/mol
Log K_{OW}n/a



Zinc hydroxystannate
ZHS
$ZnSn(OH)_6$
12027-96-2
286 g/mol
Log K_{OW}<0.1[1] (H)



Zinc stannate
ZS
O_3SnZn
12036-37-2
232 g/mol
Log K_{OW}<-1[1] (H)



exposure to TMPP (LOEC 6.3 μM) or *o*-TCP (LOEC 16.1 μM) (Behl et al., 2015). Considering the observed *in vivo* and *in vitro* effects of *o*-TCP, TMPP is classified as having a moderate neurotoxic potential and appears not suitable as AFR. However, it should be noted that commercial TMPP nowadays contains no or only very little *o*-TCP. On the other hand, toxicity data on the non-*ortho* TCPs that currently dominate TMPP are at present too limited to consider TMPP as a suitable alternative FR.

2.1.12. Resorcinol bis[di(2,6-dimethylphenyl) phosphate] (PBDMPP, CAS nr 139189-30-3)

Information on PBDMPP is general lacking. A few fish and algae studies indicate a low toxicity (European Chemicals Agency, 2015), though studies on neurotoxicity are absent. The lack of information hampers proper evaluation of the suitability of PBDMPP as alternative FR.

2.1.13. Tris(2-butoxyethyl) phosphate (TBOEP, CAS nr 78-51-3)

TBOEP is frequently found in indoor air and dust with up to 4711 μg/g in a daycare center (Fromme et al., 2014b), up to 22 μg/g in car dust (Brandsma et al., 2014), 1000 ng/g lw in perch (measured in fish close to known sources; Sundkvist et al., 2010), 63 ng/g lw in human milk (Sundkvist et al., 2010), and 425 ng/g in human adipose tissue (LeBel et al., 1989). There is a significant correlation between the level of TBOEP in indoor air and the level of the metabolite di-(2-butoxyethyl) phosphate (DBOEP) in urine (Fromme et al., 2014b; Van den Eede et al., 2013). Also, it has recently been shown that TBOEP undergoes trophic magnification (Brandsma et al., 2015). However, only limited information on toxicity and underlying mechanisms is available for TBOEP. Repeated oral dosing of rats (up to 2.24 ml/kg) results in a significant reduction in nerve conduction velocity accompanied by degenerating myelin sheets and axonal swelling (Laham et al., 1984a,b). Single oral doses (up to 3200 mg/kg for females and 9000 mg/kg for males) result in the same electrophysiological and morphological effects, though females are more susceptible than males (Laham et al., 1985). The acute oral LD_{50} in hens exceeds 5000 mg/kg and this results in ~45% inhibition of AChE in the brain (Carrington et al., 1990). TBOEP causes general toxicity in the developing zebrafish, though the effect concentrations (LOEC 50 μM) are higher than values reported in the environment (Han et al., 2014). *In vitro*, TBOEP may have endocrine disrupting effects (Kojima et al., 2013). TBOEP is classified as having a low neurotoxic potential, however, considering the abundant presence of TBOEP and its metabolites in human and environmental samples, there is a clear need for additional research.

2.1.14. Tris(2-ethylhexyl) phosphate (TEHP, CAS nr 78-42-2)

Trace levels of TEHP are found in indoor air (Hartmann et al., 2004; Makinen et al., 2009) and it is measured in house dust at up to 3.7 μg/g (Dodson et al., 2012). Little is known about the toxicity of TEHP, although no (neuropathological) abnormalities are observed in an acute oral neurotoxicity study in hens (up to 2500 mg/kg bw; MacFarland and Punte, 1966). One *in vitro* study reported that TEHP may have potential endocrine disrupting effects (Kojima et al., 2013). There is clearly not enough data to classify TEHP, which argues for additional research on environmental levels and human exposure to obtain a full toxicology profile for risk assessment.

2.1.15. Tris(ethyl) phosphate (TEP, CAS nr 78-40-0)

So far, only one study reported the presence of TEP in house dust, at levels <0.05 μg/g (Van den Eede et al., 2011). An *in vivo* study described cholinergic-mediated induction of narcosis in rats following TEP exposure, with a $t_{1/2}$ of TEP in the brain of 8 h for weanlings and 30 h for adults (Brown and Murphy, 1971). Adult hens exposed to a single oral dose of 2000 mg/kg bw displayed several (neurological) acute symptoms, including apathy, decreased motility, and poor reflexes. However, no relevant decrease of cholinesterase activity in brain and blood plasma is observed and there is no evidence for delayed neurotoxicity (European Chemicals Agency, 2015). In addition, no neurotoxicity is observed in hens receiving 10 mg/kg bw TEP intramuscularly (Davies et al., 1960). Another study using rats indicated some small reductions in brain and plasma cholinesterase activity following exposures up to 6700 mg/kg bw (Gumbmann et al., 1968). As the neurotoxic potential appears low, TEP may be a suitable alternative, though additional research including information on bioavailability, toxicokinetics and human exposure is required for a full risk assessment.

2.1.16. Tris(isobutyl) phosphate (TIBP, CAS nr 126-71-6)

TIBP is observed in oceans (Moller et al., 2012) and recently also in food webs (Brandsma et al., 2015) and house dust (up to 0.18 μg/g; Brandsma et al., 2014). In rats, no embryotoxicity has been observed (Ruckman et al., 1999). Only two neurotoxicity-related studies are available. One indicates that even after administrating hens two doses of 5000 mg/kg bw no effects are observed that could be attributed to exposure (European Chemicals Agency, 2015). The other study, also using hens, shows that 5000 mg/kg bw TIBP does not inhibit brain AChE or NTE and does not produce delayed neurotoxicity (European Chemicals Agency, 2015). TIBP is classified as having a low neurotoxic potential, however, additional research including information on *in vivo* effects and human exposure is desirable before TIBP can be considered as a safe alternative FR.

2.1.17. Tris(methyl) phosphate (TMP, CAS nr 512-56-1)

TMP is not available in the ECHA database yet, but studies indicate its presence in the environment although discrepancies exist regarding its genotoxic effects (UNEP, 1994). No data on serum, breast milk and dust concentrations are available. Recent studies are lacking, but degeneration of nerve fibers in the spinal cord or peripheral nerves has been observed in a chronic (daily during two years) repeated dose study in rats exposed to 100 mg/kg bw in the first and 50 mg/kg bw in the second year (Bomhard et al., 1997). Another study also indicated neurotoxic effects in dogs exposed daily to 1 or 2 ml TMP (probably the pure liquid; dose or purity not mentioned), that develop neuropathy as a distally accentuated, primary axonal lesion (Schaeppi et al., 1984). Additionally, repeated exposure in rabbits (cutaneous 2 ml/kg bw or oral 0.3 ml/kg bw) resulted in several neurotoxic effects, including spasticity, unsteadiness, weakness of extremities, and fine tremors (Deichmann and Witherup, 1946). On the other hand, no evidence of neurotoxic effects was found in adult hens after subcutaneous treatment (Hollingshaus et al., 1981). Due to the scarcity of recent (*in vitro* and *in vivo*) toxicity studies and human exposure data, TMP cannot be classified.

2.1.18. Tris(butyl) phosphate (TNBP, CAS nr 126-73-8)

TNBP is described as 'severely irritating to man' and is one of the most abundant OPFRs in indoor air (Marklund et al., 2005). Considerable

Notes to Table 4:
Table presents full name, abbreviation, molecular formula, CAS-number, molecular weight, Log K_{OW}, and chemical structure of the selected flame retardants.
[1]Waaijers et al. (2013).
[2]van der Veen and de Boer (2012).
[3]Krikorian et al. (1987).
[4]US EPA (2006).
[5]US EPA (2004).
[6]Bergman et al. (2012).
n/a: not applicable; H: hydrophilic (see Table 1); L: lipophilic (see Table 1).

concentrations are measured in human breast milk (Sundkvist et al., 2010), and dust concentrations are associated with asthma and allergic rhinitis (Araki et al., 2014). A recent exposure study demonstrated the presence of TNBP metabolites like dibutyl phosphate in urine of occupationally exposed humans (Schindler et al., 2014). Neurotoxicity studies are contradictory as TNBP is reportedly not neurotoxic to rats following either acute (15.8 mg/kg bw, single dose; Johannsen et al., 1977) or subchronic exposures (diet containing up to 1% TNBP; Hisae et al., 1980), while in the study of Laham et al. (1983) rats exposed to 0.42 ml/kg for 14 days show a reduction in the conduction velocity of the caudal nerve and morphological changes, such as retraction of Schwann cell processes surrounding unmyelinated fibers. Another study reported clinical signs of toxicity and reduced motor activity levels in an acute exposure study in rats (1000 mg/kg) (European Chemicals Agency, 2015). In addition, TNBP decreases cholinesterase activity to some extent when applied to rats and rabbits in acute oral or intraperitoneal applications (no dose mentioned) or during subchronic inhalation (13.6 mg/m^3) (European Chemicals Agency, 2015). Single sublethal exposure of hens (1500 mg/kg) does not result in nerve damage, clinical signs of toxicity or significant inhibition of brain NTE or AChE (Carrington, 1989). Based on the available data, TNBP is classified as having a low neurotoxic potential, but considering its abundance additional exposure data are required.

2.1.19. Tris(phenyl) phosphate (TPHP, CAS nr 115-86-6)

TPHP is better studied than most other OPFRs. It has been measured in (dust in) houses, offices and cars at levels similar to or greater than those measured for PBDEs in the same samples (Brommer et al., 2012; Mizouchi et al., 2015; Stapleton et al., 2009). Due to the high vapor pressure, inhalation of TPHP in indoor air may play a significant role for human exposure (Meeker et al., 2013). For example, aircraft cabin air is contaminated with traces of TPHP-containing hydraulic fluid, which may explain elevated levels of TPHP metabolites in air crew (Schindler et al., 2014). TPHP was also reported to be present in human milk at up to 19 ng/g lw (Kim and Oh, 2014; Sundkvist et al., 2010). In addition, it has been shown that TPHP levels are up to 10,000 times higher than those of the PBDEs measured in toys, which may pose a potential health hazard for children (Ionas et al., 2014). Since no correlation between TPHP in house dust and its metabolite diphenyl phosphate (DPP) in urine is observed in adult men, TPHP in house dust may not be a primary source of exposure (Meeker et al., 2013). On the other hand, TPHP concentrations in house dust are reportedly associated with altered hormone levels and decreased semen quality (Meeker and Stapleton, 2010). In human exposure studies no evidence of neurological disease or other abnormalities in workers exposed to TPHP vapor or dust has been observed (Sutton et al., 1960). DPP has been identified as the major metabolite of TPHP in rats (Sasaki et al., 1981) and humans (Hoffman et al., 2014; Van den Eede et al., 2013), which is rapidly eliminated from the body. Due to this rapid biotransformation, the half-lives of TPHP in blood and its metabolites in urine are thought to be very short, most likely in the order of several hours. The *in vivo* neurotoxicity of TPHP has been debated since the early studies of Smith et al. (1930, 1932), who reported delayed neuropathy in cats and monkeys exposed to TPHP in acute and short-term studies, while Wills et al. (1979) could not demonstrate ataxia or neuropathic damage in cats. On the other hand, the commercial cresyl diphenyl phosphate product (which contains about 35% TPHP) has been shown to induce several effects in rats, including acute neurotoxicity at 300 mg/kg (Vainiotalo et al., 1987). In another study, a no observed adverse effect level (NOAEL) of 161 mg/kg/d in rats has been determined for decreased weight gain and neurological effects (Illinois Environmental Protection Agency, 2007). TPHP is not considered to be a potent anti-cholinesterase agent, however, exposure to 150 to 300 mg/kg bw TPHP does inhibit cholinesterase in rats, *in vitro* as well as *in vivo* (Bingham et al., 2001). In recent studies, exposure of zebrafish to 0.3 μM on 0–5 dpf had an impact on cognitive endpoints in adulthood (Oliveri et al., 2015). Changes in behavior and development were observed in larvae on 6 dpf (LOEC 0.7 μM, measured 0.5–2.5 h after exposure) and 1–5 dpf exposure (LOEC 0.4 μM (behavior), LOEC 2 μM (development)) (Behl et al., 2015; Jarema et al., 2015). In addition, a decrease in larval development of *C. elegans* following 48 h of incubation is observed (0.9 μM) (Behl et al., 2015). *In vitro* studies report cytotoxicity in PC12 cells, and inhibition of GABA- and $\alpha_4\beta_2$ nACh receptors at (tens of) micromolar levels of TPHP (Flaskos et al., 1998; Gant et al., 1987; Hendriks et al., 2012b; Padilla et al., 1987; Vainiotalo et al., 1987). In addition, clear effects on ROS production as well as on basal and depolarization-evoked changes in $[Ca^{2+}]_i$ are observed in PC12 cells (LOEC 1 μM) (Hendriks et al., 2014b). Additionally, the mean firing rate in rat cortical neuronal networks is reduced following 1 h exposure (16.3 μM) (Behl et al., 2015). In human embryonic stem cell-derived neurons, both cell viability and neurite outgrowth were decreased (Behl et al., 2015). TPHP has a moderate neurotoxic potential and is labeled by the ECHA as a compound with dangerous effects for the environment (European Chemicals Agency, 2015) and is consequently not considered a suitable replacement for BFRs.

2.1.20. Summary neurotoxicity of halogen-free organophosphorous flame retardants

In general, a lack of exposure and toxicological data hampers proper risk assessment. Clearly, more research is needed to obtain full toxicological profiles since eight of the selected non-halogenated OPFRs could not be classified. Based on the reviewed studies, ALPI, BPDPP, DCP, EHDPP, IDDP, TBOEP, TEP, TIBP, and TNBP may be suitable alternatives to replace BFRs (also see Table 5). However, it should be mentioned that it is essential to have a complete toxicological profile for risk assessment before large scale use of a substitute. TMPP and TPHP have a medium-high neurotoxic potential and are therefore probably not suitable substitutes.

2.2. Neurotoxicity of halogenated organophosphorous flame retardants

2.2.1. 2,2-Bis(chloromethyl)-1,3-propanediol bis[bis(2-chloroethyl) phosphate] (BCMP-BCEP, CAS nr 38051-10-4)

No data on serum and breast milk concentrations are available for BCMP-BCEP (also known as V6) while significant dust concentrations are found in car and house dust (Fang et al., 2012). In rats, decreased AChE levels are observed following exposure to 500 mg/kg BCMP-BCEP (European Chemicals Agency, 2015). Although no other specific neurotoxicity data are available, no significant effects on mortality, gross developmental malformations, delayed hatching, or obvious signs of impaired locomotion were observed in a zebrafish developmental toxicity assay exposed up to 50 μM (McGee et al., 2012). As the overall neurotoxic potential appears low, BCMP-BCEP may be a suitable alternative FR, though additional data on eco-, *in vivo*-, and *in vitro* toxicity and human exposure are required for a full risk assessment.

2.2.2. Tris(chloroethyl) phosphate (TCEP, CAS nr 115-96-8)

TCEP is a quite well studied OPFR and has been measured in breast milk as well as in dust (Kim and Oh, 2014; Mizouchi et al., 2015). Measurements of TCEP in rat brains (up to 700 mg/kg bw) indicate that TCEP is readily absorbed from the gastro-intestinal tract and distributed to all brain regions (Herr et al., 1991). In addition, metabolism and excretion is nearly complete in 72 h. Other *in vivo* studies report toxic effects on pyramidal neurons in the hippocampus in both acute exposed rats (275 mg/kg bw: Tilson et al., 1990; 300 mg/kg bw: Herr et al., 1991) and subchronic exposed rats (16 weeks, up to 700 mg/kg bw) (Matthews et al., 1990). Exposed mice (200 mg/kg bw ip) show an increase in spontaneous ambulatory activity, which is suggested to be caused by antagonistic effects of TCEP on the GABA-R (Umezu et al., 1998). However, in a recent study using rat pups of exposed dams (up to 90 mg/kg bw from GD 10 to weaning) the authors could not confirm the developmental neurotoxicity produced by TCEP (Moser et al., 2015). In a zebrafish developmental toxicity assay also no significant effects

(up to 50 μM) are observed (McGee et al., 2012). In another zebrafish study, neurobehavioral effects were evaluated by determining the threshold for larval swimming activity and indicated that the neurobehavioral effect threshold (31.4 μM) was below the acute toxicity threshold (Dishaw et al., 2014). Recently, behavioral changes were observed in zebrafish larvae on 6 dpf after acute (LOEC 12 μM) and developmental exposure (LOEC 12 μM) (Jarema et al., 2015). *In vitro* TCEP (at 50 μM) promotes differentiation into the cholinergic phenotype of PC12 cells (Dishaw et al., 2011) and decreases cell viability (at 40 μM) (Ta et al., 2014). In addition, protein levels of GAP-43 and tubulins are decreased, while CAMK-II and neurofilament-H are increased (Ta et al., 2014). As the overall neurotoxic potential is classified as low, TCEP appears to be a suitable alternative FR, although additional research including human exposure studies, bioavailability and toxicokinetics is required for a full risk assessment.

2.2.3. Tris(2-chloroisopropyl) phosphate (TCIPP, CAS nr 13674-84-5)

TCIPP is found in dust (Mizouchi et al., 2015) and its metabolite bis(1-chloro-2-propyl) phosphate can be measured in human urine (Dodson et al., 2014). In a zebrafish developmental assay, no effects up to 50 μM were observed (McGee et al., 2012), and the threshold for effects on larval swimming activity is 100 μM (Dishaw et al., 2014). *In vitro*, TCIPP (at 50 μM) promoted differentiation into the cholinergic phenotype of PC12 cells (Dishaw et al., 2011). In chicken embryonic neuronal cells, exposure up to 300 μM did not induce significant effects on the cell viability (Crump et al., 2012). Despite the low neurotoxicity, carcinogenicity is reported (WHO, 1998), clearly arguing for more research, including human exposure studies, to obtain a full toxicological profile.

2.2.4. Tris-(2,3-dibromopropyl) phosphate (TDBPP, CAS nr 126-72-7)

Data on TDBPP are scarce though it is stated that it is mutagenic (St John et al., 1976), and it is found (together with its metabolite) in urine of children wearing TDBPP-treated sleepwear (Blum et al., 1978). In zebrafish, overt toxicity occurs at 3.3 μM while the neurobehavioral effect threshold for larval swimming activity is as low as 0.56 μM (Dishaw et al., 2014). *In vitro*, 50 μM TDBPP promotes differentiation of PC12 cells into dopaminergic and cholinergic phenotypes (Dishaw et al., 2011). Considering the mutagenic effects and moderate neurotoxic potential, TDBPP is not a suitable alternative FR.

2.2.5. Tris-(1,3-dichloropropyl) phosphate (TDCIPP, CAS nr 13674-87-8)

TDCIPP in house dust is associated with altered hormone levels and decreased sperm quality in men (Meeker and Stapleton, 2010; Meeker et al., 2013), and the metabolite bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) is measured in human urine (Butt et al., 2014). While no developmental neurotoxicity (based on neurobehavioral tests) is observed in rats exposed up to 150 mg/kg/d (GD 10 to weaning) (Moser et al., 2015), overt neurotoxic effects like leg and wing weakness are observed in chickens orally exposed for five days to >1200 mg/kg (Ulsamer et al., 1980). In a recent *in ovo* study, chickens derived from eggs exposed to TDCIPP at 100 ng/g (egg injections at incubation day 0) achieved lower maximum velocity in the open field test than controls (Bradley et al., 2015). Moreover, chickens derived from eggs exposed to

Table 5
Overview of the (neuro)toxicity of alternative flame retardants.

Flame retardant	Abbreviation	Production volume	Ecotoxicity	*In vivo* toxicity	*In vitro* toxicity	*In vivo* neurotoxicity	Zebrafish neurotoxicity	*In vitro* neurotoxicity	Effects on AChE	Effects on NTE	Neurotoxic potential*
Organophosphorous flame retardants											
Aluminium diethylphosphinate	ALPI	nd	L–M[1]	L[1]	L[1]	L[2]	nd	N[3,4]	nd	nd	L
Bisphenol A bis(diphenyl phosphate)	BPA-BDPP	HPV[1]	H[1]	L[1]	L[1]	nd	nd	N[3,4]	nd	nd	nc
Resorcinol bis(diphenyl phosphate)	BPDPP	LPV[1]	L–H[1]	L–M[1]	L[1]	nc	nd	L[3,4]	nd	L[5]	L
Diphenylcresylphosphate	DCP	LPV[6]	M[6]	L[6]	L[6]	L[7]	nd	L[7]	L[8]	L[7]	L
Dimethyl methylphosphonate	DMMP	nd	L[5]	L[5]	L[5]	L[5]	nd	nd	nd	nd	nc
9,10-Dihydro-9-oxa-10-phosphaphenanthrene-10-oxide	DOPO	nd	M[6]	nd	L[6]	nd	nd	L[3,4]	nd	nd	nc
Ethylhexyl diphenylphosphate	EHDPP	HPV[5]	L[5]	L[5]	L[5]	L[5]	L[a,9,10]	L[10]	nd	nd	L
Isodecyl diphenyl phosphate	IDDP	HPV[5]	L–M[5]	L[5]	L[5]	L[5]	L[a,9,10]	N[10]	nd	nd	L
Isopropyl phenyl phosphate	IPPP	nd	nd	L[11]	nd	nd	nd	nd	nd	nd	nc
Melamine polyphosphate	MPP	nd	L[1]	L[1]	nd	nd	nd	M[3,4]	nd	nd	nc
Tris(methylphenyl) phosphate, mixture of *ortho*-, *meta*- and *para*-tricresylphosphate**	TMPP	HPV[5]	H[6]	M–H[6]	L[6]	L[12]	L[9]	M[13,14]	L[15]	L[15]	M
Resorcinol bis[di(2,6-dimethylphenyl) phosphate]	PBDMPP	LPV[5]	L[5]	L[5]	L[5]	nd	nd	nd	nd	nd	nc
Tris(2-butoxyethyl) phosphate	TBOEP	LPV[5]	L[5]	L[5]	L[5]	L[16]	nd	nd	L[16]	nd	L
Tris(2-ethylhexyl) phosphate	TEHP	HPV[5]	L[5]	L[5]	L[17]	L[18]	nd	nd	nd	nd	nc
Tris(ethyl) phosphate	TEP	HPV[5]	L[5]	L[5]	nd	L[5]	nd	nd	L[5]	nd	L
Tris(isobutyl) phosphate	TIBP	HPV[5]	L[5]	L[5]	nd	L[5]	nd	nd	L[5]	L[5]	L
Tris(methyl) phosphate	TMP	LPV[19]	L[19]	L–M[19]	L[19]	L–H[20]	nd	nd	nd	nd	nc
Tris(butyl) phosphate	TNBP	HPV[5]	L–M[5]	M[21]	M[5]	L[22]	nd	nd	L[23]	L[23]	L
Tris(phenyl) phosphate	TPHP	HPV[1]	M–H[1]	L[1]	L[1]	L[1]	M[a,9,10,24]	L[3,4]	L[25]	nd	M
Halogenated organophosphorous flame retardants											
2,2-Bis(chloromethyl)-1,3-propanediol bis[bis(2-chloroethyl)phosphate]	BCMP-BCEP	LPV[5]	L–M[5]	L[5]	L[5]	L	N[26]	nd	L[5]	nd	L
Tris(chloroethyl) phosphate	TCEP	LPV[5]	L[5]	L[5]	L[26]	L[27,28,29]	N[9,30]	N[31]	nd	nd	L
Tris(2-chloroisopropyl) phosphate	TCIPP	HPV[5]	L[5]	L[5]	L–H[5]	L[5]	N[26]	N[32]	nd	nd	L
Tris-(2,3-dibromopropyl)phosphate	TDBPP	nd	nd	nd	nd	nd	M[30]	N[31]	nd	nd	M
Tris-(2,3-dichloropropyl)phosphate	TDCIPP	HPV[33]	L[34]	M[33]	M[33]	L[34]	H[a,9,24,30,35]	L[31]	nd	nd	H
Inorganic flame retardants									nd	nd	
Ammonium polyphosphate	APP	HPV[1]	L–M[1]	L[1]	L[1]	nd	nd	L[3,4]	nd	nd	nc
Aluminium trihydroxide	ATH	HPV[1]	L–H[1]	L[1]	L[1]	L[36]	nd	H[3,4]	nd	nd	H
Antimony trioxide	ATO	HPV[5]	L–M[5]	L[5]	L[5]	nd	nd	L[3,4]	nd	nd	nc
Magnesium hydroxide	MHO	HPV[1]	L[1]	L[1]	L[5]	nd	nd	L[3,4]	nd	nd	nc
Zinc hydroxystannate	ZHS	LPV[1]	L[1]	L–M[1]	L[1]	nd	nd	H[3,4]	nd	nd	nc
Zinc stannate	ZS	LPV[1]	L[1]	L[1]	L[5]	L[2]	nd	H[3,4]	nd	nd	H

1000 ng/g showed reduced density and lower number of degenerate Purkinje cells, possibly indicating disruption of neurodevelopment (Bradley et al., 2015). In zebrafish, overt neurotoxicity is observed following five days of exposure to 10 μM, and the threshold for effects on larval swimming activity is 3.14 μM (Dishaw et al., 2014). Another zebrafish-study demonstrates that parental exposure to TDCIPP during three months can result in adverse neurodevelopment in offspring at concentrations as low as 0.2 μM (Wang et al., 2015). Recently, increased activity was observed in zebrafish larvae exposed to 0.03 μM TDCIPP on 0–5 dpf, and increased locomotion was observed in adult fish exposed to 0.3 μM (Oliveri et al., 2015). Behavioral changes were also observed in larvae on 6 dpf after acute (LOEC 3.8 μM, measured 0.5–2.5 h after exposure) and developmental exposure (LOEC 1.2 μM, exposure 1–5 dpf) (Jarema et al., 2015). Additionally, a decrease in larval development of *C. elegans* was observed following 48 h incubation (LOEC 9.8 μM) (Behl et al., 2015). *In vitro*, TDCIPP displays concentration-dependent neurotoxicity in PC12 cells, including inhibition of DNA synthesis (LOEC 10 μM) and differentiation into dopaminergic and cholinergic phenotypes (LOEC 10 μM) (Dishaw et al., 2011). Another study using PC12 cells demonstrated a reduction in the levels of GAP-43, tubulin and neurofilament-H, but increased CAMK-II levels following exposure to 15 μM (no lower concentrations were tested), whereas at 5 μM, a decrease in cell viability was observed (Ta et al., 2014). The mean firing rate in rat cortical neuronal networks is reduced following 1 h exposure (LOEC 15.8 μM) (Behl et al., 2015). In chicken embryonic neuronal cells cytotoxic effects are observed at concentrations >10 μM (Crump et al., 2012). As TDCIPP has a high neurotoxic potential, it is not considered a suitable alternative FR.

2.2.6. Summary neurotoxicity of halogenated organophosphorous flame retardants

BCMP-BCEP, TCEP and TCIPP are classified as having a low neurotoxic potential. Despite the incomplete toxicological profile and need for additional research, these FRs may be suitable alternatives to replace BFRs. However, it should be mentioned that many halogenated chemicals, including some BFRs and PCBs, have proven to be persistent, bioaccumulative, and/or toxic in the environment, and to animals and humans. TDBPP and TDCIPP have a medium and high neurotoxic potential, respectively, and are probably not suitable as an alternative.

2.3. Neurotoxicity of inorganic halogen-free flame retardants

2.3.1. Ammonium polyphosphate (APP, CAS nr 68333-79-9)

Studying the (neuro)toxicity of APP is hampered by the hydrolysis of APP into monomeric ammonium phosphate in contact with water (Clariant, 2010). APP is also reported to break down into ammonia and phosphate in soil and sewage (German Federal Environmental Agency et al., 2001). *In vivo* toxicity data on APP are lacking, although some *in vitro* data are available. In PC12 and B35 cells, APP induces cytotoxicity, increased ROS levels, and disturbance of depolarization-evoked Ca^{2+}-homeostasis at submicromolar concentrations (Hendriks et al., 2014b). In addition, APP inhibits $\alpha_4\beta_2$ nACh receptors (LOEC 1.3 mM) (Hendriks et al., 2012b). Considering the expected low bioavailability of the polymer and assuming that considerable hydrolysis occurs, the test solutions used in these *in vitro* studies likely contain primarily monomers, which changes the classification of APP from a high *in vitro* neurotoxic potential (assuming an average chain length of

Notes to Table 5:
AChE: acetylcholinesterase; nc: not enough data to classify; nd; no data available; NTE: neuropathy target esterase.
[1] Waaijers et al. (2013).
[2] Hendriks et al. (2014a).
[3] Hendriks et al. (2012a).
[4] Hendriks et al. (2014b).
[5] European Chemicals Agency (2015).
[6] van der Veen and de Boer (2012).
[7] Sprague and Castles (1985).
[8] Vainiotalo et al. (1987).
[9] Jarema et al. (2015).
[10] Behl et al. (2015).
[11] Cascieri and MacKellar (1978).
[12] Craig (1999).
[13] Hausherr et al. (2014).
[14] Li and Casida (1998).
[15] Jortner et al. (2005).
[16] Carrington et al. (1990).
[17] Kojima et al. (2013).
[18] MacFarland and Punte (1966).
[19] UNEP (1994).
[20] Bomhard et al. (1997).
[21] Johannsen et al. (1977).
[22] Laham et al. (1983).
[23] Carrington (1989).
[24] Oliveri et al. (2015).
[25] Bingham et al. (2001).
[26] Föllmann and Wober (2006).
[27] Matthews et al. (1990).
[28] Tilson et al. (1990).
[29] Umezu et al. (1998).
[30] Dishaw et al. (2014).
[31] Dishaw et al. (2011).
[32] Crump et al. (2012).
[33] WHO (1998).
[34] Ulsamer et al. (1980).
[35] Wang et al. (2015).
[36] Bilkei-Gorzo (1993).
* The neurotoxic potential is only assessed when data was available for at least two neurotoxic endpoints (*in vivo* neurotoxicity, zebrafish, *in vitro* neurotoxicity, effects on AChE, and/or effects on NTE) and is based on the most potent sub-classification. H; high potential, M: moderate potential, L; low potential, see also Table 1.
** (Neuro)toxicity data mainly based on the *ortho*-isomer.
[a] Based on zebrafish and *C. elegans* data.

Table 6
Human exposure data of alternative flame retardants.

	Abbreviation	$t_{1/2}$ days (d) or hours (h)	Human serum concentration (μg/g)	Human breast milk concentration (ng/g lw)	Human urinary metabolites (ng/ml)	Dust concentration (μg/g)
Organophosphorous flame retardants						
Aluminium diethylphosphinate	ALPI	nd	nd	nd	nd	nd
Bisphenol A bis(diphenyl phosphate)	BPA-BDPP	nd	nd	nd	nd	1300[1]
Resorcinol bis(diphenyl phosphate)	BPDPP	2.7 d (rat)[2]	nd	nd	nd	520[1]
Diphenylcresylphosphate	DCP	nd	nd	nd	nd	nd
Dimethyl methylphosphonate	DMMP	3–6 h (rat)[3]	nd	nd	nd	nd
9,10-Dihydro-9-oxa-10-phosphaphenanthrene-10-oxide	DOPO	nd	nd	nd	nd	nd
Ethylhexyl diphenylphosphate	EHDPP	nd	nd	nd	nd	nd
Isodecyl diphenyl phosphate	IDDP	nd	nd	nd	nd	nd
Isopropyl phenyl phosphate	IPPP	nd	nd	nd	nd	nd
Melamine polyphosphate	MPP	nd	nd	nd	nd	nd
Tris(methylphenyl) phosphate, mixture of *ortho*-, *meta*- and *para*-tricresylphosphate*	TMPP	46 h (rat)[4] 1–4 d (hen)[5]	nd	nd	nd	12.5[6]
Resorcinol bis[di(2,6-dimethylphenyl) phosphate]	PBDMPP	nd	nd	nd	nd	nd
Tris(2-butoxyethyl) phosphate	TBOEP	nd	nd	63[7]	Bis(2-butoxyethyl) phosphate, 0.35[8]	4711[9]
Tris(2-ethylhexyl) phosphate	TEHP	nd	nd	nd	nd	51[10]
Tris(ethyl) phosphate	TEP	nd	nd	nd	nd	0.72[11]
Tris(isobutyl) phosphate	TIBP	nd	nd	nd	nd	0.18[12]
Tris(methyl) phosphate	TMP	nd	nd	nd	nd	<LOD
Tris(butyl) phosphate	TNBP	25 h (rat)[13]	nd	57[7]	Dibutyl phosphate, 0.16[14]	60.6[11]
Tris(phenyl) phosphate	TPHP	Several hours (human)[15,16]	0.15[17]	19[17]	Diphenyl phosphate, 0.51[18]	62[19]
Halogenated organophosphorous flame retardants						
2,2-Bis(chloromethyl)-1,3-propanediol bis[bis(2-chloroethyl)phosphate]	BCMP-BCEP	≤113 h (human)[13]	nd	nd	nd	12,500[20]
Tris(chloroethyl) phosphate	TCEP	nd	nd	42[21]	nd	4.1[10]
Tris(2-chloroisopropyl) phosphate	TCIPP	nd	nd	nd	Bis(1-chloro-2-propyl) phosphate, 0.17[14]	2.5[10]
Tris-(2,3-dibromopropyl)phosphate	TDBPP	nd	nd	nd	nd	nd
Tris-(2,3-dichloropropyl)phosphate	TDCIPP	nd	nd	nd	bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), 2.4[22]	1580[23]
Inorganic flame retardants						
Ammonium polyphosphate	APP	nd	nd	nd	nd	nd
Aluminium trihydroxide	ATH	nd	nd	nd	nd	nd
Antimony trioxide	ATO	9.3 d (rat)[13]	nd	nd	nd	nd
Magnesium hydroxide	MHO	nd	nd	nd	nd	nd
Zinc hydroxystannate	ZHS	nd	nd	nd	nd	nd
Zinc stannate	ZS	nd	nd	nd	nd	nd

LOD: limit of detection; lw: lipid weight; nd: no data available; $t_{1/2}$: half-life.
[1] Brandsma et al. (2013).
[2] Freudenthal et al. (2000).
[3] Blumbach et al. (2000).
[4] Abou-Donia et al. (1990).
[5] Suwita and Abou-Donia (1990).
[6] van der Veen and de Boer (2012).
[7] Sundkvist et al. (2010).
[8] Van den Eede et al. (2015).
[9] Fromme et al. (2014b).
[10] Mizouchi et al. (2015).
[11] Tajima et al. (2014).
[12] Brandsma et al. (2014).
[13] European Chemicals Agency (2015).
[14] Dodson et al. (2014).
[15] Hoffman et al. (2014).
[16] Van den Eede et al. (2013).
[17] Johnson et al. (2010).
[18] Cequier et al. (2015).
[19] Kanazawa et al. (2010).
[20] Fang et al. (2012).
[21] Kim and Oh (2014).
[22] Butt et al. (2014).
[23] Meeker et al. (2013).
* Data are mainly based on the *ortho*-isomer.

1000) to a low *in vitro* neurotoxic potential (assuming the monomer). Since there are not enough data available to classify APP, additional toxicological and exposure studies are required to determine for example if effects are due to the polymer or monomer before APP can be considered as a suitable alternative FR.

2.3.2. Aluminum trihydroxide (ATH, CAS nr 21645-51-2)

Data on toxicity and environmental presence of ATH are generally lacking. The acute toxicity for ATH in rats is very low, though adverse effects on the learning ability and diminished cholinergic activity have been observed in rats (Bilkei-Gorzo, 1993). Noteworthy, inhalation of

ATH by rabbits and rats results in transfer of Al^{3+} to the brain (Rollin et al., 1991; Schlesinger et al., 2000). Additional studies reported *in vitro* neurotoxicity of ATH at submicromolar levels, including induction of neurites in neuroblastoma cells (Zatta et al., 1992), increase in ROS levels and disturbance of the Ca^{2+}-homeostasis in neuronal cell lines (Hendriks et al., 2014b), *N*-methyl-D-aspartate (NMDA) receptor binding in human cerebral cortex (Hubbard et al., 1989), and inhibition of $\alpha_4\beta_2$ nACh receptors (Hendriks et al., 2012b). Given the high neurotoxic potential, the suitability of ATH as an alternative FR appears limited.

2.3.3. Antimony trioxide (ATO, CAS nr 1309-64-4)

Despite its use in *e.g.* fire fighter uniforms, the degree of exposure to ATO appears limited (de Perio et al., 2010; Sundar and Chakravarty, 2010). One study indicated the absence of a correlation between personal ATO exposure and textile industry workers following measurement in urine (Iavicoli et al., 2002). ATO is not metabolized, but excreted *via* the feces and (to a lesser extent) urine. Half-lives in rats exposed orally for 14 days are estimated to be 9.3 days and rats display increasing brain concentrations of ATO following 24 weeks of exposure (European Chemicals Agency, 2015). Another study reported the transfer of ATO over the placental barrier after injection and oral administration in mice, and transfer into milk following oral and intravenous application in cattle (European Chemicals Agency, 2015). At low micromolar concentrations (9.4 μM), ATO shows clear antagonistic effects on the $\alpha_4\beta_2$ nACh receptor. The lack of toxicity data for ATO hampers classification, but since ATO is considered by the ECHA (European Chemicals Agency, 2015) as 'suspected of causing cancer but not sufficient for classification', it does not appear to be a suitable alternative FR.

2.3.4. Magnesium hydroxide (MHO, CAS nr 1309-42-8)

Exposure and *in vivo* toxicity data of MHO are largely lacking. It is expected that Mg^{2+} will dissociate (for instance in the stomach) from MHO and about 40% of the Mg^{2+} will bind to proteins to the same degree as endogenous Mg^{2+}. However, neurotoxic effects of Mg^{2+} are unlikely given its key role in a wide range of physiological cellular processes and expected exposure levels. While MHO was recently shown to increase ROS levels in B35 cells (LOEC 4.1 μM), a number of other *in vitro* neurotoxic endpoints is not significantly affected (Hendriks et al., 2014b). Due to the lack of additional toxicity studies, there are not enough data to classify MHO.

2.3.5. Zinc hydroxystannate (ZHS, CAS nr 12027-96-2)

Toxicity data on ZHS are scarce, although it is known that metallic tin and its inorganic salts have a low toxicity (Cima, 2011). ZHS inhibits $\alpha_4\beta_2$ nACh receptors already at submicromolar concentrations (Hendriks et al., 2012b). Additionally, ZHS reduces cell viability, increases ROS production, and strongly reduces depolarization-evoked Ca^{2+} increases in neuronal cell lines (LOEC 0.005 μM) (Hendriks et al., 2014b). Based on their stability and low solubility (Waaijers et al., 2013), the observed *in vitro* neurotoxic effects appear to be intrinsic to ZHS as the metals are not expected to ionize in test solutions to levels sufficiently high to induce toxicity. Given the scarce toxicity data, ZHS cannot be classified yet and additional research on *in vivo* toxicity and human exposure are required.

2.3.6. Zinc stannate (ZS, CAS nr 12036-37-2)

Although no data on (human) exposure or toxicity are available, ZS was shown to induce only insignificant changes in LTP and synaptic protein levels in neonatally exposed mice (single exposure on PND 10 to 211 μmol/kg bw) (Hendriks et al., 2014a). Nevertheless, ZS reduces cell viability, increases ROS production, and strongly reduces depolarization-evoked Ca^{2+} increases in neuronal cell lines (LOEC 0.006 μM) (Hendriks et al., 2014b), indicating a high *in vitro* neurotoxic potential. The observed differences between these *in vivo* and *in vitro* studies may be due to low bioavailability and/or rapid excretion *in vivo*, although this needs to be confirmed. Based on the existing data, ZS is classified as having a high neurotoxic potential.

2.3.7. Summary neurotoxicity of inorganic halogen-free flame retardants

ATH and ZHS are classified as having a high neurotoxic potential, while the lack on data precludes the classification of APP, ATO, MHO, and ZHS. However, it should be mentioned that inorganic substances will behave differently than organic substances concerning *e.g.* bioavailability, metabolism and biodegradation.

3. Risk assessment of AFRs

As can be concluded from the reviewed data, BFRs and AFRs share some modes of action on functional neurotransmission endpoints. Following the neurotoxic potential of the AFRs as shown in Table 5, the inorganic AFRs seem to have a higher neurotoxic potential compared to the OPFRs, at least *in vitro*. However, whether the AFRs are of concern for human health and the environment also depends on additional factors, including biotransformation, abundance in the environment, physicochemical properties of the compound, human plasma concentrations, toxic effects *in vivo*, toxicokinetics, *etc.* (see also Table 6). Evaluation of potential (neuro)toxic effects of combined exposure of compounds (with or without metabolites) is also of importance, since additive, antagonistic and synergistic interactions between environmental compounds have already been shown in several *in vitro* studies (Gao et al., 2009; Hendriks et al., 2010; Mariani et al., 2015; Pellacani et al., 2012; Tagliaferri et al., 2010; Westerink, 2013).

3.1. Bioavailability

Physicochemical properties like the molecular weight and Log K_{OW} determine the ability of a toxicant to enter the animal or human blood circulation following ingestion (deBruyn and Gobas, 2007; Gulden et al., 2002; Hestermann et al., 2000). Most FRs are (highly) lipophilic (see Table 4) and are therefore expected to bind significantly to serum proteins (*e.g.* albumin), resulting in (very) low free available concentrations. Large molecules (*i.e.* the polymers MPP and APP) also have a low bioavailability due to their high molecular weight. Because of the high molecular weight of plasma proteins, they cannot cross capillary walls. Consequently, the fraction of FRs bound to plasma proteins is not immediately available for distribution into the extracellular space or filtration and excretion by the kidneys. As a result, it can be expected that these chemicals will not readily cause toxic effects. However, it should be mentioned that although the majority of the lipophilic chemicals is bound to plasma proteins, they will dissociate from the protein until equilibrium between the vascular space and extravascular space is reached. Also, active transport processes are not limited by the binding of chemicals to plasma proteins, and since the kidneys are not able to filtrate these large molecules the toxicants may remain in the body for a long period.

Hydrophilic compounds are less likely to bind plasma proteins. As a consequence, these chemicals are theoretically freely available in gut, blood and/or extracellular space. However, for inorganic substances or substances that ionize in *e.g.* the stomach, the Log K_{OW} is less relevant. Inorganic substances have in general a lower bioavailability as they will dissociate into their ion constituents. Following partitioning, the free metal ions will have a complex chemistry with their surrounding physiological environment, depending on their ionic state and an additional long list of physic–chemical parameters (acidity, hardness, redox status, *etc.*). Although data on the bioavailability of AFRs are scarce, it was recently observed that at least in zebrafish OPFRs increase in tissue concentrations with increasing hydrophobicity of the parent compound (Dishaw et al., 2014).

3.2. Toxicokinetics

Since BFRs and possibly also AFRs are potentially more toxic during (brain) development, it is essential to understand maternal kinetic parameters (*i.e.* absorption, distribution, metabolism and excretion) in order to describe the dose available to target tissues (*e.g.* placenta) after exposure. Mobilization of body-fat containing toxicants during *e.g.* lactation results in high concentrations in milk, and exposure of offspring with their vulnerable developing brain may occur. Due to the lipophilicity of most OPFRs, transfer from the aqueous environment of the intestine across cell membranes is generally a passive process, although this process depends also on the size and molecular weight. The compounds have a low affinity for blood, which frequently results in accumulation in lipid-rich tissues like adipose tissue but also brain and liver. Nevertheless, differences in absorption rate and ability to enter cells are expected for AFRs as also observed among congeners of *e.g.* PBDEs, mainly as a consequence of the number and position of the halogen molecules. PBDEs are primarily hydroxylated and dehalogenated to increase the water solubility, which facilitates excretion from the body, but also increases their neurotoxic potential. Whether the same applies to AFRs remains to be determined.

Halogen-free organophosphorous flame retardants are known to be readily metabolized and excreted in the urine as dialkyl and diaryl compounds (Butt et al., 2014), which can function as a biomarker for (human) exposure (also see Table 6). However, major metabolites have not been conclusively identified yet, and information to relate pharmacokinetic parameters to metabolite levels is limited (Cequier et al., 2015; Dodson et al., 2014; Van den Eede et al., 2015). Consequently, measuring metabolites in urine is – so far – not a valid method to identify internal dose and brain concentrations. Additional research is needed to investigate how urinary metabolites might be related to internal dose and brain concentrations.

3.3. Routes of exposure and internal concentrations

Human exposure to BFRs occurs predominantly *via* house dust and food. As a result, BFRs are frequently measured in various human tissues, including serum and breast milk. Large differences in PBDE levels in house dust have been found between countries, reflecting the large variance in worldwide market demand of different BFR classes by region (*e.g.* US vs. Europe vs. Asia) (de Wit et al., 2010), legislations prohibiting the use of particular compounds, and voluntary production stop (Jinhui et al., 2015). Consequently, average levels in the US population are significantly higher than those *e.g.* in Europe, and these levels are clearly associated with exposure to house dust (Johnson et al., 2010). It is therefore worrisome that also AFRs are (increasingly) observed in dust. As a result of the presence of (A)FRs in (house) dust, the frequent hand to mouth exposure is the most significant route of exposure in toddlers and crawling infants. However, due to accumulation of toxicants in fatty tissues and excretion *via* milk, breast-fed children with a developing nervous system are also (highly) exposed *via* human milk. Additional developmental neurotoxicity testing for the AFRs is therefore of utmost importance prior to large-scale use.

3.4. Blood–brain- and placental barrier

To protect the brain from injury by toxicants, the blood–brain barrier (BBB) separates the circulating blood from the extracellular fluid in the brain. The blood vessels in the brain tightly regulate the movement of molecules, ions, and cells between blood and brain tissue, as the brain needs highly specific ionic concentrations for proper neuronal function. Most of the properties of the BBB are manifested within the endothelial cells that form the walls of the blood vessels (Daneman, 2012). These cells are highly polarized and held together by tight junctions that greatly limit the movement of molecules and ions between blood and brain cells. Consequently, large and hydrophilic molecules are hardly able to enter the brain, whereas small and lipophilic molecules are much more likely to pass this barrier. Additionally, many molecules will be excluded from passing the BBB by efflux transporters (Loscher and Potschka, 2005). Also, the endothelial cells are covered by a glycocalyx, a complex mixture of carbohydrates, which acts as a primary barrier providing a charge/size-selective sieve that limits the interactions of molecules and cells with the endothelium (Van Teeffelen et al., 2007). No data are available on the presence of BFRs or AFRs in human brain tissue. However, some *in vivo* animal data exist and one recent study describes how PCBs may alter the BBB integrity in rats, which is suggested to be caused by cytoskeletal rearrangements and disappearance of tight junction proteins (Selvakumar et al., 2013). Additionally, a recent study indicates that BDE-47 and HBCDD both breach the BBB and accumulate in the juvenile mouse brain (Rasinger et al., 2014). In conclusion, toxicants may thus directly or indirectly affect the BBB, resulting in entering of toxicants into the brain were they may exert their adverse effects.

The placental barrier acts as a membrane between the maternal and fetal blood circulation. The transfer of any compound from the maternal to the fetal circulation involves transport across a brush border membrane, followed by transport across a basal membrane. As mentioned before, binding to plasma proteins decreases the placental transport of toxicants since generally only unbounded toxicants can pass the placental barrier. The transport of toxicants may either be passive or active *via* one of the transporters in the placenta. Clearly, toxicants with low molecular weight and high lipophilicity are more likely to pass the placental barrier by passive diffusion. Notably, the human placenta is able to metabolize toxicants *e.g. via* cytochrome P-450 enzymes, potentially increasing the neurotoxic potential. During the postnatal period, (A)FRs are transferred from the nursing mother to the child *via* human milk. Exposure to (A)FRs during (early) brain development may thus be significant, which argues for additional research and risk assessments.

4. Summary and recommendations

The toxicological and ecological concerns associated with BFRs argue for replacement by safer alternatives. Besides effects on the (developing) nervous system, the reviewed experimental animal and human epidemiological studies indicate several other adverse effects on (human) health and – at least for PBDEs –toxicologically relevant concentrations have been observed in the environment. The lessons learned from the significant adverse health effects of BFRs clearly show the need for a full (eco)toxicological risk assessment before new FRs are commercially introduced on the market and used on a large scale. To protect human health and the environment, it is of the highest importance to first thoroughly investigate the persistence, bioaccumulation and toxicity of such new FRs. From a human health point of view it is important to emphasize that a wide variety of environmental and toxicological properties should be assessed. These factors should at least include acute versus chronic low-dose exposure, bioactivation, bioconcentration factors, biodistribution, differences in susceptibility between adults and developing children, interaction with other pollutants (mixtures) and quantitative exposure pathways *via* multiple sources like dust and food. Besides conventional neurotoxicity tests like determining *in vivo* (neuro)behavioral effects, and *in vitro* cytotoxicity and Ca^{2+}-homeostasis, an increasing number of studies rely on alternative species, such as zebrafish. These studies have proven to be easy, fast and useful for investigating (developmental) neurotoxicity. Some zebrafish studies on BFRs and halogenated OPFRs already exist and the number of studies steadily increases.

With respect to neurotoxicity, this review is intended as a first step in the search for safer alternatives. Based on the reviewed *in vitro* and *in vivo* neurotoxic endpoints, the AFRs are classified as shown in Table 5 and demonstrate that some AFRs could be suitable for further testing and ultimately substitute BFRs. However, the potential suitability of the AFRs described in this review is based almost exclusively on neurotoxicity data, while for a complete risk assessment a broader set

of data (*e.g.* including data on other vulnerable targets like the (neuro)-endocrine system) is essential. In addition, effects on the environment (distribution, effects on ecosystems, *etc.*) should be taken into account. From a consumer safety perspective, the application (*e.g.* plastic housings of electronic equipment, textile coatings and polymers), flame retardant capacity, and financial benefits of the different AFRs should not be ignored either. Notably, the *in vivo* relevance of this classification ultimately depends on actual human systemic levels of these AFRs, which are – so far – unknown for most reviewed compounds. In addition, it is important to note that classification of the neurotoxic potential of both BFRs and AFRs was done without weighing the different endpoints. Moreover, this rank order is derived from studies that did show neurotoxic effects of FRs and by doing so largely excluded those studies that did not find an effect, whereas there likely already is a (strong) publication-bias towards studies that do show effects of FRs. Yet, those studies that did not show an effect of FRs, must not be ignored in any quantitative risk assessment. In fact, future quantitative risk assessments must take them into account and judge their credibility by the same criteria that are applied to 'effect-studies' in any regulatory decisions to be made.

In general, an overall scarcity of exposure and toxicological data is currently hampering proper risk assessment and clearly more research is needed to obtain a full toxicological profile of the AFRs. The scarcity of data also emphasizes the need for caution with respect to the large scale use of these not yet fully characterized flame retardants.

Transparency document

The Transparency document associated with this article can be found, in the online version.

References

Abb, M., Stahl, B., Lorenz, W., 2011. Analysis of brominated flame retardants in house dust. Chemosphere 85, 1657–1663.

Abdallah, M.A., Harrad, S., 2011. Tetrabromobisphenol-A, hexabromocyclododecane and its degradation products in UK human milk: relationship to external exposure. Environ. Int. 37, 443–448.

Abdallah, M.A., Harrad, S., 2014. Polybrominated diphenyl ethers in UK human milk: implications for infant exposure and relationship to external exposure. Environ. Int. 63, 130–136.

Abou-Donia, M.B., 1981. Organophosphorus ester-induced delayed neurotoxicity. Annu. Rev. Pharmacol. Toxicol. 21, 511–548.

Abou-Donia, M.B., Nomeir, A.A., Bower, J.H., Makkawy, H.A., 1990. Absorption, distribution, excretion and metabolism of a single oral dose of [14C]tri-o-cresyl phosphate (TOCP) in the male rat. Toxicology 65, 61–74.

Clean Production Action, Rossi, M., Heine, L., 2007. The Green Screen for Safer Chemicals: Evaluating Flame Retardants for TV Enclosures. Version 1.0. p. 17.

Adgent, M.A., Hoffman, K., Goldman, B.D., Sjödin, A., Daniels, J.L., 2014. Brominated flame retardants in breast milk and behavioural and cognitive development at 36 months. Paediatr. Perinat. Epidemiol. 28, 48–57.

Agency, I.E.P., 2007. Report on Alternatives to the Flame Retardant DecaBDE: Evaluation of Toxicity, Availability, Affordability, and Fire Safety Issues — A Report to the Governor and the General Assembly.

Al-Mousa, F., Michelangeli, F., 2012. Some commonly used brominated flame retardants cause Ca^{2+}-ATPase inhibition, beta-amyloid peptide release and apoptosis in SH-SY5Y neuronal cells. PLoS One 7, e33059.

Araki, A., Saito, I., Kanazawa, A., Morimoto, K., Nakayama, K., Shibata, E., Tanaka, M., Takigawa, T., Yoshimura, T., Chikara, H., Saijo, Y., Kishi, R., 2014. Phosphorus flame retardants in indoor dust and their relation to asthma and allergies of inhabitants. Indoor Air 24, 3–15.

Bailey, J., Levin, E., 2015. The neurobehavioral toxicity of FireMaster 550® in zebrafish (*Danio rerio*): chronic developmental and acute adolescent exposures. Neurotoxicol. Teratol. 49, 118.

Bailey, J., Oliveri, A., Levin, E.D., 2013. Zebrafish model systems for developmental neurobehavioral toxicology. Birth Defects Res. C Embryo Today Rev. 99, 14–23.

Ballesteros-Gómez, A., Brandsma, S.H., de Boer, J., Leonards, P.E.G., 2014. Analysis of two alternative organophosphorus flame retardants in electronic and plastic consumer products: resorcinol bis-(diphenylphosphate) (PBDPP) and bisphenol A bis (diphenylphosphate) (BPA-BDPP). Chemosphere 116, 10–14.

Bayer Material Science, 2010. Prüfung auf Neurotoxische Wirkung bei Hühnern. Diphenylcresylphosphate (CAS# 26444–49–5).

Behl, M., Hsieh, J., Shafer, T.J., Mundy, W.R., Rice, J.R., Boyd, W.A., Freedman, J.H., Hunter, E.S., Jarema, K., Padilla, S.S., Tice, R.R., 2015. Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity. Neurotoxicol. Teratol. 52, 181–193.

Berghuis, S.A., Soechitram, S.D., Hitzert, M.M., Sauer, P.J.J., Bos, A.F., 2013. Prenatal exposure to polychlorinated biphenyls and their hydroxylated metabolites is associated with motor development of three-month-old infants. Neurotoxicology 38, 124–130.

Bergman, Å., Rydén, A., Law, R.J., de Boer, J., Covaci, A., Alaee, M., Birnbaum, L., Petreas, M., Rose, M., Sakai, S., Van den Eede, N., van der Veen, I., 2012. A novel abbreviation standard for organobromine, organochlorine and organophosphorus flame retardants and some characteristics of the chemicals. Environ. Int. 49, 57–82.

Bilkei-Gorzo, A., 1993. Neurotoxic effect of enteral aluminium. Food Chem. Toxicol. 31, 357–361.

Bingham, E., Cohrssen, B., Powell, C.H., 2001. Patty's Toxicology. Patty's Toxicology. John Wiley & Sons, New York, p. V6 967.

Blum, A., Gold, M.D., Ames, B.N., Jones, F.R., Hett, E.A., Dougherty, R.C., Horning, E.C., Dzidic, I., Carroll, D.I., Stillwell, R.N., Thenot, J.P., 1978. Children absorb Tris–BP flame retardant from sleepwear: urine contains the mutagenic metabolite, 2,3-dibromopropanol. Science 201, 1020–1023.

Blumbach, K., Pahler, A., Deger, H.M., Dekant, W., 2000. Biotransformation and male rat-specific renal toxicity of diethyl ethyl- and dimethyl methylphosphonate. Toxicol. Sci. 53, 24–32.

Bomhard, E.M., Krinke, G.J., Rossberg, W.M., Skripsky, T., 1997. Trimethylphosphate: a 30-month chronic toxicity/carcinogenicity study in Wistar rats with administration in drinking water. Fundam. Appl. Toxicol. 40, 75–89.

Boon, J.P., Lewis, W.E., Tjoen-A-Choy, M.R., Allchin, C.R., Law, R.J., de Boer, J., ten Hallers-Tjabbes, C.C., Zegers, B.N., 2002. Levels of polybrominated diphenyl ether (PBDE) flame retardants in animals representing different trophic levels of the North Sea food web. Environ. Sci. Technol. 36, 4025–4032. http://dx.doi.org/10.1021/es0158298.

Bowers, W.J., Wall, P.M., Nakai, J.S., Wade, M., Li, N., Yagminas, A., 2015. Behavioural and thyroid effects of *in utero* and lactational exposure of Sprague Dawley rats to the polybrominated diphenyl ethers mixture DE71. Neurotoxicol. Teratol. 52, 127–142.

Bradley, M., Rutkiewicz, J., Mittal, K., Fernie, K., Basu, N., 2015. *In ovo* exposure to organophosphorous flame retardants: survival, developmente, neurochemical, and behavioral changes in white leghorn chickens. Neurotoxicol. Teratol. 52, 228–235.

Bradner, J.M., Suragh, T.A., Caudle, W.M., 2013. Alterations to the circuitry of the frontal cortex following exposure to the polybrominated diphenyl ether mixture, DE-71. Toxicology 312C, 48–55.

Brandsma, S.H., de Boer, J., van Velzen, M.J.M., Leonards, P.E.G., 2014. Organophosphorus flame retardants (PFRs) and plasticizers in house and car dust and the influence of electronic equipment. Chemosphere 116, 3–9.

Brandsma, S.H., Leonards, P.E.G., Leslie, H.A., de Boer, J., 2015. Tracing organophosphorus and brominated flame retardants and plasticizers in an estuarine food web. Sci. Total Environ. 505, 22–31.

Brandsma, S.H., Sellstrom, U., de Wit, C.A., de Boer, J., Leonards, P.E.G., 2013. Dust measurement of two organophosphorus flame retardants, resorcinol bis(diphenylphosphate) (RBDPP) and bisphenol A bis(diphenylphosphate) (BPA-BDPP), used as alternatives for BDE-209. Environ. Sci. Technol. 47, 14434–14441.

Brommer, S., Harrad, S., Van den Eede, N., Covaci, A., 2012. Concentrations of organophosphate esters and brominated flame retardants in German indoor dust samples. J. Environ. Monit. 14, 2482–2487.

Brown, D.R., Murphy, S.D., 1971. Metabolic factors which influence triethyl phosphate-induced narcosis in rats. J. Pharmacol. Exp. Ther. 179, 396–403.

Buratovic, S., Viberg, H., Fredriksson, A., Eriksson, P., 2014. Developmental exposure to the polybrominated diphenyl ether PBDE 209: neurobehavioural and neuroprotein analysis in adult male and female mice. Environ. Toxicol. Pharmacol. 38, 570–585.

Butt, C.M., Congleton, J., Hoffman, K., Fang, M., Stapleton, H.M., 2014. Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. Environ. Sci. Technol. 48, 10432–10438.

Cariou, R., Antignac, J.P., Zalko, D., Berrebi, A., Cravedi, J.P., Maume, D., Marchand, P., Monteau, F., Riu, A., Andre, F., Le Bizec, B., 2008. Exposure assessment of French women and their newborns to tetrabromobisphenol-A: occurrence measurements in maternal adipose tissue, serum, breast milk and cord serum. Chemosphere 73, 1036–1041.

Carlson, K., Ehrich, M., 2001. Organophosphorus compounds alter intracellular F-actin content in SH-SY5Y human neuroblastoma cells. Neurotoxicology 22, 819–827.

Carrington, C.D., 1989. Prophylaxis and the mechanism for the initiation of organophosphorous compound-induced delayed neurotoxicity. Arch. Toxicol. 63, 165–172.

Carrington, C.D., Lapadula, D.M., Othman, M., Farr, C., Nair, R.S., Johannsen, F., Abou-Donia, M.B., 1990. Assessment of the delayed neurotoxicity of tributyl phosphate, tributoxyethyl phosphate, and dibutylphenyl phosphate. Toxicol. Ind. Health 6, 415–423.

Cascieri, T., MacKellar, F., 1978. Abstracts of papers for the seventeenth annual meeting of the Society of Toxicology, San Francisco, California March 12–16, 1978. Toxicol. Appl. Pharmacol. 45, 219–362.

Cequier, E., Sakhi, A.K., Marcé, R.M., Becher, G., Thomsen, C., 2015. Human exposure pathways to organophosphate triesters — a biomonitoring study of mother–child pairs. Environ. Int. 75, 159–165.

Chang, P.A., Wu, Y.J., 2006. Effect of tri-o-cresyl phosphate on cytoskeleton in human neuroblastoma SK-N-SH cell. Mol. Cell. Biochem. 290, 145–151.

Chen, X., Huang, C., Wang, X., Chen, J., Bai, C., Chen, Y., Chen, X., Dong, Q., Yang, D., 2012. BDE-47 disrupts axonal growth and motor behavior in developing zebrafish. Aquat. Toxicol. 120–121, 35–44.

Chen, J., Liufu, C., Sun, W., Sun, X., Chen, D., 2010. Assessment of the neurotoxic mechanisms of decabrominated diphenyl ether (PBDE-209) in primary cultured neonatal rat hippocampal neurons includes alterations in second messenger signaling and oxidative stress. Toxicol. Lett. 192, 431–439.

Chen, J., Sun, Y., Wang, P., Long, D., Li, W., Li, L., Wu, Y., 2013. Induction of autophagy by TOCP in differentiated human neuroblastoma cells lead to degradation of cytoskeletal components and inhibition of neurite outgrowth. Toxicology 310, 92–97.
Chen, A., Yolton, K., Rauch, S.A., Webster, G.M., Hornung, R., Sjodin, A., Dietrich, K.N., Lanphear, B.P., 2014. Prenatal polybrominated diphenyl ether exposures and neurodevelopment in U.S. children through 5 years of age: the HOME Study. Environ. Health Perspect. 122, 856–862.
Chou, C., Hsiao, Y., Ko, F., Cheng, J., Cheng, Y., Chen, T., 2010. Chronic exposure of 2,2′,4,4′-tetrabromodiphenyl ether (PBDE-47) alters locomotion behavior in juvenile zebrafish (*Danio rerio*). Aquat. Toxicol. 98, 388–395.
Cima, F. (2011). Tin: environmental pollution and health effects. In Encyclopedia of Environmental Health (Jerome O. Nriagu, Ed.) pp 351–359. Elsevier, Burlington.
Clariant, 2010. Human Health and Environmental Fact Sheet — Ammonium Polyphosphate (Exolit AP422).
Cope, R.B., Kacew, S., Dourson, M., 2015. A reproductive, developmental and neurobehavioral study following oral exposure of tetrabromobisphenol A on Sprague–Dawley rats. Toxicology 329, 49–59.
Costa, L.G., Giordano, G., 2007. Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. Neurotoxicology 28, 1047–1067.
Costa, L.G., Giordano, G., 2011. Is decabromodiphenyl ether (BDE-209) a developmental neurotoxicant? Neurotoxicology 32, 9–24.
Costa, L.G., de Laat, R., Tagliaferri, S., Pellacani, C., 2013. A mechanistic view of polybrominated diphenyl ether (PBDE) developmental neurotoxicity. Toxicol. Lett. 230, 282–294.
Cowell, W.J., Lederman, S.A., Sjodin, A., Jones, R., Wang, S., Perera, F., Wang, R., Rauh, V.A., Herbstman, J., 2015. Prenatal exposure to polybrominated diphenyl ethers and child behavior at 3–7 years. Neurotoxicol. Teratol. 52, 143–150.
Craig, P.H., 1999. Evaluation of the hazards of industrial exposure to tricresyl phosphate:a review and interpretation of the literature. J. Toxicol. Environ. Health B 2, 281–300.
Crump, D., Chiu, S., Kennedy, S.W., 2012. Effects of Tris(1,3-dichloro-2-propyl) phosphate and Tris(1-chloropropyl) phosphate on cytotoxicity and mRNA expression in primary cultures of avian hepatocytes and neuronal cells. Toxicol. Sci. 126, 140–148.
D'Hulst, C., Atack, J.R., Kooy, R.F., 2009. The complexity of the $GABA_A$ receptor shapes unique pharmacological profiles. Drug Discov. Today 14, 866–875.
Daneman, R., 2012. The blood–brain barrier in health and disease. Ann. Neurol. 72, 648–672.
Davies, D.R., Holland, P., Rumens, M.J., 1960. The relationship between the chemical structure and neurotoxicity of alkyl organophosphorus compounds. Br. J. Pharmacol. Chemother. 15, 271–278.
de Perio, M.A., Durgam, S., Caldwell, K.L., Eisenberg, J., 2010. A health hazard evaluation of antimony exposure in fire fighters. J. Occup. Environ. Med. 52, 81–84.
de Wit, C.A., Björklund, J.A., Thuresson, K., 2012. Tri-decabrominated diphenyl ethers and hexabromocyclododecane in indoor air and dust from Stockholm microenvironments 2: indoor sources and human exposure. Environ. Int. 39, 141–147.
de Wit, C.A., Herzke, D., Vorkamp, K., 2010. Brominated flame retardants in the Arctic environment — trends and new candidates. Sci. Total Environ. 408, 2885–2918.
deBruyn, A.M., Gobas, F.A., 2007. The sorptive capacity of animal protein. Environ. Toxicol. Chem. 26, 1803–1808.
Deichmann, W.B., Witherup, S., 1946. Observations on the effects of trimethyl phosphate upon experimental animals. J. Pharmacol. Exp. Ther. 88, 338–342.
Dingemans, M.M., de Groot, A., van Kleef, R.G., Bergman, A., van den Berg, M., Vijverberg, H.P., Westerink, R.H., 2008. Hydroxylation increases the neurotoxic potential of BDE-47 to affect exocytosis and calcium homeostasis in PC12 cells. Environ. Health Perspect. 116, 637–643.
Dingemans, M.M., Heusinkveld, H.J., Bergman, A., van den Berg, M., Westerink, R.H., 2010. Bromination pattern of hydroxylated metabolites of BDE-47 affects their potency to release calcium from intracellular stores in PC12 cells. Environ. Health Perspect. 118, 519–525.
Dingemans, M.M., Heusinkveld, H.J., de Groot, A., Bergman, A., van den Berg, M., Westerink, R.H., 2009. Hexabromocyclododecane inhibits depolarization-induced increase in intracellular calcium levels and neurotransmitter release in PC12 cells. Toxicol. Sci. 107, 490–497.
Dingemans, M.M., Ramakers, G.M., Gardoni, F., van Kleef, R.G., Bergman, A., Di Luca, M., van den Berg, M., Westerink, R.H., Vijverberg, H.P., 2007. Neonatal exposure to brominated flame retardant BDE-47 reduces long-term potentiation and postsynaptic protein levels in mouse hippocampus. Environ. Health Perspect. 115, 865–870.
Dingemans, M.M., van den Berg, M., Westerink, R.H., 2011. Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. Environ. Health Perspect. 119, 900–907.
Dishaw, L.V., Hunter, D.L., Padnos, B., Padilla, S., Stapleton, H.M., 2014. Developmental exposure to organophosphate flame retardants elicits overt toxicity and alters behavior in early life stage zebrafish (*Danio rerio*). Toxicol. Sci. 142, 445–454.
Dishaw, L.V., Powers, C.M., Ryde, I.T., Roberts, S.C., Seidler, F.J., Slotkin, T.A., Stapleton, H.M., 2011. Is the PentaBDE replacement, Tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. Toxicol. Appl. Pharmacol. 256, 281–289.
Dodson, R.E., Perovich, L.J., Covaci, A., Van den Eede, N., Ionas, A.C., Dirtu, A.C., Brody, J.G., Rudel, R.A., 2012. After the PBDE phase-out: a broad suite of flame retardants in repeat house dust samples from California. Environ. Sci. Technol. 46, 13056–13066.
Dodson, R.E., Van den Eede, N., Covaci, A., Perovich, L.J., Brody, J.G., Rudel, R.A., 2014. Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. Environ. Sci. Technol. 48, 13625–13633.
Domingo, J.L., 2004. Human exposure to polybrominated diphenyl ethers through the diet. J. Chromatogr. A 1054, 321–326.
Domingo, J.L., 2012. Polybrominated diphenyl ethers in food and human dietary exposure: a review of the recent scientific literature. Food Chem. Toxicol. 50, 238–249.
Du, M., Zhang, D., Yan, C., Zhang, X., 2012. Developmental toxicity evaluation of three hexabromocyclododecane diastereoisomers on zebrafish embryos. Aquat. Toxicol. 112–113, 1–10.
Eriksson, P., Fischer, C., Wallin, M., Jakobsson, E., Fredriksson, A., 2006. Impaired behaviour, learning and memory, in adult mice neonatally exposed to hexabromocyclododecane (HBCDD). Environ. Toxicol. Pharmacol. 21, 317–322.
Eriksson, P., Jakobsson, E., Fredriksson, A., 2001. Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? Environ. Health Perspect. 109, 903–908.
Eriksson, P., Viberg, H., Jakobsson, E., Örn, U., Fredriksson, A., 2002. A brominated flame retardant, 2,2′,4,4′,5-pentabromodiphenyl ether: uptake, retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. Toxicol. Sci. 67, 98–103.
Eskenazi, B., Chevrier, J., Rauch, S.A., Kogut, K., Harley, K.G., Johnson, C., Trujillo, C., Sjodin, A., Bradman, A., 2013. *In utero* and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. Environ. Health Perspect. 121, 257–262.
Eto, M., Casida, J.E., Eto, T., 1962. Hydroxylation and cyclization reactions involved in the metabolism of tri-o-cresyl phosphate. Biochem. Pharmacol. 11, 337–352.
European Chemicals Agency, 2015. ECHA Database.
European Union, 2006. Regulation (EC) No 1907/2006 of the European Parliament and of the Council Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Establishing a European Chemicals Agency.
Fan, C., Besas, J., Kodavanti, P.R.S., 2010. Changes in mitogen-activated protein kinase in cerebellar granule neurons by polybrominated diphenyl ethers and polychlorinated biphenyls. Toxicol. Appl. Pharmacol. 245, 1–8.
Fan, X., Kubwabo, C., Rasmussen, P.E., Wu, F., 2014. Simultaneous determination of thirteen organophosphate esters in settled indoor house dust and a comparison between two sampling techniques. Sci. Total Environ. 491-492, 80–86.
Fang, M., Webster, T.F., Gooden, D., Cooper, E.M., McClean, M.D., Carignan, C., Makey, C., Stapleton, H.M., 2012. Investigating a novel flame retardant known as V6: measurements in baby products, house dust, and car dust. Environ. Sci. Technol. 47, 4449–4454.
Flaskos, J., McLean, W.G., Fowler, M.J., Hargreaves, A.J., 1998. Tricresyl phosphate inhibits the formation of axon-like processes and disrupts neurofilaments in cultured mouse N2a and rat PC12 cells. Neurosci. Lett. 242, 101–104.
Föllmann, W., Wober, J., 2006. Investigation of cytotoxic, genotoxic, mutagenic, and estrogenic effects of the flame retardants tris-(2-chloroethyl)-phosphate (TCEP) and tris-(2-chloropropyl)-phosphate (TCPP) *in vitro*. Toxicol. Lett. 161, 124–134.
Fonnum, F., Mariussen, E., 2009. Mechanisms involved in the neurotoxic effects of environmental toxicants such as polychlorinated biphenyls and brominated flame retardants. J. Neurochem. 111, 1327–1347.
Fowler, M.J., Flaskos, J., McLean, W.G., Hargreaves, A.J., 2001. Effects of neuropathic and non-neuropathic isomers of tricresyl phosphate and their microsomal activation on the production of axon-like processes by differentiating mouse N2a neuroblastoma cells. J. Neurochem. 76, 671–678.
Freudenthal, R.I., McDonald, L.J., Johnson, J.V., McCormick, D.L., Henrich, R.T., 2000. Comparative metabolism and toxicokinetics of ^{14}C-Resorcinol bis-diphenylphosphate (RDP) in the rat, mouse, and monkey. Int. J. Toxicol. 19, 233–242.
Fromme, H., Hilger, B., Kopp, E., Miserok, M., Volkel, W., 2014a. Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and "novel" brominated flame retardants in house dust in Germany. Environ. Int. 64, 61–68.
Fromme, H., Lahrz, T., Kraft, M., Fembacher, L., Mach, C., Dietrich, S., Burkardt, R., Völkel, W., Göen, T., 2014b. Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). Environ. Int. 71, 158–163.
Gant, D.B., Eldefrawi, M.E., Eldefrawi, A.T., 1987. Action of organophosphates on $GABA_A$ receptor and voltage-dependent chloride channels. Fundam. Appl. Toxicol. 9, 698–704.
Gao, P., He, P., Wang, A., Xia, T., Xu, B., Xu, Z., Niu, Q., Guo, L., Chen, X., 2009. Influence of PCB153 on oxidative DNA damage and DNA repair-related gene expression induced by PBDE-47 in human neuroblastoma cells *in vitro*. Toxicol. Sci. 107, 165–170.
Garcia-Reyero, N., Escalon, B.L., Prats, E., Stanley, J.K., Thienpont, B., Melby, N.L., Baron, E., Eljarrat, E., Barcelo, D., Mestres, J., Babin, P.J., Perkins, E.J., Raldua, D., 2014. Effects of BDE-209 contaminated sediments on zebrafish development and potential implications to human health. Environ. Int. 63, 216–223.
Gassmann, K., Schreiber, T., Dingemans, M.M., Krause, G., Roderigo, C., Giersiefer, S., Schuwald, J., Moors, M., Unfried, K., Bergman, A., Westerink, R.H., Rose, C.R., Fritsche, E., 2014. BDE-47 and 6-OH-BDE-47 modulate calcium homeostasis in primary fetal human neural progenitor cells *via* ryanodine receptor-independent mechanisms. Arch. Toxicol. 88, 1537–1548.
Gee, J.R., Moser, V.C., 2008. Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. Neurotoxicol. Teratol. 30, 79–87.
Genskow, K.R., Bradner, J.M., Hossain, M.M., Richardson, J.R., Michael Caudle, W., 2015. Selective damage to dopaminergic transporters following exposure to the brominated flame retardant, HBCDD. Neurotoxicol. Teratol. 52, 162–169.
German Federal Environmental Agency, Leisewitz, A., Kruse, H., Schramm, E., 2001. Substituting Environmentally Relevant Flame Retardants: Assessment Fundamentals — Results and Summary Overview.
Gulden, M., Morchel, S., Tahan, S., Seibert, H., 2002. Impact of protein binding on the availability and cytotoxic potency of organochlorine pesticides and chlorophenols *in vitro*. Toxicology 175, 201–213.

Gumbmann, M.R., Gagné, W.E., Williams, S.N., 1968. Short-term toxicity studies of rats fed triethyl phosphate in the diet. Toxicol. Appl. Pharmacol. 12, 360–371.

Hamers, T., Kamstra, J.H., Sonneveld, E., Murk, A.J., Kester, M.H., Andersson, P.L., Legler, J., Brouwer, A., 2006. *In vitro* profiling of the endocrine-disrupting potency of brominated flame retardants. Toxicol. Sci. 92, 157–173.

Han, Z., Wang, Q., Fu, J., Chen, H., Zhao, Y., Zhou, B., Gong, Z., Wei, S., Li, J., Liu, H., Zhang, X., Liu, C., Yu, H., 2014. Multiple bio-analytical methods to reveal possible molecular mechanisms of developmental toxicity in zebrafish embryos/larvae exposed to tris(2-butoxyethyl) phosphate. Aquat. Toxicol. 150, 175–181.

Hartmann, P.C., Bürgi, D., Giger, W., 2004. Organophosphate flame retardants and plasticizers in indoor air. Chemosphere 57, 781–787.

Hausherr, V., van Thriel, C., Krug, A., Leist, M., Schobel, 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, 274–284.

He, P., Wang, A., Xia, T., Gao, P., Niu, Q., Guo, L., Xu, B., Chen, X., 2009. Mechanism of the neurotoxic effect of PBDE-47 and interaction of PBDE-47 and PCB153 in enhancing toxicity in SH-SY5Y cells. Neurotoxicology 30, 10–15.

He, J., Yang, D., Wang, C., Liu, W., Liao, J., Xu, T., Bai, C., Chen, J., Lin, K., Huang, C., Dong, Q., 2011. Chronic zebrafish low dose decabrominated diphenyl ether (BDE-209) exposure affected parental gonad development and locomotion in F1 offspring. Ecotoxicology 20, 1813–1822.

Hendriks, H.S., Koolen, L.A., Dingemans, M.M., Viberg, H., Lee, I., Leonards, P.E., Ramakers, G.M., Westerink, R.H., 2014a. Effects of neonatal exposure to the flame retardant tetrabromobisphenol-A, aluminum diethylphosphinate or zinc stannate on long-term potentiation and synaptic protein levels in mice. Arch. Toxicol. http://dx.doi.org/10.1007/s00204-014-1366-8 (in press).

Hendriks, H.S., Meijer, M., Muilwijk, M., van den Berg, M., Westerink, R.H., 2014b. A comparison of the *in vitro* cyto- and neurotoxicity of brominated and halogen-free flame retardants: prioritization in search for safe(r) alternatives. Arch. Toxicol. 88, 857–869.

Hendriks, H.S., van Kleef, R.G., Westerink, R.H., 2012b. Modulation of human $\alpha_4\beta_2$ nicotinic acetylcholine receptors by brominated and halogen-free flame retardants as a measure for *in vitro* neurotoxicity. Toxicol. Lett. 213, 266–274.

Hendriks, H.S., van Kleef, R.G., van den Berg, M., Westerink, R.H., 2012a. Multiple novel modes of action involved in the *in vitro* neurotoxic effects of tetrabromobisphenol-A. Toxicol. Sci. 128, 235–246.

Hendriks, H.S., Antunes Fernandes, E.C., Bergman, A., van den Berg, M., Westerink, R.H., 2010. PCB-47, PBDE-47, and 6-OH-PBDE-47 differentially modulate human $GABA_A$ and $\alpha_4\beta_2$ nicotinic acetylcholine receptors. Toxicol. Sci. 118, 635–642.

Henrich, R., Ryan, B.M., Selby, R., Garthwaite, S., Morrissey, R., Freudenthal, R.I., 2000. Two-generation oral (diet) reproductive toxicity study of resorcinol bis-diphenylphosphate (Fyrolflex RDP) in rats. Int. J. Toxicol. 19, 243–255.

Henschler, D., 1958. Tricresylphosphate poisoning; experimental clarification of problems of etiology and pathogenesis. Klin. Wochenschr. 36, 663–674.

Henschler, D., Schmuck, G., van Aerssen, M., Schiffmann, D., 1992. The inhibitory effect of neuropathic organophosphate esters on neurite outgrowth in cell cultures: a basis for screening for delayed neurotoxicity. Toxicol. in Vitro 6, 327–335.

Herbstman, J.B., Mall, J.K., 2014. Developmental exposure to polybrominated diphenyl ethers and neurodevelopment. Curr. Environ. Health Rep. 1, 101–112.

Herbstman, J.B., Sjodin, A., Kurzon, M., Lederman, S.A., Jones, R.S., Rauh, V., Needham, L.L., Tang, D., Niedzwiecki, M., Wang, R.Y., Perera, F., 2010. Prenatal exposure to PBDEs and neurodevelopment. Environ. Health Perspect. 118, 712–719.

Herr, D.W., Sanders, J.M., Matthews, H.B., 1991. Brain distribution and fate of tris(2-chloroethyl) phosphate in Fischer 344 rats. Drug Metab. Dispos. 19, 436–442.

Hestermann, E.V., Stegeman, J.J., Hahn, M.E., 2000. Serum alters the uptake and relative potencies of halogenated aromatic hydrocarbons in cell culture bioassays. Toxicol. Sci. 53, 316–325.

Hisae, O., Shinshi, O., Kogo, H., 1980. Toxicity of tri-n-butyl phosphate, with special reference to organ weights, serum components and cholinesterase activity in male rats. Toxicol. Lett. 6, 81–85.

Hoffman, K., Daniels, J.L., Stapleton, H.M., 2014. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. Environ. Int. 63, 169–172.

Hollingshaus, J.G., Armstrong, D., Toia, R.F., McCloud, L., Fukuto, T.R., 1981. Delayed toxicity and delayed neurotoxicity of phosphonothioate and phosphonothioate esters. J. Toxicol. Environ. Health 8, 619–627.

Huang, S.C., Giordano, G., Costa, L.G., 2010. Comparative cytotoxicity and intracellular accumulation of five polybrominated diphenyl ether congeners in mouse cerebellar granule neurons. Toxicol. Sci. 114, 124–132.

Hubbard, C.M., Redpath, G.T., Macdonald, T.L., VandenBerg, S.R., 1989. Modulatory effects of aluminum, calcium, lithium, magnesium, and zinc ions on [^{3}H]MK-801 binding in human cerebral cortex. Brain Res. 486, 170–174.

Iavicoli, I., Caroli, S., Alimonti, A., Petrucci, F., Carelli, G., 2002. Biomonitoring of a worker population exposed to low antimony trioxide levels. J. Trace Elem. Med. Biol. 16, 33–39.

Ionas, A.C., Dirtu, A.C., Anthonissen, T., Neels, H., Covaci, A., 2014. Downsides of the recycling process: harmful organic chemicals in children's toys. Environ. Int. 65, 54–62.

Jarema, K.A., Hunter, D.L., Shaffer, R.M., Behl, M., Padilla, S., 2015. Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish. Neurotoxicol. Teratol. 52, 194–209.

Jiang, C., Zhang, S., Liu, H., Zeng, Q., Xia, T., Chen, Y., Kuang, G., Zhao, G., Wu, X., Zhang, X., Wang, A., 2012. The role of the IRE1 pathway in PBDE-47-induced toxicity in human neuroblastoma SH-SY5Y cells *in vitro*. Toxicol. Lett. 211, 325–333.

Jinhui, L., Yuan, C., Wenjing, X., 2015. Polybrominated diphenyl ethers in articles: a review of its applications and legislation. Environ. Sci. Pollut. Res. Int.

Johannsen, F.R., Wright, P.L., Gordon, D.E., Levinskas, G.J., Radue, R.W., Graham, P.R., 1977. Evaluation of delayed neurotoxicity and dose–response relationships of phosphate esters in the adult hen. Toxicol. Appl. Pharmacol. 41, 291–304.

Johansson, N., Viberg, H., Fredriksson, A., Eriksson, P., 2008. Neonatal exposure to decabrominated diphenyl ether (PBDE 209) causes dose–response changes in spontaneous behaviour and cholinergic susceptibility in adult mice. Neurotoxicology 29, 911–919.

Johnson, M.K., Lotti, M., 1980. Delayed neurotoxicity caused by chronic feeding of organophosphates requires a high-point of inhibition of neurotoxic esterase. Toxicol. Lett. 5, 99–102.

Johnson, P.I., Stapleton, H.M., Sjodin, A., Meeker, J.D., 2010. Relationships between polybrominated diphenyl ether concentrations in house dust and serum. Environ. Sci. Technol. 44, 5627–5632.

Jortner, B.S., Hancock, S.K., Hinckley, J., Flory, L., Colby, L., Tobias, L., Williams, L., Ehrich, M., 2005. Neuropathological studies of rats following multiple exposure to tri-ortho-tolyl phosphate, chlorpyrifos and stress. Toxicol. Pathol. 33, 378–385.

Kanazawa, A., Saito, I., Araki, A., Takeda, M., Ma, M., Saijo, Y., Kishi, R., 2010. Association between indoor exposure to semi-volatile organic compounds and building-related symptoms among the occupants of residential dwellings. Indoor Air 20, 72–84.

Kicinski, M., Viaene, M.K., Den Hond, E., Schoeters, G., Covaci, A., Dirtu, A.C., Nelen, V., Bruckers, L., Croes, K., Sioen, I., Baeyens, W., Van Larebeke, N., Nawrot, T.S., 2012. Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study. Environ. Heal. 11 (86-069X-11-86).

Kim, U., Oh, J., 2014. Tetrabromobisphenol A and hexabromocyclododecane flame retardants in infant–mother paired serum samples, and their relationships with thyroid hormones and environmental factors. Environ. Pollut. 184, 193–200.

Kim, K.H., Bose, D.D., Ghogha, A., Riehl, J., Zhang, R., Barnhart, C.D., Lein, P.J., Pessah, I.N., 2011. Para- and ortho-substitutions are key determinants of polybrominated diphenyl ether activity toward ryanodine receptors and neurotoxicity. Environ. Health Perspect. 119, 519–526.

Kodavanti, P.R., Derr-Yellin, E.C., 2002. Differential effects of polybrominated diphenyl ethers and polychlorinated biphenyls on [^{3}H]arachidonic acid release in rat cerebellar granule neurons. Toxicol. Sci. 68, 451–457.

Kodavanti, P.R., Ward, T.R., 2005. Differential effects of commercial polybrominated diphenyl ether and polychlorinated biphenyl mixtures on intracellular signaling in rat brain *in vitro*. Toxicol. Sci. 85, 952–962.

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, 76–83.

Krikorian, S.E., Chorn, T.A., King, J.W., 1987. Determination of octanol/water partition coefficients of certain organophosphorus compounds using high-performance liquid chromatography. Quant. Struct. Act. Relat. 6, 65–69.

Laham, S., Long, G., Schrader, K., Szabo, J., 1984a. Induction of electrophysiological and morphological changes in Sprague–Dawley rats fed tributoxyethyl phosphate. J. Appl. Toxicol. 4, 42–48.

Laham, S., Szabo, J., Long, G., 1983. Effects of tri-n-butyl phosphate on the peripheral nervous system of the Sprague–Dawley rat. Drug Chem. Toxicol. 6, 363–377.

Laham, S., Szabo, J., Long, G., 1984b. Short term neurotoxicity studies on tributoxyethyl phosphate orally administered to Sprague–Dawley rats. Chemosphere 13, 801–812.

Laham, S., Szabo, J., Long, G., Schrader, K., 1985. Dose–response toxicity studies on tributoxyethyl phosphate orally administered to Sprague–Dawley rats. Am. Ind. Hyg. Assoc. J. 46, 442–448.

LeBel, G.L., Williams, D.T., Berard, D., 1989. Triaryl/alkyl phosphate residues in human adipose autopsy samples from six Ontario municipalities. Bull. Environ. Contam. Toxicol. 43, 225–230.

Lema, S.C., Schultz, I.R., Scholz, N.L., Incardona, J.P., Swanson, P., 2007. Neural defects and cardiac arrhythmia in fish larvae following embryonic exposure to 2,2′,4,4′-tetrabromodiphenyl ether (PBDE 47). Aquat. Toxicol. 82, 296–307.

Li, W., Casida, J.E., 1998. Organophosphorus neuropathy target esterase inhibitors selectively block outgrowth of neurite-like and cell processes in cultured cells. Toxicol. Lett. 98, 139–146.

Li, T., Wang, W., Pan, Y., Xu, L., Xia, Z., 2013. A hydroxylated metabolite of flame-retardant PBDE-47 decreases the survival, proliferation, and neuronal differentiation of primary cultured adult neural stem cells and interferes with signaling of ERK5 MAP kinase and Neurotrophin 3. Toxicol. Sci. 134, 111–124.

Linares, V., Belles, M., Domingo, J.L., 2015. Human exposure to PBDE and critical evaluation of health hazards. Arch. Toxicol. 89, 335–356.

Lonky, E., Reihman, J., Darvill, T., Mather Sr., J., Daly, H., 1996. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J. Great Lakes Res. 22, 198–212.

Lorber, M., 2008. Exposure of Americans to polybrominated diphenyl ethers. J. Expo. Sci. Environ. Epidemiol. 18, 2–19.

Loscher, W., Potschka, H., 2005. Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. Prog. Neurobiol. 76, 22–76.

Lotti, M., Johnson, M.K., 1980. Repeated small doses of a neurotoxic organophosphate. Monitoring of neurotoxic esterase in brain and spinal cord. Arch. Toxicol. 45, 263–271.

Macaulay, L.J., Bailey, J.M., Levin, E.D., Stapleton, H.M., 2015. Persisting effects of a PBDE metabolite, 6-OH-BDE-47, on larval and juvenile zebrafish swimming behavior. Neurotoxicol. Teratol. 52, 119–126.

MacFarland, H.N., Punte Jr., C.L., 1966. Toxicological studies on tri-(2-ethylhexyl)-phosphate. Arch. Environ. Health 13, 13–20.

Madia, F., Giordano, G., Fattori, V., Vitalone, A., Branchi, I., Capone, F., Costa, L.G., 2004. Differential *in vitro* neurotoxicity of the flame retardant PBDE-99 and of the PCB Aroclor 1254 in human astrocytoma cells. Toxicol. Lett. 154, 11–21.

Maine Department of Environmental Protection and Maine Center for Disease Control & Prevention, 2007. Brominated Flame Retardants: Third Annual Report to the Maine Legislature.

Makinen, M.S., Makinen, M.R., Koistinen, J.T., Pasanen, A.L., Pasanen, P.O., Kalliokoski, P.J., Korpi, A.M., 2009. Respiratory and dermal exposure to organophosphorus flame

retardants and tetrabromobisphenol A at five work environments. Environ. Sci. Technol. 43, 941–947.
Mariani, A., Fanelli, R., Re Depaolini, A., De Paola, M., 2015. Decabrominated diphenyl ether and methylmercury impair fetal nervous system development in mice at documented human exposure levels. Dev. Neuropsychol. 75, 23–38.
Marklund, A., Andersson, B., Haglund, P., 2005. Organophosphorus flame retardants and plasticizers in air from various indoor environments. J. Environ. Monit. 7, 814–819.
Matthews, H.B., Dixon, D., Herr, D.W., Tilson, H., 1990. Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicol. Ind. Health 6, 1–15.
Maurice, N., Olry, J., Cariou, R., Dervilly-Pinel, G., Le Bizec, B., Travel, A., Jondreville, C., Schroeder, H., 2015. Short-term effects of a perinatal exposure to the HBCDD α-isomer in rats: assessment of early motor and sensorial development and level of anxiety in pups. Neurotoxicol. Teratol. 52, 170–180.
McGee, S.P., Cooper, E.M., Stapleton, H.M., Volz, D.C., 2012. Early zebrafish embryogenesis is susceptible to developmental TDCPP exposure. Environ. Health Perspect. 120, 1585–1591.
Meeker, J.D., Stapleton, H.M., 2010. House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. Environ. Health Perspect. 118, 318–323.
Meeker, J.D., Cooper, E.M., Stapleton, H.M., Hauser, R., 2013. Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environ. Health Perspect. 121, 580–585.
Mizouchi, S., Ichiba, M., Takigami, H., Kajiwara, N., Takamuku, T., Miyajima, T., Kodama, H., Someya, T., Ueno, D., 2015. Exposure assessment of organophosphorus and organobromine flame retardants *via* indoor dust from elementary schools and domestic houses. Chemosphere 123, 17–25.
Moller, A., Sturm, R., Xie, Z., Cai, M., He, J., Ebinghaus, R., 2012. Organophosphorus flame retardants and plasticizers in airborne particles over the Northern Pacific and Indian Ocean toward the polar regions: evidence for global occurrence. Environ. Sci. Technol. 46, 3127–3134.
Moser, V., Phillips, P.M., Hedge, J.M., McDaniel, K.L., 2015. Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCPP) and tris(2-chloro-ethyl)phosphate (TCEP). Neurotoxicol. Teratol. 52, 236–247.
Nakajima, A., Saigusa, D., Tetsu, N., Yamakuni, T., Tomioka, Y., Hishinuma, T., 2009. Neurobehavioral effects of tetrabromobisphenol A, a brominated flame retardant, in mice. Toxicol. Lett. 189, 78–83.
National Toxicology Program, 1987. Toxicology and Carcinogenesis Studies of Dimethyl Methylphosphonate.
Nishimaki-Mogami, T., Minegishi, K., Tanaka, A., Sato, M., 1988. Isolation and identification of metabolites of 2-ethylhexyl diphenyl phosphate in rats. Arch. Toxicol. 61, 259–264.
Oliveri, A.M., Bailey, J.M., Levin, E.D., 2015. Developmental exposure to organophosphate flame retardants causes behavioral effects in larval and adult zebrafish. Neurotoxicol. Teratol. 52, 220–227.
Padilla, S.S., Grizzle, T.B., Lyerly, D., 1987. Triphenyl phosphite: *in vivo* and *in vitro* inhibition of rat neurotoxic esterase. Toxicol. Appl. Pharmacol. 87, 249–256.
Pellacani, C., Tagliaferri, S., Caglieri, A., Goldoni, M., Giordano, G., Mutti, A., Costa, L.G., 2012. Synergistic interactions between PBDEs and PCBs in human neuroblastoma cells. Environ. Toxicol. 29, 418–427.
Peltier, M.R., Koo, H., Getahun, D., Menon, R., 2015. Does exposure to flame retardants increase the risk for preterm birth? J. Reprod. Immunol. 107, 20–25.
Qiu, X., Bigsby, R.M., Hites, R.A., 2009. Hydroxylated metabolites of polybrominated diphenyl ethers in human blood samples from the United States. Environ. Health Perspect. 117, 93–98.
Rasinger, J.D., Carroll, T.S., Lundebye, A.K., Hogstrand, C., 2014. Cross-omics gene and protein expression profiling in juvenile female mice highlights disruption of calcium and zinc signalling in the brain following dietary exposure to CB-153, BDE-47, HBCD or TCDD. Toxicology 321, 1–12.
Rollin, H.B., Theodorou, P., Kilroe-Smith, T.A., 1991. Deposition of aluminium in tissues of rabbits exposed to inhalation of low concentrations of Al_2O_3 dust. Br. J. Ind. Med. 48, 389–391.
Roze, E., Meijer, L., Bakker, A., Van Braeckel, K.N., Sauer, P.J., Bos, A.F., 2009. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ. Health Perspect. 117, 1953–1958.
Ruckman, S.A., Green, O.P., Palmer, A.K., Klimisch, H., 1999. Tri-isobutylphosphate: a prenatal toxicity study in rats. Toxicol. Lett. 105, 231–237.
Ryan, B.M., Henrich, R., Mallett, E., Freudenthal, R.I., 2000. Developmental toxicity study of orally administered resorcinol bis-diphenylphosphate (RDP) in rabbits. Int. J. Toxicol. 19, 257–264.
Sagiv, S., Kogut, K., Gaspar, F., Gunier, R., Harley, K., Parra, K., Villaseñor, D., Bradman, A., Holland, N., Eskenazi, B., 2015. Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9–12 years of age. Neurotoxicol. Teratol. 52, 151–161.
Sasaki, K., Takeda, M., Uchiyama, M., 1981. Toxicity, absorption and elimination of phosphoric acid triesters by killifish and goldfish. Bull. Environ. Contam. Toxicol. 27, 775–782.
Schaeppi, U., Krinke, G., Kobel, W., 1984. Prolonged exposure to trimethylphosphate induces sensory motor neuropathy in the dog. Neurobehav. Toxicol. Teratol. 6, 39–50.
Schindler, B.K., Koslitz, S., Weiss, T., Broding, H.C., Brüning, T., Bünger, J., 2014. Exposure of aircraft maintenance technicians to organophosphates from hydraulic fluids and turbine oils: a pilot study. Int. J. Hyg. Environ. Health 217, 34–37.
Schlesinger, R.B., Snyder, C.A., Chen, L.C., Gorczynski, J.E., Menache, M., 2000. Clearance and translocation of aluminum oxide (alumina) from the lungs. Inhal. Toxicol. 12, 927–939.
Selvakumar, K., Bavithra, S., Ganesh, L., Krishnamoorthy, G., Venkataraman, P., Arunakaran, J., 2013. Polychlorinated biphenyls induced oxidative stress mediated neurodegeneration in hippocampus and behavioral changes of adult rats: anxiolytic-like effects of quercetin. Toxicol. Lett. 222, 45–54.
Shaw, S.D., Blum, A., Weber, R., Kannan, K., Rich, D., Lucas, D., Koshland, C.P., Dobraca, D., Hanson, S., Birnbaum, L.S., 2010. Halogenated flame retardants: do the fire safety benefits justify the risks? Rev. Environ. Health 25, 261–305.
Sjödin, A., Patterson Jr., D.G., Bergman, Å., 2003. A review on human exposure to brominated flame retardants — particularly polybrominated diphenyl ethers. Environ. Int. 29, 829–839.
Smith, M.I., Elvove, E., Frazier, W.H., 1930. The pharmacological action of certain phenol esters with special reference to the etiology of so-called ginger paralysis. Public Health Rep. 45, 2509–2524.
Smith, M.I., Engel, E.W., Stohlman, E.F., 1932. Further studies on the pharmacology of certain phenol esters with special reference to the relation of chemical constitution and physiologic action. Natl. Inst. Health Bull. 160, 1–53.
Sprague, G.L., Castles, T.R., 1985. Estimation of the delayed neurotoxic potential and potency for a series of triaryl phosphates using an *in vitro* test with metabolic activation. Neurotoxicology 6, 79–86.
St John, L.E., Eldefrawi, M.E., Lisk, D.J., 1976. Studies of possible absorption of a flame retardant from treated fabrics worn by rats and humans. Bull. Environ. Contam. Toxicol. 15, 192–197.
Stapleton, H.M., Eagle, S., Sjödin, A., Webster, T.F., 2012. Serum PBDEs in a North Carolina toddler cohort: associations with handwipes, house dust, and socioeconomic variables. Environ. Health Perspect. 120, 1049–1054.
Stapleton, H.M., Klosterhaus, S., Eagle, S., Fuh, J., Meeker, J.D., Blum, A., Webster, T.F., 2009. Detection of organophosphate flame retardants in furniture foam and U.S. house dust. Environ. Sci. Technol. 43, 7490–7495.
Striggow, F., Ehrlich, B.E., 1997. Regulation of intracellular calcium release channel function by arachidonic acid and leukotriene B4. Biochem. Biophys. Res. Commun. 237, 413–418.
Sundar, S., Chakravarty, J., 2010. Antimony toxicity. Int. J. Environ. Res. Public Health 7, 4267–4277.
Sundkvist, A.M., Olofsson, U., Haglund, P., 2010. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. J. Environ. Monit. 12, 943–951.
Sutton, W.L., Ten Haar, C.J., Miller, F.A., Scherberger, R.F., Riley, E.C., Roudabush, R.L., Fassett, D.W., 1960. Studies on the industrial hygiene and toxicology of triphenyl phosphate. Arch. Environ. Health 1, 33–46.
Suwita, E., Abou-Donia, M.B., 1990. Pharmacokinetics and metabolism of a single subneurotoxic oral dose of tri-o-cresyl phosphate in hens. Arch. Toxicol. 64, 237–241.
Ta, N., Li, C., Fang, Y., Liu, H., Lin, B., Jin, H., Tian, L., Zhang, H., Zhang, W., Xi, Z., 2014. Toxicity of TDCPP and TCEP on PC12 cell: changes in CAMKII, GAP43, tubulin and NF-H gene and protein levels. Toxicol. Lett. 227, 164–171.
Tagliaferri, S., Caglieri, A., Goldoni, M., Pinelli, S., Alinovi, R., Poli, D., Pellacani, C., Giordano, G., Mutti, A., Costa, L.G., 2010. Low concentrations of the brominated flame retardants BDE-47 and BDE-99 induce synergistic oxidative stress-mediated neurotoxicity in human neuroblastoma cells. Toxicol. in Vitro 24, 116–122.
Tajima, S., Araki, A., Kawai, T., Tsuboi, T., Ait Bamai, Y., Yoshioka, E., Kanazawa, A., Cong, S., Kishi, R., 2014. Detection and intake assessment of organophosphate flame retardants in house dust in Japanese dwellings. Sci. Total Environ. 478, 190–199.
Tilson, H.A., Veronesi, B., McLamb, R.L., Matthews, H.B., 1990. Acute exposure to tris(2-chloroethyl)phosphate produces hippocampal neuronal loss and impairs learning in rats. Toxicol. Appl. Pharmacol. 106, 254–269.
Tropepe, V., Sive, H.L., 2003. Can zebrafish be used as a model to study the neurodevelopmental causes of autism? Genes Brain Behav. 2, 268–281.
U.S. Environmental Protection Agency (EPA), 2004. High production volume chemical voluntary testing program, test plan isodecyl diphenyl phosphate.
U.S. Environmental Protection Agency (EPA), 2006. High production volume chemical voluntary testing program, test plan and robust summaries 2-ethylhexyl diphenyl phosphate.
U.S. Environmental Protection Agency (EPA), 2008. Flame Retardants in Printed Circuit Boards (Draft).
Ulsamer, A.G., Osterberg, R.E., McLaughlin Jr., J., 1980. Flame-retardant chemicals in textiles. Clin. Toxicol. 17, 101–131.
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, 109–116.
Umwelt Bundes Amt, 2001. Substituting Environmentally Relevant Flame Retardants: Assessment Fundamentals.
UNEP, 1994. Trimethyl Phosphate.
Union, E., 2008. Regulation (EC) No 1272/2008 of the European Parliament and of the Council on Classification, Labelling and Packaging of Substances and Mixtures.
Vainiotalo, S., Verkkala, E., Savolainen, H., Nickels, J., Zitting, A., 1987. Acute biological effects of commercial cresyl diphenyl phosphate in rats. Toxicology 44, 31–44.
Van den Berg, M., Birnbaum, L., Bosveld, A.T., Brunstrom, B., Cook, P., Feeley, M., Giesy, J.P., Hanberg, A., Hasegawa, R., Kennedy, S.W., Kubiak, T., Larsen, J.C., van Leeuwen, F.X., Liem, A.K., Nolt, C., Peterson, R.E., Poellinger, L., Safe, S., Schrenk, D., Tillitt, D., Tysklind, M., Younes, M., Waern, F., Zacharewski, T., 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ. Health Perspect. 106, 775–792.
Van den Eede, N., Dirtu, A.C., Neels, H., Covaci, A., 2011. Analytical developments and preliminary assessment of human exposure to organophosphate flame retardants from indoor dust. Environ. Int. 37, 454–461.
Van den Eede, N., Heffernan, A.L., Aylward, L.L., Hobson, P., Neels, H., Mueller, J.F., Covaci, A., 2015. Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. Environ. Int. 74, 1–8.

Van den Eede, N., Maho, W., Erratico, C., Neels, H., Covaci, A., 2013. First insights in the metabolism of phosphate flame retardants and plasticizers using human liver fractions. Toxicol. Lett. 223, 9–15.
Van der Veen, I., de Boer, J., 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88, 1119–1153.
Van Teeffelen, J.W., Brands, J., Stroes, E.S., Vink, H., 2007. Endothelial glycocalyx: sweet shield of blood vessels. Trends Cardiovasc. Med. 17, 101–105.
Viberg, H., 2009. Neonatal ontogeny and neurotoxic effect of decabrominated diphenyl ether (PBDE 209) on levels of synaptophysin and tau. Int. J. Dev. Neurosci. 27, 423–429.
Viberg, H., Fredriksson, A., Eriksson, P., 2002. Neonatal exposure to the brominated flame retardant 2,2′,4,4′,5-pentabromodiphenyl ether causes altered susceptibility in the cholinergic transmitter system in the adult mouse. Toxicol. Sci. 67, 104–107.
Viberg, H., Fredriksson, A., Eriksson, P., 2003a. Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. Toxicol. Appl. Pharmacol. 192, 95–106.
Viberg, H., Fredriksson, A., Eriksson, P., 2004. Neonatal exposure to the brominated flame-retardant, 2,2′,4,4′,5-pentabromodiphenyl ether, decreases cholinergic nicotinic receptors in hippocampus and affects spontaneous behaviour in the adult mouse. Environ. Toxicol. Pharmacol. 17, 61–65.
Viberg, H., Fredriksson, A., Jakobsson, E., Orn, U., Eriksson, P., 2003b. Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicol. Sci. 76, 112–120.
Viberg, H., Mundy, W., Eriksson, P., 2008. Neonatal exposure to decabrominated diphenyl ether (PBDE 209) results in changes in BDNF, CaMKII and GAP-43, biochemical substrates of neuronal survival, growth, and synaptogenesis. Neurotoxicology 29, 152–159.
Waaijers, S.L., Kong, D., Hendriks, H.S., de Wit, C.A., Cousins, I.T., Westerink, R.H.S., Leonards, P.E.G., Kraak, M.H.S., Admiraal, W., de Voogt, P., Parsons, J.R., 2013. Persistence, bioaccumulation, and toxicity of halogen-free flame retardants. Rev. Environ. Contam. Toxicol. 222, 1–71.
Wang, Q., Lai, N.L., Wang, X., Guo, Y., Lam, P.K., Lam, J.C., Zhou, B., 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, 5123–5132.
Wei, G., Li, D., Zhuo, M., Liao, Y., Xie, Z., Guo, T., Li, J., Zhang, S., Liang, Z., 2015. Organophosphorus flame retardants and plasticizers: sources, occurrence, toxicity and human exposure. Environ. Pollut. 196, 29–46.
Westerink, R.H., 2013. Modulation of cell viability, oxidative stress, calcium homeostasis, and voltage- and ligand-gated ion channels as common mechanisms of action of (mixtures of) non-dioxin-like polychlorinated biphenyls and polybrominated diphenyl ethers. Environ. Sci. Pollut. Res. Int. 21, 6373–6383.
WHO, 1998. Flame Etardants: Tris-(Chloropropyl)Phosphate and Tris-(2-Chloroethyl)Phosphate. EHC, p. 209.
Wills, J.H., Barron, K., Groblewski, G.E., Benitz, K.F., Johnson, M.K., 1979. Does triphenyl phosphate produce delayed neurotoxic effects? Toxicol. Lett. 4, 21–24.
Winneke, G., Ranft, U., Wittsiepe, J., Kasper-Sonnenberg, M., Furst, P., Kramer, U., Seitner, G., Wilhelm, M., 2013. Behavioral sexual dimorphism in school-age children and early developmental exposure to dioxins and PCBs: a follow-up study of the Duisburg cohort. Environ. Health Perspect.
Wu, S., Ji, G., Liu, J., Zhang, S., Gong, Y., Shi, L., 2015. TBBPA induces developmental toxicity, oxidative stress, and apoptosis in embryos and zebrafish larvae (*Danio rerio*). Environ. Toxicol. http://dx.doi.org/10.1002/tox.22131 (in press).
Xing, T., Chen, L., Tao, Y., Wang, M., Chen, J., Ruan, D., 2009. Effects of decabrominated diphenyl ether (PBDE 209) exposure at different developmental periods on synaptic plasticity in the dentate gyrus of adult rats *in vivo*. Toxicol. Sci. 110, 401–410.
Xing, T., Yong, W., Chen, L., Tang, M., Wang, M., Chen, J., Ruan, D., 2010. Effects of decabrominated diphenyl ether (PBDE 209) on voltage-gated sodium channels in primary cultured rat hippocampal neurons. Environ. Toxicol. 25, 400–408.
Yang, F., Ding, J., Huang, W., Xie, W., Liu, W., 2014. Particle size-specific distributions and preliminary exposure assessments of organophosphate flame retardants in office air particulate matter. Environ. Sci. Technol. 48, 63–70.
Yang, J., Yang, Z., Zhang, T., 2010. Action potential changes associated with impairment of functional properties of sodium channels in hippocampal neurons induced by melamine. Toxicol. Lett. 198, 171–176.
Yu, K., He, Y., Yeung, L.W.Y., Lam, P.K.S., Wu, R.S.S., Zhou, B., 2008. DE-71-induced apoptosis involving intracellular calcium and the Bax–mitochondria–caspase protease pathway in human neuroblastoma cells *in vitro*. Toxicol. Sci. 104, 341–351.
Zatta, P., Perazzolo, M., Facci, L., Skaper, S.D., Corain, B., Favarato, M., 1992. Effects of aluminum speciation on murine neuroblastoma cells. Mol. Chem. Neuropathol. 16, 11–22.
Zhang, S., Kuang, G., Zhao, G., Wu, X., Zhang, C., Lei, R., Xia, T., Chen, J., Wang, Z., Ma, R., Li, B., Yang, L., Wang, A., 2013. Involvement of the mitochondrial p53 pathway in PBDE-47-induced SH-SY5Y cells apoptosis and its underlying activation mechanism. Food Chem. Toxicol. 62, 699–706.
Zhang, C., Liu, F., Liu, X., Chen, D., 2010. Protective effect of N-acetylcysteine against BDE-209-induced neurotoxicity in primary cultured neonatal rat hippocampal neurons *in vitro*. Int. J. Dev. Neurosci. 28, 521–528.
Zhao, J., Xu, T., Yin, D., 2014. Locomotor activity changes on zebrafish larvae with different 2,2′,4,4′-tetrabromodiphenyl ether (PBDE-47) embryonic exposure modes. Chemosphere 94, 53–61.
Zheng, X., Zhu, Y., Liu, C., Liu, H., Giesy, J.P., Hecker, M., Lam, M.H., Yu, H., 2012. Accumulation and biotransformation of BDE-47 by zebrafish larvae and teratogenicity and expression of genes along the hypothalamus–pituitary–thyroid axis. Environ. Sci. Technol. 46, 12943–12951.