Supplemental Material

Neurotoxicity of Brominated Flame Retardants: (In-)Direct Effects of Parent and Hydroxylated Polybrominated Diphenyl Ethers on the (Developing) Nervous System

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Abbreviations supplemental

n.a.	not applicable
n.d.	not detected
OH-PBDE	hydroxylated polybrominated diphenyl ether
PBDE	polybrominated diphenyl ether

Supplemental Material, Table 1. Human serum levels of PBDEs and PBDE metabolites[a].

sample	PBDEs	median (range; ng/g lipids)	references
18-months old, US	BDE-47	n.a. (245)	
	ΣPBDE[b]	n.a. (651)	Fischer et al. 2006
2-6 year olds, Australia	ΣPBDE	41 (33 - 49)	Toms et al. 2009
adults, the Netherlands	BDE-47	0.8 (0.1 - 6.1)	
	ΣPBDE	3.3 (0.5 - 33.1)	
	6-OH-BDE-47	n.d. (n.d.)	Meijer et al. 2008
adults, Sweden	BDE-47	3.5 (n.d. - 8.3)	
	ΣPBDE[b]	20.3 (8.6 - 50.5)	Karlsson et al. 2007
adults, Spain	BDE-47	2.4 (0.3 - 9)	
	ΣPBDE[b]	12 (5.5 - 43)	Ramos et al. 2007
adults, South-China	BDE-47	1.0 (0.4 - 3.6)	
	ΣPBDE	4.4 (1.6 - 17)	Bi et al. 2006
adults, US	BDE-47	10 (<10 - 511)	Petreas et al. 2003
adults, US	BDE-47	28 (9.2 - 310)	
	ΣPBDE	37 (15 - 580)	Mazdai et al. 2003
adults, US	BDE-47	15.2 (8.0 - 28.9)	
	ΣPBDE	34.0 (17.9 - 50.8)	
	6-OH-BDE-47	0.3 (0.1 - 0.5)	
	ΣOH-PBDE	6.3 (3.8 - 11.3)	Qiu et al. 2009
adults, Korea	6-OH-BDE-47	<4 (<4 – 177)[c]	Wan et al. 2010
cord blood, South-China	BDE-47	1.4 (0.1 - 4.9)	
	ΣPBDE	3.9 (1.5 - 12)	Bi et al. 2006
cord blood, Spain	BDE-47	3.3 (<0.1 - 35)	
	ΣPBDE[b]	17 (6.3 - 82)	Gómara et al. 2007
cord blood, Sweden	BDE-47	0.98 (0.3 - 3.3)	
	ΣPBDE	1.7 (0.5 - 4.3)	Guvenius et al. 2003
cord blood, the Netherlands	6-OH-BDE-47	n.d. (n.d.)	Meijer et al. 2008
cord blood, US	BDE-47	25 (8.4 - 210)	
	ΣPBDE	39 (14 - 460)	Mazdai et al. 2003
cord blood, US	BDE-47	13.45 (2.6 - 550.9)	
	ΣPBDE	30.9 (4.7 - 797.6)	
	6-OH-BDE-47	1.0 (0.1 - 62.1)	
	ΣOH-PBDE	22.0 (2.0 - 899.1)	Qiu et al. 2009
cord blood, Korea	6-OH-BDE-47	26 (<4 – 127)[c]	Wan et al. 2010
electronics dismantlers, US	BDE-47	4.8 (<0.5 - 23.4)	
	ΣPBDE[b]	26 (7.5 - 37.3)	Sjödin et al. 1999
electronics dismantlers, Norway	BDE-47	4.0 (mean; 0.9 - 15)	
	ΣPBDE	8.8 (mean; 3.8 - 24)	Thomsen et al. 2001
computer technicians, Sweden	BDE-47	1.3 (<1.0 - 13.6)	Jakobsson et al. 2002
e-waste dismantlers, South-China	BDE-47	9.5 (n.d. - 180)	
	ΣPBDE[b]	600 (140 - 8500)	Bi et al. 2007
foam workers, US	BDE-47	77.8 (19.5 - 540)	
	ΣPBDEs	160 (67 - 973)	Stapleton et al. 2008
14 year-olds working	BDE-47	n.a. (330.5)	
on waste-dump, Nicaragua	ΣPBDEs[b]	n.a. (656.5)	
(pooled samples)	6-OH-BDE-47	n.a. (6.2)	
	ΣOH-PBDE	n.a. (61.5)	Athanasiadou et al. 2008

n.d., not detected; n.a., not applicable; (OH-)PBDE, (hydroxylated) polybrominated diphenyl ethers
[a] for a more extensive review, see Frederiksen et al. 2009, [b] including BDE-209, [c] unit = pg/g ww.

Supplemental Material, Toxicokinetics of PBDEs and OH-PBDEs

In wildlife as well as human tissues, PBDE congeners BDE-28, BDE-47, BDE-99, BDE-100, BDE-153 and BDE-183 are particularly observed, as well as, although at lower concentrations, BDE-209 (reviewed in Hakk and Letcher 2003). Usually, BDE-47 is the predominant congener in biotic samples (for reviews see Frederiksen et al. 2009; Hites 2004).

PBDEs have been detected in liver, blood, milk and adipose tissues, occasionally at high concentrations, in both wildlife (for reviews see de Wit 2002; Law et al. 2003) and human tissues, including breast milk (Bradman et al. 2007; Petreas et al. 2003; Schecter et al. 2003; Sjödin et al. 2004; reviewed in Frederiksen et al. 2009). Toxicokinetics studies in rodents (Chen et al. 2006; Hakk et al. 2002; Örn and Klasson-Wehler 1998; Sanders et al. 2006a; Staskal et al. 2006; von Meyerinck et al. 1990; reviewed in Darnerud et al. 2001; Hakk and Letcher 2003) demonstrated high absorption and slow elimination as well as accumulation in adipose tissue after a single oral dose of tetra-, penta- and hexaBDEs. Studies in fish showed an efficient absorbance of PBDEs, with a negative correlation with bromination degree (Burreau et al. 1997, 2004). BDE-209 has also been detected in bird's eggs, birds, fish and marine mammals (reviewed in Law et al. 2006) as well as human tissues (reviewed in Frederiksen et al. 2009) despite its poor absorption in the gastrointestinal tract, low solubility, high log octanol-water partition coefficient (K_{ow}) and molecular weight (Mörck et al. 2003). Ecotoxicological concern has arisen from the observation of very high concentrations of BDE-209 in birds of prey in North-China. This observation is a sign of significant biomagnifications of BDE-209 in terrestrial food chains (Chen et al. 2007).

In addition to parent PBDE congeners, hydroxylated and methoxylated PBDEs (OH- and MeO-PBDEs) have also been detected in marine and freshwater fish, sea birds as well as dolphins, seals and polar bears (Gebbink et al. 2008; Houde et al. 2009; Kelly et al. 2008; Kierkegaard et al. 2004; Malmvärn et al. 2005; Marsh et al. 2004; McKinney et al. 2006; Olsson et al. 2000; Routti et al. 2009; Verreault et al. 2005; Wan et al. 2009).

In *in vivo* toxicokinetics studies, OH-PBDEs were detected in liver, lung, plasma, feces and bile after oral administration of BDE-47 or BDE-99 to rats (Chen et al. 2006; Hakk et al. 2002; Marsh et al. 2006; Örn and Klasson-Wehler 1998). OH-PBDEs have also been observed in plasma after intraperitonal administration of an equimolar mixture of environmentally relevant PBDEs to rats (Malmberg et al. 2005). Intravenous administration of BDE-47, BDE-99, BDE-100 or BDE-153 to mice revealed that hydroxylated metabolites were formed from all four PBDEs. BDE-99 was observed to be most readily metabolized by oxidation and oxidation/debromination, while debromination was not observed for the other PBDEs (Staskal et al. 2006). In contrast, metabolism of BDE-153 after oral administration is minimal (Qiu et al. 2007; Sanders et al. 2006b), which is suggested to be due to the absence of Br-atoms with 2 adjacent unsubstituted C-atoms. In support of this explanation, the presence of several OH-PBDEs was observed in feces after oral administration of BDE-154, in which a Br-atom with two unsubstituted adjacent C-atoms is present (Hakk et al. 2009). After oral administration of BDE-209 to rats, several methoxylated and acetylated metabolites were detected in bile and feces (Mörck et al. 2003). In addition, hydroxylated octa- and nonaBDEs were also detected in plasma and the liver after oral or intravenous administration of BDE-209 to rats (Sandholm et al. 2003; Riu et al. 2008). After subchronic low dose administration of DE-71 through the feed to rats, OH-PBDEs were identified in feces (Huwe et al. 2007). In mice, OH-PBDEs were observed in plasma after oral or subcutaneous exposure to DE-71 (Qiu et al. 2007).

Formation of OH-PBDEs from BDE-47 was also demonstrated using phenobarbital-induced rat liver microsomes (Hamers et al. 2008). Recently, the formation of OH-PBDEs was also investigated in human primary hepatocytes exposed to BDE-99 or BDE-209. These cells metabolized BDE-99 into OH-PBDEs while in contrast, OH-PBDEs were not detected after exposure to BDE-209 (Stapleton et al. 2009). Recently, *in vitro* biotransformation of parent, OH- and MeO-PBDEs in rainbow trout, chicken and rat microsomes suggested an additional metabolic pathway, i.e., formation of OH-PBDEs from MeO-PBDEs (Wan et al. 2009).

A distribution study with radiolabeled PBDEs in mice showed that fetal uptake during gestation was relatively limited, while maternal transfer via breast milk resulted in transfer of approximately 20% of the administered dose to the offspring (Darnerud and Risberg 2006). Assuming similar toxicokinetics of PBDEs in humans during gestation and lactation, this suggests that exposure through lactation is also from a quantitative point of view an important exposure route for PBDEs as well as OH-PBDEs in humans (Lacorte and Ikonomou 2009). In fetal liver and placental tissue, CYP enzyme activity is present (Hakkola et al. 1998). Placental transfer of hydroxylated polychlorinated biphenyls (OH-PCBs) has been demonstrated in experimental studies (Meerts et al. 2002). Although placental transfer of OH-PBDEs has not yet been proven, it is not unlikely (especially for lower-brominated PBDEs), due to the structural resemblance with OH-PCBs. Therefore, the internal fetal exposure to OH-PBDEs may be due to fetal hydroxylation and/or placental transfer.

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