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Neurotoxicity and risk assessment of brominated and alternative flame retardants

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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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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.