Environment International 74 (2015) 170–180

Contents lists available at ScienceDirect

Environment International

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

Review

Human health risk associated with brominated flame-retardants (BFRs)

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ARTICLE INFO

Article history:
Received 10 March 2014
Accepted 16 September 2014
Available online 29 October 2014

Keywords:
PBDEs
Reproductive
Endocrine disruption
Behavior
Fish
Fish oil

ABSTRACT

The purposes of this review are to assess the human exposure and human and experimental evidence for adverse effects of brominated flame-retardants (BFRs) with specific focus on intake from seafood. The leakage of BFRs from consumer products leads to exposure of humans from fetal life to adulthood. Fish and fish products contain the highest levels of BFRs and dominate the dietary intake of frequent fish eaters in Europe, while meat, followed by seafood and dairy products accounted for the highest US dietary intake. House dust is also reported as an important source of exposure for children as well as adults. The levels of BFRs in the general North American populations are higher than those in Europe and Japan and the highest levels are detected in infants and toddlers. The daily intake via breast milk exceeds the RfD in 10% of US infants.

BFRs including PBDEs, HBCDs and TBBP-A have induced endocrine-, reproductive- and behavior effects in laboratory animals. Furthermore, recent human epidemiological data demonstrated association between exposure to BFRs and similar adverse effects as observed in animal studies.

Fish including farmed fish and crude fish oil for human consumption may contain substantial levels of BFRs and infants and toddlers consuming these products on a daily basis may exceed the tolerable daily intake suggesting that fish and fish oil alone represent a risk to human health. This intake comes in addition to exposure from other sources (breast milk, other food, house dust). Because potential harmful concentrations of BFRs and other toxicants occur in fish and fish products, research on a wider range of products is warranted, to assess health hazard related to the contamination of fish and fish products for human consumption.

Contents

1. Introduction

Brominated flame-retardants consist of different groups of chemicals with a range of physiochemical properties. Diverse BFRs currently and

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http://dx.doi.org/10.1016/j.envint.2014.09.006
0160-4120/

previously used in a wide variety of industrial applications include polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBP-A), hexabromocyclododecane (HBCD), polybrominated biphenyls (PBBs) and other brominated compounds (Fig. 1). However, at present, only decaBDEs, HBCD and TBBP-A are used.

PBDEs are a family of 209 possible chemicals (congeners) that are structurally similar to PCBs. They consist of two halogenated aromatic rings, which are grouped into penta, octa, and deca depending on the number of bromine added to the molecule. PBDEs in the environment mainly originate from three commercial mixtures, which have been applied, to furniture, textiles, electronics and building materials to prevent fires. The available commercial PBDE products are not single congeners but rather a mixture of congeners with an average number bromine attached. In the United States, PBDEs are marketed with trade names: DE-60F, DE-61, DE-62, and DE-71 applied to pentaBDE mixtures; DE-79 applied to octaBDE mixtures; and DE 83R and Saytex 102E applied to decaBDE mixtures.

PentaBDE and octaBDE were banned in the EU in 2004 while these mixtures were voluntarily phased out by the manufacturers in the US at the end of 2004. DecaBDE is still being used, however, in the EU, use is only permitted in plastics and in the US the principal producers announced an end to production by 2013 (Darnerud, 2008). The PBDE concentration in humans and the environment is leveling off or declining in Europe probably due to the prohibition of penta- and octaBDE mixtures (Fängström et al., 2008; Law et al., 2014). In contrast, a leveling off or downward trend is not apparent in North America (Domingo, 2012; Park et al., 2011).

Hexabromocyclododecane (HBCD or HBCDD) is one of the major BFRs. HBCD has 16 possible stereo-isomers with different biological activities (Covaci et al., 2006). The technical mixture/commercial formulation of HBCD contains three isomers: 75–89% g-HBCD, 10–13% a-HBCD and 1–12% b-HBCD. HBCD is used in construction and insulation boards, packaging material, electrical and electronic equipment, upholstered fabric and textiles, bed mattress, furniture, seatings, draperies, wall coverings, indoor textiles and automobile indoor textiles. At present, according to Bromine Science and Environmental Forum (BSEF), the brominated flame retardant industry panel, HBCD is the only suitable flame retardant for some of these applications. The global production of HBCD was 16,700 metric tons per year in 2001 and 23,000 tons per year in 2008. This correlates well with a sharp increase of the HBCD concentrations detected in the environment from 2001 onward (Darnerud, 2008), and is most probably caused by the increased use of HBCD when other BFRs were banned (pentaBDE, octaBDE) or restricted (decaBDE).

Tetrabromobisphenol A (TBBPA) is currently the most widely used brominated flame retardant (BFR) with an annual demand of about 130,000 metric tons in 2002 of which approximately 85% are used in East Asia (http://www.bsef.com/uploads/doc/BSEf_TBBPA_15-10f.pdf). TBBPA-containing materials are used in the manufacturing of office and home electronic equipment, such as computer boards, printers, copiers, mobile phones, televisions, and washing machines. Despite the fact that TBBPA binds covalently to plastic polymers thereby reducing the risk of leakage into the environment, TBBPA has been detected in abiotic and biotic samples including humans. Investigation of concentrations in serum taken from hospital patients in Norway revealed slight increases from 1985 to 1999 with the highest values (average 0.71 ng/g lipids) detected in young children up to 4 years of age (Thomsen et al., 2002). The half-life of TBBPA is reported to be about 2 days in humans, which may lead to bioaccumulation under condition of continuous uptake (Covaci et al., 2006, 2009).

BFRs are used to protect the public from fires by reducing the flammability of combustible materials and the use corresponds with a drastic drop in fire incidences in the last 40 years (Birnbaum and Staskal, 2004). Most of them are not fixed in the polymer by chemical binding, and can therefore freely leak to the surrounding environment. Except for TBBPA, the chemical structure of BFRs makes them persistent in the environment and promotes accumulation and biomagnification in living organisms including humans and wildlife. BFRs are now ubiquitous and can be detected in air, water, soil, fish, birds and mammals including humans (Hites et al., 2004). The lower brominated PBDEs appear to be more bio-accumulative compared to the higher brominated PBDEs (Watanabe and Sakai, 2003). In Sweden an increasing trend of PBDEs was observed in wildlife and humans from 1970 to about 2000 which then was leveling off after 2000. For HBCD and TBBPA a continuous increase has been reported during the whole period (1970–2007; Bignert et al., 2007; Darnerud, 2008). The levels of PBDEs in humans are considerably higher in the USA and Canada compared to Europe and Japan and in contrast to the leveling off observed in Norway and Sweden the concentration is still rising in the US breast milk (Darnerud, 2008; Eggesbø et al., 2011; Hites, 2004; Thomsen et al., 2010). For the general population food is identified as the main source of exposure. Because most BFRs are highly lipid soluble, fatty fish, fish oils and fatty foods of animal origin are potential sources of human exposure. Other exposure routes such as inhalation/ingestion of dust have also been suggested to contribute significantly (D'Hollander et al., 2010). Furthermore, certain occupational groups such as workers handling electronic equipment are reported to have higher tissue levels than the general population (Domingo, 2012; Frederiksen et al., 2009; Jakobsson et al., 2002; Qu et al., 2007). The widespread contamination of the environment and the detection of BFRs in wildlife and humans have raised concerns on possible adverse health effects. As exposure appears to be highest in children, a major current concern relates to the possible developmental effects of BFRs. Experimental studies in rodents have demonstrated that BFRs have the potential to disrupt endocrine functions by interfering with thyroid, androgen and estrogen signaling systems. Furthermore, BFRs are reported to induce morphological changes in liver and kidneys as well as neurodevelopmental- and reproductive effects (Darnerud, 2008; Kuriyama et al., 2005; Lilienthal et al., 2006; Yan et al., 2012). In humans, no large-scale epidemiological study has so far been published (Roth and Wilks, 2014). However, recent studies have reported significant relationship between BFR and thyroid hormone concentrations and adverse neuro-developmental- and reproductive effects in humans (Bradman et al., 2012; Harley et al., 2010; Herbstman et al., 2010; Hoffman et al., 2012; Main et al., 2007).

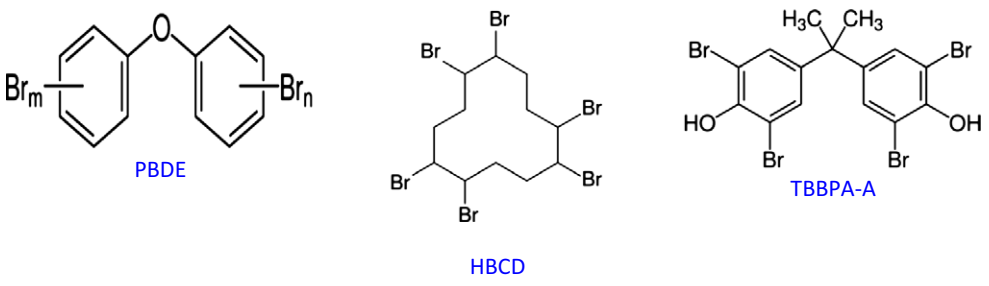

Fig. 1. Structural formula of PBDEs, HBCDs and TBBP-A.

2. Toxicity

Despite huge knowledge gaps, some data on toxicity of BFRs and in particular PBDEs are available. PBDEs have low acute toxicity with oral LD50s > 5 g/kg. The different PBDEs appear to have similar toxicological profile with liver, kidney and thyroid as the main target organs. In subchronic exposure studies in rats, no observed adverse effect level (NOAEL) values are in g/kg/day for decaBDE while <10 mg/kg/day for the lower brominated BDEs suggesting decaBDE as less potent (Costa and Giordano, 2007). Available data have demonstrated that BFRs have the potential to adversely affect endocrine functions and the central nervous and reproductive systems. The endocrine disrupting potency of BFRs is illustrated by the fact that various congeners are able to interact with estrogen, progesterone and androgen receptors (Hamers et al., 2006; Meerts et al., 2001). BFRs have also been found to inhibit enzymes involved in steroid hormone metabolism (Lai and Cai, 2012). Hydroxylated BDEs are structurally very similar to thyroid hormones and have been reported to displace the endogenous hormones from the thyroxin plasma transporter protein transthyretin (TTR; Meerts et al., 2001).

2.1. Effects on thyroid hormones (TH)

In different rodent studies, developmental (fetal/postnatal/prepubertal) exposure to PBDEs showed a consistent reduction in T4 while effects on T3 and thyroid stimulating hormone (TSH) were less consistent. Significant reduction of T4 was observed following exposure to PBDEs with doses as low as 0.14–0.7 mg/kg (Andrade et al., 2004; Fowles et al., 1994). Furthermore, reduced T4 is also documented in adult female rats exposed to 55 mg/kg/day HBCD. The same study reported increased pituitary weight, increased immunostaining of TSH in the pituitary, increased thyroid weight, and thyroid follicle cell activation. The most sensitive parameter observed was 10% increase in thyroid weight following exposure to 1.6 mg/kg/day (van der Ven et al., 2006). In rat offspring exposed prenatally to 16 mg/kg/day TBBP-A decreased T4 was observed at a dose of 16 mg/kg/day but not at 5 mg/kg/day (Meerts et al., 1999). Decrease in T3 and an increase in TSH in males but not females, were observed following peripubertal exposure to 30 or 60 mg/kg/day DE-71 (commercial penta-mixture). Another study reported a decrease in T3 in female rats following exposure to 100 or 300 mg/kg/day DE-71 or 60 or 100 mg/kg/day DE-79 (commercial octa-mixture) on post-natal days (PND) 28–32 (Stoker et al., 2004; Zhou et al., 2001). Administration of 300 mg/kg/day BDE 99 (2,2′,4,4′,5-pentabromodiphenyl ether) on gestation day (gd) 6 resulted in reductions of T4 in both male and female offspring on PND 22 (Kuriyama et al., 2007). In adult rats orally exposed to an environmental relevant mixture of PBDEs for 70 days reduced thickness of the thyroid gland epithelium at a dose of 20 μg/kg/day was observed (Ernest et al., 2012).

The developing brain is dependent on TH for normal development, and abnormal TH levels will result in an impaired brain growth and differentiation, leading to mental retardation both in animals and in man (Darnerud, 2008). Small differences in serum thyroid hormone levels during pregnancy or at birth have been shown to be associated with deficits in cognitive function (LaFranchi, 2010). For example, significant lower IQ scores were found in children of women with thyroid deficiency during pregnancy, even though hormone levels were not outside population reference range (Haddow et al, 1999; Morreale de Escobar et al, 2000).

However, the Mental Development Index of Children with congenital hypothyroidism was also affected by the age of onset of treatment with thyroid hormone, rather than the specific serum free T_4 concentration (Bongers-Schokking, 2001). Thus the degree of thyroid hormone insufficiency is not the only variable affecting human development; the duration of insufficiency and developmental timing are also critical, representing a challenge for risk assessment. Consequently, the disturbances of TH induced by BFRs in animal models may in part explain the developmental neurotoxic effects observed in animal models (Eriksson et al., 2002; Viberg et al., 2003). The lowest doses giving effects in these experiments were in the range of 0.1–1 mg/kg b.w. (Sand et al., 2004).

2.2. Effects on sex hormones

Effects of BFRs on sex hormones are documented in different in vitro systems. Depending on which BFR, both induction and inhibition of estrogenic and androgen signaling are reported (Cantón et al., 2005; Hamers et al., 2006; Kitamura et al., 2005; Lai and Cai, 2012). In vivo reports on sex hormone effects are still few but the area is expanding. For example, alterations in sex hormone profiles have been reported, including reductions in circulating estradiol and testosterone in adult male offspring (Lilienthal et al., 2006) and lower circulating estradiol concentrations in young female rat offspring exposed to 700 μg/kg of BDE 47 on gestational day (gd) 6 (Talsness, 2008). Administration of 60 or 300 μg/kg BDE 99 on gd 6 induced a reduction in sperm count without an influence on circulating testosterone concentrations in adult male rats (Kuriyama et al., 2005). Furthermore, in male rats exposed to BDE 99, delayed puberty was observed at doses of 1 and 10 mg/kg (Lilienthal et al., 2006). In female rats exposed to a single dose of 140 μg/kg BDE 47 reduced ovary weight and histological changes in the thyroids were documented. In the male offspring, 700 mg/kg decreased the level of follicle stimulating hormone (FSH) at postnatal day 22 (Andrade et al., 2004). The observed changes in sperm and ovarian follicle count may be caused by alterations in gonadotropins and/or sex hormones as well as of thyroid hormone disruption. In animal studies, thyroid hormone has been shown to play an integral role in testicular development (Cooke and Meisami, 1991) and affect ovarian follicular maturation (Baldridge et al., 2004).

In a one generation reproductive toxicology study, increased testes weights, testosterone levels and aromatase (Cyp19) activity were observed in male pups exposed to a dose of 0.5 mg/kg/day TBBPA, suggesting TBBPA as a reproductive toxic environmental contaminant (van der Ven et al., 2008). van der Ven and colleagues also studied endocrine/reproductive effects of HBCD using the same study design as for TBBPA and showed that HBCD produced diverse developmental effects in the exposed offspring. Furthermore, the most sensitive effect observed with a no observed adverse effect level (NOAEL) of 56 μg/kg/day was decreased trabecular bone mineral density of the tibia (van der Ven et al., 2009). Comparing the human TBBPA and HBCD exposure with the animal data suggests that the current use of TBBPA and HBCD may also be a matter of concern for human health (van der Ven et al., 2008). However, in recent risk assessments issued by EFSA in 2011 and 2012 it was concluded that current dietary exposure to TBBPA and HBCD in the European Union does not raise a health concern (EFSA, 2011b, 2013).

2.3. Effects on neurodevelopment

In a series of experiments, developmental neurotoxicity of various PBDEs was studied in mice. All congeners tested (BDE 47, 99, 53, 183, 203, and 209) so far, have induced long-term changes in spontaneous locomotor activity which the authors interpret as a decrease in habituation (Eriksson et al., 2002; Viberg et al., 2003, 2006). In another mouse study neurobehavioral development was investigated following oral administration of 0.6, 6.0 and 30.0 mg/kg/day BDE 99 from gd 7 to PND 21. Hyperactivity was found in the offspring at all dose levels (Branchi et al., 2002). In a follow-up study the same effect was reproduced at a dose of 18 mg/kg/day between gd 6 and PND 21 (Branchi et al., 2003). In a rat study BDE 99 administered as a single dose of either 0.06 mg/kg or 0.3 mg/kg on gestational day 6 induced hyperactivity at both doses on postnatal day 71 (Kuriyama et al., 2005). The adipose tissue levels of BDE 99 measured in the rats exposed to 0.06 mg/kg (Kuriyama et al., 2007) were only approximately 3 times

higher than the maximum breast milk levels measured in US mothers (Schecter et al., 2003). In addition to affecting locomotor activity PBDEs are also reported to induce cognitive impairment in mice (Eriksson et al, 2001) and rats (Dufault et al., 2005). Sex hormone related behavior changes were demonstrated in a rat study where exposure to BDE 99 from gd 10 to 18 at a dose of 10 mg/kg/day increased sweet preference in male rats on PND 120 (Lilienthal et al., 2006). Because sweet preference is higher in females, the authors suggested that BDE 99 induced a feminization of the males. In the same study, alterations in testosterone and estradiol were found in the males at weaning and on PND 120. In adult rats exposed to multiple doses of BDE 47 for 30 days dose-dependent spatial learning and memory deficits, and reduced levels of intracellular glutamate receptors at all exposure doses (0.1, 0.5 and 1 mg/kg/day) were observed giving a LOAEL of 100 μg/kg/day (Yan et al., 2012). In 2-month-old rats exposed to a single oral dose of PBDE 47 (1, 5, and 10 μg/g) and/or PCB 153 (5 μg/g) on post-natal day (PND) 10 decreased thyroid and uterus weights and increased ovary weight were observed at the highest doses of BDE 47. Furthermore, in all BDE 47 exposure groups, learning and memory deficits and reduced levels of T4 were observed compared to controls. In addition, significant synergistic interaction between BDE 47 and PCB 153 was demonstrated (He et al., 2011).

The current data on potential neuro-toxic effects of HBCD is limited to a few studies. Alterations of spontaneous behavior with initial hyperactivity, followed by impaired habituation were observed in mice, neonatally exposed to a single oral dose of 0.9 mg/kg or 13.5 mg/kg body weight HBCD on PND 10 (Eriksson et al., 2006). In the same study, decreased spatial learning and memory skills were documented in the exposed mice. In an in vitro study, HBCD inhibited dopamine uptake into synaptosomes and synaptic vesicles in the lower micromolar range (Fonnum and Mariussen, 2009). In a one generation reproduction study, rats were administered HBCD via the diet and adverse effects on dopamine-dependent behavior and hearing function were found in the adult offspring (Lilienthal et al., 2009).

As for HBCD, very few studies have evaluated neuro-developmental effects of TPPB-A However, Lilienthal et al. (2008) used the same study design as for HBCD and demonstrated effects on dopamine-dependent behavior and hearing function in offspring exposed to 8 mg/kg/day TPPB-A. Furthermore, in vitro studies showed that HBCD can potentially disrupt TR-mediated transactivation and impairs Purkinje cell dendritogenesis, in primary cerebellar culture derived from newborn rat (Ibhazehiebo et al., 2011). In vitro studies demonstrated TBBPA-induced inhibition of dopamine uptake into synaptic vesicles and reduced uptake of dopamine and GABA into brain synaptosomes (Fonnum and Mariussen, 2009). At low micromolar concentrations, enhanced formation of free radicals via a MAP kinase-dependent pathway was observed in human neutrophil granulocytes (Reistad et al., 2005).

2.4. Effects of BFR in humans

Little data is available on effects of BFRs in humans. However, the available data suggest that BFR exposure may affect behavior and reproduction as observed in animal studies. In a Danish–Finish study the levels of PBDEs in breast milk were associated with cryptorchidism and increased serum LH (Main et al., 2007). In a study among Mexican immigrants in California, it was documented that higher maternal serum levels of PBDEs increased the time to pregnancy in women trying to get pregnant (Harley et al., 2010). In Taiwan, elevated PBDE levels in breast milk were correlated with lower birth weight, length, lower head, and chest circumference (Chao et al., 2010). In this study, the daily intake of PBDEs via milk was 21 ng/kg/day, which is far below exposure levels in Canada (280 ng/kg/day; Jones-Otazo et al., 2005) and the US (306 ng/kg/day; Schecter et al., 2003). In a more recent study from Taiwan, a significant inverse association between BDE 209 and the cognitive scale was found as well as a positive correlation between BDE 196 and the language scale (Chao et al., 2011). In California USA significant associations of both maternal prenatal and childhood PBDE exposures with poorer attention, fine motor coordination, and cognition in early school age children were shown (Eskenazi et al., 2013). In another recent study, significant associations were demonstrated between prenatal serum PBDE levels and lower scores on tests of mental and physical development at 12–48 and 72 months (Herbstman et al., 2010). Likewise, Roze et al. (2009), demonstrated associations between prenatal exposure to PBDEs and behavior changes at school age. Furthermore, associations between increasing sumPBDEs in mother's milk (colostrum) and decreasing mental development scores were demonstrated in Spanish infants (Gascon et al., 2012). However, because of differences and limitations in study designs, the epidemiological evidence does currently not support a strong causal association between PBDEs and adverse neurodevelopmental and neurobehavioral outcomes (Roth and Wilks, 2014). Therefore, Roth and Wilks (2014) suggest assessing potential adverse effects of PBDEs on human brain functions using more harmonized study designs and exposure assessments and repeated testing with larger study populations.

Since maternal TH concentrations play a crucial role in fetal brain development (Haddow et al., 1999) it has thus been suggested that PBDEs may affect neurodevelopment and reproduction by disrupting TH homeostasis (Harley et al., 2010). Interestingly, recent human epidemiological studies have reported an association between PBDE exposure and changes in TH and TSH levels (Chevrier et al., 2011; Dallaire et al., 2009; Johnson et al., 2013; Turyk et al., 2008). It is also known that diseases of the thyroid hormone affect the reproductive capacity of women. Hypothyroidism is associated with hyperprolactinemia, which inhibits the release of pituitary gonadotropin and gonadal steroids, which in turn inhibit ovulation. Although less is known about the role of thyroid hormones in the development of the reproductive system, it is reported that they are involved in gonad development in both sexes (Talsness, 2008).

3. Toxicokinetics

Toxicokinetic studies in rats and mice have demonstrated that the lower brominated congeners are well absorbed following oral exposure (80%) and dermal (60%) exposure (Staskal et al., 2006). The highest concentrations of the lower brominated BDEs are found in adipose tissue but considerable levels are also detected in various tissues including the brain. In contrast, only 10% of an oral dose of decaBDE is absorbed and bioaccumulation appears to occur mainly in the liver (Morck et al., 2003). Lower brominated BDEs are metabolized by mixed function oxidases to hydroxylated (OH–) and methoxylated (MeO–) metabolites (Hakk et al., 2002; Van den Bergh et al., 2013) whereas decaBDE is metabolized to lower brominated compounds (Morck et al., 2003). Species differences in metabolic capacity appear to occur with higher urinary excretion in mice compared to rats (Ørn and Klasson-Wehler, 1998). Furthermore, difference in metabolic rate between genders is reported with higher urinary excretion in males compared to females (Staskal et al., 2006). Metabolic capacity is reported to be lower in developing rodents compared to adults (Staskal et al., 2006). Moreover, PBDEs are secreted in milk and suckling infants had higher tissue levels than their dams. For example, maternal exposure of BDE 99 resulted in up to 17-fold higher levels in the brain of rat pups compared to controls (Oskarsson and Möller, 2004). Furthermore fetal exposure to BDE 99 resulted in higher levels in the rat offspring at birth and PND 22 compared to the mothers (Kuriyama et al., 2007), suggesting long term accumulation following in utero exposure. In contrast, maternal administration of decaBDE resulted in low levels in the fetus. However when exposing pregnant rats to radioactive labeled BDE 209 14% of the radioactivity still remained in the fetuses 19 days after exposure indicating that PBD 209 is metabolized to more persistent metabolites which are transferred to the fetus (Riu et al., 2008).

Toxicokinetic studies in rodents suggest that absorption, distribution, metabolism and excretion of PBDEs are dependent on congener, gender

and species and that significant amount is transferred to the fetus via the placenta and the pup via the milk. It is also documented that the ability to eliminate PBDEs from the body is reduced in pups suggesting that developing individuals are more at risk of accumulating high levels of PBDEs compared to adults.

PBDE half-life tends to increase at decreasing PBDE bromination (Bakker et al., 2008; von Meyerinck et al., 1990). Half-lives ranging from 19 to 119 days were shown in rats exposed to single doses of commercial mixtures. The estimated whole-body half-life of the individual congener BDE 99 was about 6 days (Hakk et al., 2002), while a half-life of 8.6 days was reported for BDE 209 in rats (Huwe and Smith, 2007). In mice, available data on kinetic properties of individual PBDE congeners are restricted to BDE 47 showing half-lives of 1.5 to 23 days (Staskal et al., 2006). In a study on non-occupational adult humans in Sweden, the whole body half-lives of BDE 47 (tetraBDE), BDE 99 and -100 (pentaBDEs) and BDE 153 and 154 (hexaBDEs) were estimated from the daily intake and the total body burden under steady conditions. The results from this study are summarized in Table 1 (Geyer et al., 2004). Bakker et al. (2008) estimated half-lives in a Dutch human population and reported comparable half-life estimates as in the Swedish study. Trudel et al. (2011) used PBDE uptake values in combination with PBDE biomonitoring data from the literature as input for a pharmacokinetic model to derive elimination half-lives and showed median half-life estimates at 1100, 510, 280, 670, 2700, 480 and 1000 days for BDE 28, 47, 99, 100, 153, 154 and 183, respectively. For BDE 209, a median value of 7 days was found based on the concentration in blood, whereas a median of 4 days was found when calculations were based on levels in both blood and breast milk. These recent half-life estimates are in the same order of magnitude as those previously reported confirming that BDE 209 has a different pharmacokinetic behavior than the lower brominated PBDEs. The available literature also provides robust evidence of considerably longer half-life in humans compared to rodents (years versus days; Hakk et al., 2002; Staskal et al., 2006).

4. Human exposure

The diet appears to be the major source of exposure of the general populations and among foods, fish and fish oil based products have the highest content of BFRs followed by meat and dairy products (Darnerud, 2008; EFSA, 2011a; Hites et al., 2004; Law et al., 2014). Despite considerable variation, the current mean PBDE concentration in breast milk from Europe and Japan is 2 ng/g: lipid weight (Inoue et al., 2006; Polder et al., 2008; Thomsen et al., 2010), whereas the concentrations in breast milk from the United States and Canada are higher (range = 9.60–1291 ng/g lipid weight; Law et al., 2014; Park et al., 2011; Schecter et al., 2003). It has been estimated that a breastfed baby may be exposed to up to 440 ng/kg/day compared to 1 ng/kg/day for adults (Toms et al., 2008, 2009). It is shown that the pattern of occurrence of these brominated pollutants in breast milk is generally related to their occurrence in food (Pratt et al, 2013). However, house dust is also reported as an important source of exposure for children as well as adults (Abdallah and Harrad, 2014; Jones-Otazo et al., 2005; Toms et al., 2008, 2009). PBDEs were measured in matched serum samples from Swedish mothers and their toddlers (11–15 months of age). Congener-to-congener correlations within the mother or toddler cohorts suggested diet as an important exposure pathway for tetra-nonaBDEs for mothers, breastfeeding as a predominant exposure pathway for tetra-hexaBDEs, and dust for octa-decaBDEs for toddlers (Sahlström et al., 2014). Domingo (2012) reported significant positive associations between PBDEs in breast milk and house dust suggesting that indoor environment also plays a prominent role for adults. Li et al. (2014) estimated daily PBDE intake and uptakes through inhalation, ingestion, and dermal routes for Shanghai residents. Among the three routes, ingestion (84.7–92.9%) was dominating when considering uptake efficiency but exposure from house dust indicating that intake from air and house dust also contributes significantly to the exposure (15.3–7.1%).

The highest levels of BFRs are detected in infants and young children while the concentrations appear not to vary with age in adults (Fischer et al., 2006; Law et al., 2014; Thomsen et al., 2010). BFRs are also reported to cross the placenta and similar concentrations are detected in maternal and fetal blood (Fischer et al., 2006). Furthermore, levels of PBDEs up to 98.5 ng/g are detected in fetal liver (Schecter et al., 2007). High levels of BFRs are also reported in occupationally exposed workers (Law et al., 2014; Park et al., 2011). For example in a group of computer dismantlers, serum PBDE levels were 26 ng/g compared to 3.3 ng/g in a reference group of hospital cleaners (Sjödin et al., 1999).

Table 1
Estimated elimination half-lives of lower brominated PBDEs in humans. Table from Geyer et al. (2004).

Estimated half-life mean (range) in humans		
Congener	Days	Years
BDE 47	664 (556–926)	1.8 (1.5–2.5)
BDE 99	1040 (663–1442)	2.9 (1.8–3.95)
BDE 100	573 (469–660)	1.6 (1.3–1.8)
BDE 154	1214 (837–1560)	3.3 (2.3–4.3)
BDE 153	2380 (1300–4530)	6.5 (3.6–12.4)

5. Concentrations in food and intake estimates

In contrast to declining levels of PCBs and DDTs, the levels of PBDEs have increased in aquatic and marine organisms globally over the last 20 years (Hites et al., 2004; Montie et al., 2010). Although the levels in wild fish are documented to be lower in Europe compared to North America, the BFR concentrations in European farm-raised salmon are significantly higher than in farmed fish raised in North and South America (Hites et al., 2004). Hites et al. also documented significantly lower levels in wild salmon compared to farm raised salmon.

Despite the difference documented by Hites et al., yearly measurements by the Norwegian Institute of Nutrition and Seafood Research (NIFES) as part of their yearly surveillance programs on contaminants in seafood show comparable concentration between Norwegian and North American farmed salmon (Table 2). The concentrations of BFRs in cod from Oslofjord are significantly higher than cod from remote areas such as Bear Island and Svalbard suggesting a close association between the levels in wild fish and the level of urbanization (Jenssen et al., 2007).

In a review paper from 2014, BFR levels in fish were reported for a number of areas and fish species. In fish from the Gila River in Arizona,

Table 2
Concentrations (ng/g) of BFRs (PBDEs, HBCDs, TBBP-A) in Norwegian farmed salmon through 2003–2008 (http://nifes.no/en/seafood-data-2/).

Farmed Atlantic salmon (*Salmo salar*)		
Year	Samples	Mean (range)
∑*PBDEs*		
2008	47	1.3 (0.86–2)
2007	786	1.5 (0.02–3.85)
2007	24	1.3 (0.4–2)
2006	64	1.2 (0.6–2.4)
2005	46	1.9 (0.6–3.9)
2004	12	2.4 (1.5–3.5)
2003	20	2.5 (1.1–4)
∑*HBCD*		
2008	14	0.5 (<0.5–1)
2007	86	0.82 (<0.2–0.5–4.7)
2006	64	<0.5
2005	46	(<0.5–0.9)
TBBP-A		
2008	10	<1

USA, high concentrations of ∑ BDEs were reported (up to 12.7 mg kg^{-1} wet weight; Law et al., 2014). From markets in Australia ∑ BDE11 concentrations of 1.0–45 μg kg^{-1} fresh weight were measured in edible fish. BDE 209 was the dominant congener, followed by BDE 47 and BD E99. Despite some evidence of decreasing trends in some species and locations, elevated concentrations of BDEs in fish are still reported.

In China, relatively low levels (0.19 μg kg^{-1} wet weight) of HBCD were determined in 12 edible fish species from South China. This was at the lower end of the concentration range observed globally. Sum HBCD concentrations were higher in both freshwater and seawater farmed fish compared to wild marine fish, suggesting that human activities probably represent an important input source of HBCD in aquaculture (Law et al., 2014).

Farmed fish are fed concentrated feed high in fish oils. Although the BFR concentrations in these feed samples are quite variable, they are generally similar to or greater than in the farmed salmon (Table 3). When comparing the levels of PBDEs in different fish feed there were no significant differences among the four locations (British Columbia, Eastern Canada, Chile, and Scotland) where the feed was purchased, among the three continents (North America, South America, and Europe) where the feed was purchased, or between the two purchase periods. However, there was a significant difference between the two feed companies (Hites et al., 2004).

Because fish oil products have a relatively high lipid content the concentration of lipophilic pollutants including BFRs may also be elevated if they have not been removed during the manufacturing process. The concentrations detected in selected omega-3 products from Norway, Spain, the United Kingdom and Canada are indicated in Table 4 (Martí et al., 2010; Rawn et al., 2009; http://www.vkm.no/dav/2158765ff5.pdf). The highest levels appear to be in oils from shark and menhaden. However, relatively high levels of PBDEs are also found in cod liver oils on the British, Spanish and Norwegian markets.

Rawn et al. (2009) estimated the daily intake of PBDEs from oil supplements by multiplying the concentration of contaminant in each supplement with the maximum recommended daily dosage following the manufacturer's label instructions. Daily intake of PBDEs from consumption of salmon oil was estimated at 25.1 ± 54.3 ng/day while consumption of shark oil would result in PBDE intake of 185 ng/day. Furthermore, consumption of Canadian salmon gives a daily intake of 225 ng/day PBDEs, suggesting that a combined daily consumption of salmon and fish oil would give an exposure of approximately 300 ng/g PBDEs (Rawn et al., 2009).

A European monitoring program, covering the period from 2001–2009, measured PBDEs in almost 4000 food samples. The results from this monitoring documented eight PBDEs (BDE-28, -47, -99, -100, -153, -154, -183 and -209) of dietary relevance. Furthermore, BDE 209 was the most abundant in food of animal and plant origin while BDE 47 occurred at highest levels in fish and fish products and food for infants and small children. As a consequence the highest dietary exposure in humans is from BDE 209 and BDE 47 (Table 5). The relative contribution of PBDE intake from different food categories is listed in Table 6.

A summary of the estimated dietary exposure (ng/kg body weight/day) to BDE 47, BDE 99, BDE 153 and BDE 209 for the general population and high fish consumers (95th percentile) of different groups of the population is indicated in Table 7. The highest estimated intake was from BDE 47 and BDE 209. Specific population groups such as frequent fatty fish consumers had substantial higher intake of BDE 47 than the general population. Furthermore, daily intake of dietary supplements such as fish oil based products which have not been appropriately purified increases the mean daily intake of BDE 47 and BDE 99 with 2.53 and 4.27 ng/kg bw, respectively (EFSA, 2011a).

US studies demonstrated higher levels of PBDEs than reported elsewhere. Fish were most highly contaminated (median 616 pg/g), followed by meat (median 190 pg/g) and dairy products (median 32.2 pg/g). However, unlike many European countries where fish predominates, dietary intake of PBDEs in the US is mostly from meat, then fish and then dairy products (Schecter et al., 2008).

The mean levels of PBDE in human milk showed low variation across European countries. However, the individual contamination may differ significantly as indicated by the wide ranges reported from the different studies (Table 5). Estimated PBDE intake in breast feed infants was up to 20–30 times higher than the general population (EFSA, 2011a). Schecter et al. (2003, 2007) measured levels of PBDEs and HBCD in human milk. The US women's milk samples were contaminated with PBDEs from 6 to 419 ng/g, lipid weight. The concentrations of HBCDs were similar (0.16–1.2 ng/g) to European, unlike PBDEs where US levels are much higher than European levels.

The distribution of PBDE intake from different foods in Norway is shown in Table 8. The Norwegian Scientific Committee for Food Safety conducted a risk assessment on PBDEs in 2005 and estimated daily intake from food to 170 ng/day for adults in the general population. Furthermore, daily intake via maternal milk for a 6 month old infant (10 kg) was estimated to be 700 ng/day. When adding intake from cod liver oil (tran) the infant will be exposed to 750 ng/day PBDEs. The daily exposure for consumers of trout from Lake Mjøsa, Norway, was estimated to be 4130 ng/day for an adult (70 kg). The estimated intake from food and different fish oils in different countries is indicated in Table 9 (http://www.vkm.no/dav/2158765ff5.pdf). However, the exposure level among breast-fed infants is considerably higher compared to adults, causing concern because it is well documented that infants are more sensitive to chemical stress than adults (Landrigan et al., 2004).

Table 3
Total PBDE concentrations in fish feed purchased from various global suppliers. Table adapted from Hites et al. (2004).

Company	Location	Lipid conc (%)	∑ PBDE (ng/g wet weight)	∑ PBDE (ng/g lipid weight)
B	Scotland	32.85	10.92	33.24
A	British Columbia	30.23	9.27	30.67
A	British Columbia	31.69	8.88	28.0
A	Scotland	33.41	7.67	22.95
A	Scotland	28.25	6.75	23.9
B	Eastern Canada	36.32	5.68	15.6
A	Chile	33.23	5.16	15.5
B	Easter Canada	33.65	1.96	5.8
B	British Columbia	32.17	1.08	3.35
B	Chile	31.57	0.60	1.9
B	Chile	38.84	0.50	1.3
B	British Columbia	34.99	0.49	1.4

6. Voluntary and governmental actions

In order to protect health and the environment, Directive 2003/11/EC banned the placing on the market and the use as a substance or as a constituent of substances or of preparations of commercial mixtures of pentaBDEs and octaBDEs in concentrations higher than 0.1% by mass (http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:042:0045:0046:EN:PDF). Since July 2006, new electrical and electronic equipment put on the market should not contain PBBs or PBDEs as laid down in Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment. The application of the commercial mixture decaBDE in polymeric applications was specifically exempted from the requirements. As of July 2008, decaBDE can no longer be used in electronics and electrical applications as decided by the European Court of Justice (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:116:0002:0003:EN:PDF). However, according to the EU directive it is still allowed to use decaBDE in plastic. On June 2nd 2009 the European Chemicals Agency (ECHA) within the REACH framework decided to restrict the use of HBCD within the EU such that it can only be used when authorized for specific purposes.

Table 4
BDE 47, BDE 99 and ∑PBDE concentrations (ng/kg) in fish oil supplement samples.

Fish oil type	BDE 47	BDE 99	∑PBDE	Reference
Salmon oil Canada	1080	268	3260	Rawn et al. (2009)
Shark oil Canada	30,300	7190	57,700	Rawn et al. (2009)
Menhaden oil Canada	13,200	813	50,900	Rawn et al. (2009)
Seal Canada	19,400	3930	35,100	Rawn et al. (2009)
Cod liver oil Norway			9730	http://www.vkm.no/dav/2158765ff5.pdf
Cod liver oil Spain			8200–18,200	Martí et al. (2010)
Cod liver oil UK			14,600–34,200	Martí et al. (2010)

In the USA, pentaBDE, octaBDE and decaBDE are included in the US Voluntary Children's Chemical Evaluation Program (VCCEP) with the goal to give information on the effects of chemicals to enable consumers to make wise choices. Great Lakes Chemical Corp. (now Chemtura), the only US manufacturer of pentaBDE and octaBDE, voluntarily phased out the production of both mixtures at the end of 2004.

California prohibits production and distribution of products, which contain more than 0.1% pentaBDE or octaBDE after 2008. Minnesota, Rhode Island, Montana, Hawaii, Illinois, New York, Maine, Maryland, Michigan and Oregon have adapted laws similar to California and other states are considering similar actions. The Minnesota law also puts restriction on decaBDE and encourages the production of products without PBDEs. Washington and Maine also ban decaBDE for specific uses.

In December 2009, the US Environmental Protection Agency (EPA) announced the 'decaBDE Phase-Out Initiative' to eliminate the production, importation and sale of decaBDE while encouraging a shift to 'greener' alternatives. As the result of negotiations with the EPA, the two US producers of decaBDE, Albemarle Corporation and Chemtura Corporation, and the largest US importer, ICL Industrial Products, Inc., announced commitments to voluntarily phase out decaBDE in the United States (http://www.oecd.org/dataoecd/3/6/42073463.pdf).

The Stockholm Convention on POPs is a global treaty ratified by 176 parties (2013) to protect human health and the environment from chemicals that remain intact in the environment and animal and humans for long periods and have harmful impacts on human health and the environment. In 2009, tetra to heptabrominated PBDEs were added to the POP list of the Stockholm Convention (http://chm.pops.int).

7. Health based guidance values

The US Reference dose (RfD) is an estimate (with uncertainty spanning around an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg/day. The US EPA has estimated RfD values for 4 of the most abundant congeners detected in humans. The RfDs for BDE 47, 99, 153 and 209 are indicated in Table 10.

Tolerable daily intake (TDI) is an estimate of the amount of a potential harmful substance that can be taken in daily over a lifetime without appreciable health risk. TDIs are calculated on the basis of laboratory toxicity data to which uncertainty factors (UF) are applied. TDI values can be determined based on no observed adverse effect levels (NOAELs) or lowest observe adverse effect levels (LOAELs) in animal studies divided with uncertainty factors, which are used to compensate for extrapolating from less than chronic NOAEL to chronic NOAEL and for intra- and inter-species variation.

$$TDI = (NOAEL \text{ or } LOAEL)/UF$$

Based on new exposure and toxicology data the European Food Safety Authority (EFSA) published a new risk assessment on PBDEs (EFSA, 2011a). However, because there were still limitations and uncertainties in the database on PBDEs, the derivation of a health based guidance value (TDI) was not possible. Instead, the panel used a margin of exposure (MOE) approach for the risk characterization of PBDE exposure, by comparing the estimated dietary intake for the different PBDE congeners with the estimated safe daily intake.

The MOE in a population is the ratio between the safe dose and the estimate of dose or exposure in that population:

$$MOE = OAEL/\text{exposure}.$$

The typical default minimal MOE of 100 between animal study no observed adverse effect levels (NOAEL) and human exposure, covering interspecies variation = 10, and intraspecies variation = 10, is considered sufficient to conclude that there is no health concern (Aylward et al., 2011). In contrast, the EFSA risk assessment panel used a MOE as low as

Table 5
Mean (range) concentrations of PBDEs in different food categories detected in 3933 food samples collected in various European countries (EFSA, 2011a).

	BDE 47	BDE 99	BDE 153	BDE 209
Result expressed on fat weight basis (ng/g fw)				
Egg and egg products	1.30	3.20	0.74	3.98
Milk and diary	0.20	0.17	0.13	1.69
	0.52	0.44	0.28	2.83
Animal fats and vegetable oils	0.18	0.19	0.18	1.50
Result expressed on wet weight basis (ng/g ww)				
Fish and seafood	1.32	0.17	0.07	0.4
Fish meat	2.06	0.29	0.18	0.68
Products for special nutrition	1.79	0.34	0.12	2.73
Food for infants and children	0.21	0.08	0.01	–
Cod liver Norway	3.29 (12.27 2006)	0.22 (0.22 2006)	0.01 (0.04 2006)	–
Cod liver Barents sea	2.56 (3.11 2006)	0.06 (0.06 2006)	0.01 (0.04 2006)	–
Human milk NO	1.70 (0.15–56.0)	0.49 (0.16–1.42)	0.56 (ND–5.0)	0.61 (ND–5.8)
Human milk SW	1.8 (0.7 73.0)	0.50 (0.2–17.0)	0.6 (1.2–8.0)	
Human milk UK	3.0 (0.1–37)	0.90 (ND–13.0)	1.4 (ND–4.9)	
Human milk CZ	0.86 (0.16–8.13)	0.28 (0.02–2.21)	0.18 (0.03–1.14)	
Human milk DE	0.33 (0.03 15.49)	0.10 (0.03–3.65)	0.52 (0.03–6.10)	

Table 6
Range of relative contribution (%) of PBDE intake from different food categories (EFSA, 2011a).

Food category	BE 47	BDE 99	BDE 153	BDE 209
Egg and egg products	1.6–8.7	6.5–25.5	1.8–8.3	1.7–7.0
Meat and products	3.9–16.7	11.5–25.8	10.6–26.4	6.9–16.7
Animal fats and vegetable oils	4.3–20.8	1.6–8.7	15.9–36.0	19.3–43.5
Fish and seafood	32.2–78.5	5.1–29.7	2.7–17.7	2.4–16.1
Products for special nutrition	0.7–19.0	0.2–9.5	0.1–4.7	0.4–14.4

2.5, to conclude that the current dietary exposure to BDE 47, 153 and 209 in the EU does not raise a health concern. The estimated MOE for BDE 99 for young children (1–3 years old) was lower than 2.5 and the panel concluded that there is a potential health concern with respect to current dietary exposure to BDE 99.

8. Hazard and risk assessment

The EFSA risk assessment (2011) panel concluded based on the intake data and the available toxicological literature that the current dietary exposure to BDE 47, 153 and 209 in the EU does not raise a health concern while a potential health concern exists for young children (1–3 years old) with respect to current dietary exposure to BDE 99. Furthermore, even though the intake of PBDEs via milk in infants was higher than, or close to, the safety value set by EFSA it was concluded that PBDEs in human milk are unlikely to raise health concern to breast-fed infants. Dietary intake of infants (<1 year) was not considered because the panel was of the opinion that the available data were too limited to facilitate a reliable assessment of the margin of exposure (MOE) even though data exists on concentrations of PBDEs in other food and supplements such as cod liver oil (Martí et al., 2010).

Because of limitations and uncertainties in the current database on PBDEs, the derivation of a health based guidance value (TDI) was not possible and the panel used a MOE approach which is based on body burden comparison between humans and animals for the risk characterization of PBDE exposure. However, the risk assessment panel does not refer to relevant literature or justify why using a MOE approach based on body burden will help to conduct a more robust risk assessment when limited data are available. The US Environmental Protection Agency (EPA) report has concluded that when the available data are limited it is inadequate to consider body burden as an alternative dose metric for the derivation of the health based guidance value for any PBDEs (http://www.epa.gov/iris/toxreviews/1010tr.pdf). The transformation from animal to human body burden includes multiple levels of uncertainties. Firstly, as stated in the report there are considerable variations in the reported half-lives for the different congeners in both humans and rodents and calculation based on wrong half-lives increases the risk of erroneous estimates of the safe daily intake levels. Secondly, as further stated in the report, information about half-lives for BDE 99 is not available in the literature suggesting that accurate body burden comparison between rodents and humans is not possible for this congener. Thirdly, in the report the human fat percentage is set to 25%. However, considering the huge human variation in fat content, a fat content set to 25% may lead to an underestimation of the body burden for leaner individuals (Gallagher et al., 2000). Furthermore, the EFSA risk assessment panel did not include intake via house dust in the exposure calculation even though available data, which are also discussed in the EFSA risk assessment, documents substantial intakes from house dust particularly for children (D'Hollander et al., 2010). Law et al. (2014) also concluded that recent studies add weight to the hypothesis that indoor contamination can be an important driver of human body burdens of PBDEs.

Even though the panel notes that a MOE of 100 is usually used, they defined a MOE of 2.5 as a safe value. Based on the huge gaps in knowledge on kinetics and adverse effect of PBDEs, it can be questioned whether the panel should postpone drawing conclusions about human risk until robust data are available. It may also raise concern that the panel made firm conclusions based on a safety factor as low as 2.5 despite the uncertainties when assessing the human health risk for PBDEs.

The US RfD for BDE 47 and BDE 99 of 0.1 μg/kg/day gives a safe daily intake for a 6 month old baby (10 kg) of 1.0 μg/day. Schecter et al. (2003) reported 350 ng/kg PBDE (lipid weight) in breast milk (90 percentile) of US women. With an average of 4.1% fat content in human milk and a consumption of 150 g breast milk/kg body weight/day, a 6 month old infant would receive (6.1 fat/kg body weight/day∗350 ng/g∗10 kg) 21.5 μg/day which is substantially higher than the US RfD. When consuming 5 g of the most contaminated fish oil supplement indicated in Table 5, adults would receive 0.6 μg/day which is only 10 times lower than the RfD (6 μg/day for a 60 kg adult). Importantly, this adds to the exposure from other sources including 0.4 μg/day for frequent fish consumers (Table 7). In Norway, Iceland and the UK, it is recommended that infants receive a daily dose of 5 g of cod liver oil/day (http://helsedirektoratet.no/folkehelse/ernering/kostholdsrad/Documents/oppsummering-kostrad.pdf). Using the RfD of 0.1 μg/kg/day gives a safe intake of 0.5 μg/day for a 5 kg infant. Daily consumption of the cod liver oil with the highest concentrations indicated in Table 5, gives a daily dose of 0.2 μg/day, which is approximately half of the safe dose. This comes in addition to the amount of PBDEs the child would receive through breast milk, house dust and from other environmental sources (Table 7).

Recently, not only PBDEs but also various hydroxylated (OH–) and methoxylated (MeO–) metabolites of PBDEs have been found to bioaccumulate in fish and mammals including humans and the metabolites have the potential to induce various adverse effects on among other endpoints thyroxin signaling and neurotoxicity (De la Torre et al., 2013; Dingemans et al., 2011; Rotander et al., 2012). Furthermore, PBDEs and their metabolites are present in animals and

Table 7
Estimated dietary intake (ng/kg body weight) of PBDEs in different groups of the population. The estimates are based on concentrations measured in 4000 food samples (EFSA, 2011a).

Population	BDE 47 median (range)	BDE 99 median (range)	BDE 153 median (range)	BDE 209 median (range)
Infants (General pop.)	– (3.63–18.05)	– (1.54–6.93)	– (0.10–0.88)	– (2.81–12.88)
95th percentile	– (10.41–69.41)	– (3.92–20.01)	– (0.26–1.84)	– (6.33–42.23)
1–3 years (General pop.)	4.02 (1.04–6.40)	1.93 (0.58–2.99)	1.09 (0.09–1.62)	6.02 (1.55–9.69)
95th percentile	10.38 (4.44–15.57)	4.14 (1.36–6.16)	1.75 (0.20–3.18)	10.54 (2.90–17.6)
3–6 years (general pop.)	1.78 (0.82–3.61)	1.12 (0.39–1.56)	0.87 (0.07–1.42	5.36 (0.86–7.41)
95th percentile	4.86 (2.92–8.63)	1.90 (0.85–3.11)	1.53 (0.15–2.30)	8.33 (1.69–11.19)
6–10 years (general pop.)	1.27 (0.38–2.61)	0.78 (0.17–1.24)	0.66 (0.04–1.12)	3.82 (0.54–5.91)
95th percentile	3.27 (1.96–6.98)	1.45 (0.51–1.54)	1.11 (0.11–1.70)	6.59 (1.32–11.90)
10–18 years (general pop)	0.85 (0.21–1.68)	0.46 (0.09–0.66)	0.36 (0.02–0.54)	2.17 (0.34–3.17)
95th percentile	2.78 (1.24–4.60	0.97 (0.26–1.28)	0.69 (0.06–0.90)	4.25 (0.74–5.92)
General population	0.72 (0.29–1.91)	0.35 (0.11–0.65)	0.26 (0.03–0.42)	1.69 (0.35–2.82)
95th percentile	1.97 (1.10–4.51)	0.67 (0.30–1.07)	0.48 (0.07–0.67)	3.02 (0.70–4.58)
Frequent fish consumers	– (5.10–5.36)	– (0.49–0.75)	– (0.21–0.47)	– (0.11–1.77)
Supplement (fatty acids) consumers	– (0.91–2.53)	– (0.22–0.77)	– (0.05–0.46)	– (1.66–4.27)

Table 8
PBDE intake in Norway from diverse food types. The estimates are based on wet weight levels in the different food items (http://www.vkm.no/dav/2158765ff5.pdf).

Food item	Contribution %
Fatty fish	50
Lean fish	6
Fish products	17
Shell fish	3
Meat eggs	10
Dairy products	5
Bread cakes	9

humans in combinations with multiple environmental pollutants. So far most of the toxicological research has focused on single agents with almost complete neglect of mixed exposure, and only single agent exposure is currently considered by risk assessment authorities including EFSA (Lyche et al, 2012).

9. Conclusion

The widespread use of BFRs in consumer products and their persistent nature lead to ubiquitous exposure of humans and wildlife from fetal life to adulthood. The general North American human population have higher BFR levels than the European and Japanese population. BFR concentrations are higher in children than in adults. The highest levels were detected in infants and toddlers, because of exposure from breast milk and house dust. The daily intake via breast milk exceeds the RfD in 10% of US infants. Fish were most highly contaminated, followed by meat and dairy products in the US and Europe. However, unlike many European countries where fish predominates, dietary intake of PBDEs in the US is mostly from meat, then fish and then dairy products. House dust is also reported as an important source of exposure for children as well as adults. In animal studies, exposure to BFRs including PBDEs, HBCDs and TBBP-A has induced endocrine-, reproductive- and behavior effects at doses not far from the human exposure. Furthermore, recent human epidemiological studies have reported association between exposure to BFRs and similar adverse effects as observed in animal studies.

Fish including farmed fish and crude fish oil for human consumption may contain substantial levels of BFRs and infants and toddlers consuming these products on a daily basis may exceed the tolerable daily intake suggesting that fish and fish oil alone represent a risk to human health. This intake comes in addition to exposure from other sources (breast milk, other food, house dust). Because potential harmful concentrations of BFRs and other toxicants occur in fish and fish products, research on a wider range of products is warranted, to assess health hazard related to the contamination of fish and fish products for human consumption.

Table 10
RfD values estimated by US, EPA.

Congener	RfD	Reference
BDE 47	0.1 μg/kg/day	http://www.epa.gov/ncea/iris/subst/1010.htm
BDE 99	0.1 μg/kg/day	http://www.epa.gov/ncea/iris/subst/1008.htm
BDE 153	0.2 μg/kg/day	http://www.epa.gov/ncea/iris/subst/1009.htm
BDE 209	7.0 μg/kg/day	http://www.epa.gov/ncea/iris/subst/0035.htm

Acknowledgments

This work was funded by grant 172017/V10 from the Norwegian Research Council and Pronova BioPharma, Oslo, Norway.

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Table 9
Estimated dietary daily intake (ng) of [a]PBDEs (minus BDE 209) and [b]BDE (47, 99, 100, 153, 154) from different foods and breast milk.

Country	Daily intake	References
Dietary intake		
Sweden	[b]51[mb]	http://www.vkm.no/dav/2158765ff5.pdf
Sweden nursing women	[b]27[mb]	http://www.vkm.no/dav/2158765ff5.pdf
Spain	[a]97[mb]	http://www.vkm.no/dav/2158765ff5.pdf
UK	[b]90[lb]	http://www.vkm.no/dav/2158765ff5.pdf
Finland	[b]44[lb]	http://www.vkm.no/dav/2158765ff5.pdf
Norway adults	[b]170[mb]	http://www.vkm.no/dav/2158765ff5.pdf
Fish consumers Lake Mjøsa	[a]4130[mb]	http://www.vkm.no/dav/2158765ff5.pdf
Intake from breast milk and different sea food		
Canada breast milk	[a]9000[ub]	Jones-Otazo et al. (2005)
US breast milk	[a]12,800[ub]	Schecter et al. (2003)
Norway breast milk	[a]490[ub]	http://www.vkm.no/dav/2158765ff5.pdf
Canada salmon	[a]225[mb]	Rawn et al. (2009)
Canada salmon oil	[a]25[mb]	Rawn et al. (2009)
Norway cod liver oil	[a]50[mb]	http://www.vkm.no/dav/2158765ff5.pdf
Canada shark oil	[a]185[mb]	Rawn et al. (2009)

lb = lower bound, mb = medium bound, up = upper bound.

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