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Topic 3.5

Brominated flame retardants and endocrine disruption*

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Abstract: From an environmental point of view, an increasing important group of organohalogen compounds are the brominated flame retardants (BFRs), which are widely used in polymers and textiles and applied in construction materials, furniture, and electronic equipment. BFRs with the highest production volume are the polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBP-A), and hexabromocyclododecane (HBCD). Because of their persistence and low biodegradation profile, several of the PBDE congeners accumulate in biota and are widely found in the aquatic food chain. Their levels in the environment and in humans have increased during the last decades, in contrast to compounds such as polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT), for example. Humans may be exposed to PBDEs mainly through consumption of fatty food of animal origin (e.g., fish), but exposure through skin contact with textiles protected with flame retardants or through inhalation of BFRs volatilized from electronic and electric equipment may also occur. The levels of PBDEs in Swedish human milk showed a doubling in concentration every five years over the period 1972 to 1997 (2,2′,4,4′-tetraBDE being the predominant congener). The levels of penta- and hexa-BDEs increased at the same rate in ringed seals collected in the Canadian Arctic from 1981 to 2000. PBDEs exhibit a great variety of biological effects, depending on the bromine substitution pattern. PBDEs are potential endocrine disrupters, based on shared toxicity with the structurally related PCBs, polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzo-*p*-dioxins (PCDDs) (partial aryl hydrocarbon- [Ah-] receptor agonist and antagonist activity in vitro, thyroid toxicity, and immune effects), including developmental toxicity. The potency of TBBP-A to interact with thyroid hormone homeostasis is indicated from in vitro studies in which the compound competes with thyroxin (T4) for binding to transthyretin (TTR). So far, the toxicological profile of many BFRs is too incomplete and insufficient to perform an adequate risk assessment, and further information is required regarding the potential for endocrine disruption of these compounds that are of increasing environmental concern.

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INTRODUCTION

There is growing concern about the possible harmful consequences of exposure to xenobiotic compounds that are capable of modulating or disrupting the endocrine system. This concern for endocrine-disrupting chemicals (EDCs) is directed at both humans and wildlife [4,38]. Several expert working groups [1,21,44,47,48] have concluded that there is increasing evidence of adverse effects in human and wildlife reproductive health, and have discussed the hypothesis that chemicals in the environment have caused these endocrine-mediated adverse effects. Endocrine disruption is a complex area to address and it is difficult to establish causal links between exposure to suspected EDCs and any measured effects. The most prominent and persistent organic pollutants that are associated or even causally linked with endocrine disruption in wildlife and in human individuals are the organohalogen compounds (OHCs), including dichlorodiphenyltrichloroethane (DDT) and metabolites, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs). From an environmental point of view, an increasing important group of OHCs are the brominated flame retardants (BFRs)

Flame retardants constitute a diverse group of compounds used to prevent fires or minimize the extent of a fire. The worldwide annual production of flame retardants was estimated as 600 000 tons in 1992 [23]. There are three main categories of chemical flame retardants: halogenated hydrocarbons, organophosphorous compounds, and inorganic products often based on metallic hydroxides; these represent 45, 24, and 27 %, respectively, of the total market of flame retardants in 1999 (see ref. [41]). The BFRs are made up of structurally very different chemicals with a wide variety in physicochemical and reactivity characteristics [2]. Important BFRs are the polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBP-A), and hexabromocyclododecane (HBCD) (Fig. 1), high-production-volume chemicals that are widely used in polymers and textiles and applied in construction materials, furniture, and electric and electronic equipment. The annual market demand in 1999 has been estimated as 67 000 tons for PBDEs and 121 000 tons for TBBP-A [41]. The properties of PBDE congeners are variable as well [7,20]. There are three groups of industrial products of PBDEs with an average of five (pentaBDE), eight (octaBDE), or ten bromine atoms (decaBDE) in the molecule, while the theoretical number of possible congeners is 209. Further, photolytic degradation of decaBDE forms by debromination a large number of PBDE congeners not found in technical products of PBDEs [37]. PBDEs are highly lipophilic compounds and generally have a low biodegradation profile. In contrast to PCBs and DDT, the levels of some BFRs, such as PBDEs, show an increasing trend in wildlife and humans dur-

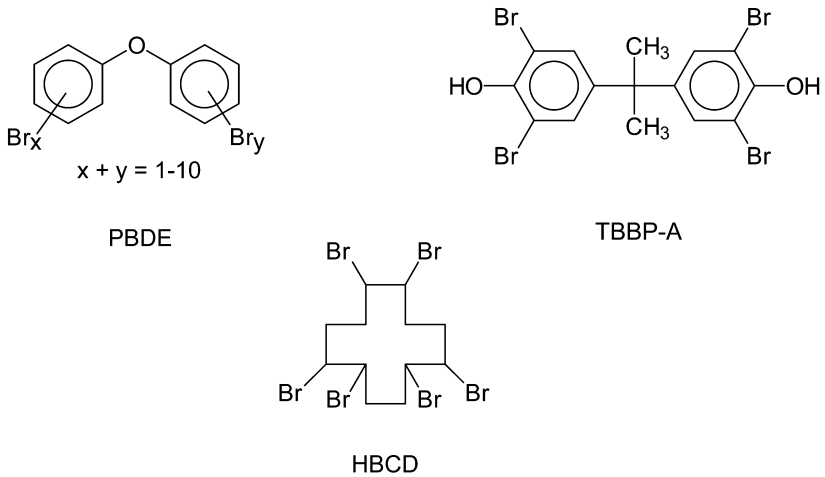

Fig. 1 Chemical structures of polybrominated diphenyl ethers (PBDE), tetrabromobisphenol A (TBBP-A), and hexabromocyclododecane (HBCD).

ing the last decades. Based on shared toxicity with the structurally related PCBs, PCDFs, and PCDDs, PBDEs are potential endocrine disruptors. Moreover, PBDEs may be contaminated with polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDDs/PBDFs), compounds that also can be formed during combustion of PBDEs. These substances are regarded as equally toxic as their chlorinated counterparts [26].

EXPOSURE DATA

PBDEs accumulate in environmental biota and are widely found in the aquatic food chain [24,36,49], including the Canadian Arctic [22]. Notably, they were found in top predators, such as the harbor seal and in the sperm whale; the latter finding indicates that PBDEs also occur in deep-sea food chains [8]. In the abiotic environment, a wide variety of PBDEs have been found, ranging from congeners with three to ten bromine atoms. From a quantitative point of view, decaBDE is the most dominant PBDE in sediments, up to milligram per kilogram (mg/kg) levels. Debromination of decaBDE may yield PBDE congeners with higher bioavailability and toxicity. Other important lower brominated PBDE congeners in sediment are 2,2′,4,4′-tetraBDE (BDE-47), 2,2′,4,4′,5-pentaBDE (BDE-99), 2,2′,4,4′,6-pentaBDE (BDE-100), and 2,2′,4,4′,5,5′-hexaBDE (BDE-153). These congeners can be found, for example, in sewage sludge and sediment up to several hundreds of micrograms per kilogram (μg/kg) dry weight [9,17], while, in addition, decabrominated BDE can be present into the mg/kg dry weight range [9].

Tissue analysis of wildlife and fish has shown that PBDEs can accumulate, with BDE-47, BDE-99, BDE-100, and BDE-153 being the dominant congeners present [7,11]. The first three are the predominant congeners present in ringed seal from the Canadian Arctic. In humans, these PBDEs have also been found in blood, adipose tissue, and milk with mean levels ranging between 4 and 16 ng/g lipid [10,32,39,42], and levels of approximately 200 ng/g lipid were reported recently in a pooled sample of human milk from the United States (levels of 132, 27, and 15 ng/g lipid of BDE-47, BDE-99, and BDE-153, respectively) [33]. Humans may be exposed to PBDEs mainly through the consumption of fatty food from animal origin (e.g., fish), but exposure through skin contact with textiles protected with flame retardants or through inhalation of BFRs volatilized from hot electrical equipment may also occur. For example, subjects working at an electronics dismantling plant had elevated plasma levels of higher brominated BDEs and TBBP-A [42].

An important observation is that, in contrast to PCBs and DDT, for example, the levels of PBDEs are increasing in human milk: a study in Sweden showed a doubling in concentration every five years over the period 1972 to 1997, with BDE-47 being the predominant congener [31] (Table 1). From 1998 to 2000, a decrease in PBDE levels was noticed that can be a consequence of the phase-out of commercial pentaBDE in Sweden [15]. The temporal trends and influence of age and gender on six BDE congeners was investigated on archived serum samples from Norway [43]. The sum of the BDEs increased from 0.44 ng/g lipids in 1977 to 3.3 ng/g in 1999, with BDE-47 being the most abundant congener. BFR levels in the different age groups were relatively similar, except for the age group of 0 to 4 years, which had 1.6 to 3.5 times higher serum concentrations, with breast milk considered the main source.

Table 1 Temporal trend of PBDEs in Swedish human milk[a].

	1972	1976	1980	84/85	1990	1994	1996	1997	1998	1999	2000
BDE-47	0.06	0.18	0.28	0.49	0.81	1.48	2.08	2.28	2.29	1.97	1.70
Sum of PBDE congeners	0.07	0.35	0.48	0.73	1.21	2.17	3.11	4.02	3.90	3.47	2.80

[a]Levels in ng/g lipid of pooled milk samples (after [15]).

PBDE concentrations showed an exponential increase in ringed seals collected from subsistence hunts in the Canadian Arctic in 1981, 1991, 1996, and 2000, with doubling of the penta- and hexa-BDE in less than five years; the current PBDE concentrations are 50 times lower than those of mono-ortho and non-ortho PCBs [22]. In fish and birds from the Baltic region, increasing levels of BDE-47, -99, and -100 have been reported since the 1970s but have begun to decline or level off in the 1990s [11], which can be a consequence of the phase-out of commercial pentaBDE in Sweden. Increasing levels of PBDEs in fish and birds are also reported for the U.S. Great Lakes, while PCBs levels have decreased during the same time frame. In different fish species collected in 2000 from the North Sea and the Celtic Sea, levels of BDE-47 were similar to levels of PCB 153 and *p*,*p*-DDE, whereas levels of hexachlorobenzene (HCB) and toxaphene (CHB-50) were lower (Fig. 2). The occurrence and fate of decaBDE is less well known, partly due to analytical difficulties and the fact that the compound has not been prioritized as an analyte, but also due to the different environmental fate of decaBDE as compared to other PBDEs. Further, little is known about other BFRs concerning environmental persistence, bioaccumulation, and toxicological effects, in spite of the fact that these compounds are also high-production-volume chemicals. TBBP-A has been detected in occupationally exposed persons, while HBCD has been found in wildlife and in environmental samples; no HBCD data on humans have so far been presented [2,3,42]. TBBP-A is rapidly excreted by mammals [16] while nothing is known about TBBP-A derivatives in this context. Thus, PBDEs have been steadily increasing over the last decades in biota (including humans), while much less has been published on other BFRs, such as TBBP-A and HBCD. Consequently, the question arises as to what extent these BFRs pose a risk to species higher in the food chain, in particular to top predators and humans. Human exposure probably occurs mainly via food in analogy to PCBs and related compounds, but occupational exposure (e.g., through handling electronic equipment) may also play a significant role. However, it should be noted that detailed information regarding the routes of human exposure to BFRs is presently lacking.

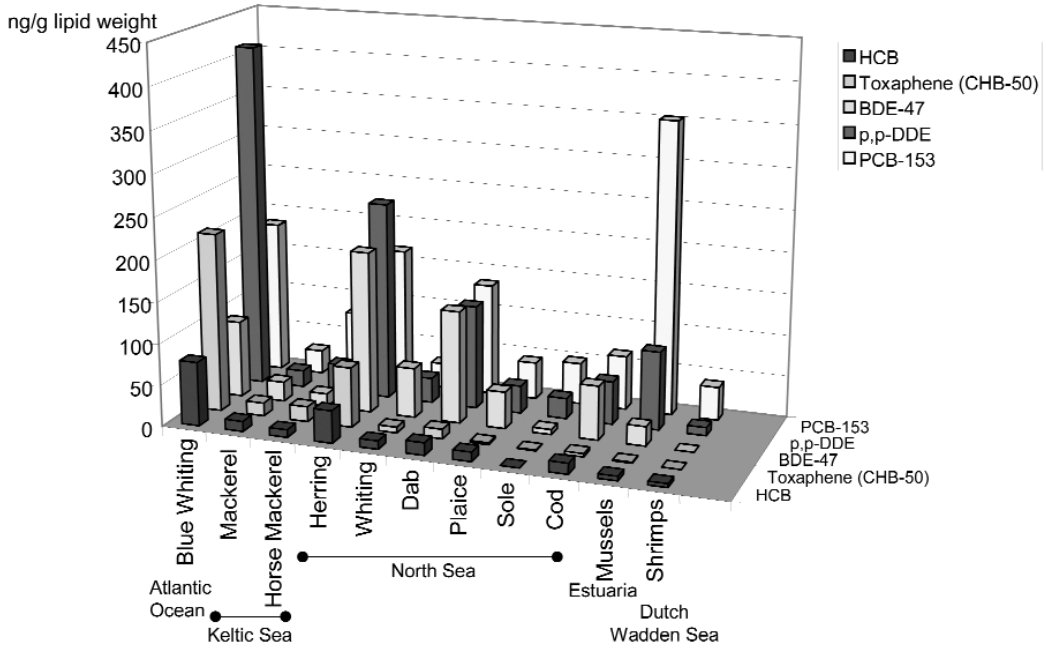

Fig. 2 Contaminant profile of fish, mussels and shrimp caught in 2000 in different waters (pooled samples of 25 animals each).

EFFECT DATA

For a review of the toxicity of BFRs, see refs. [7,19,24,25,27]. From these studies, it can be concluded that there is a lack of information regarding the potential for BFRs to cause endocrine disruption. Alteration of endocrine function by BFRs is realistic as there are striking resemblances in toxicological effects between the chlorinated aromatic hydrocarbons PCBs, PCDFs, and PCDDs and the PBDEs (i.e., partial aryl hydrocarbon- (Ah-) receptor agonist and antagonist activity in vitro, thyroid toxicity, and immune effects). Thus, PBDEs may produce toxic effects in a number of ways. The structural resemblance to thyroxin may explain interaction with the thyroid hormone system, and effects on thyroid function seem to be a sensitive endpoint. Decreased serum T4 levels were shown in mice exposed to a penta-BDE mixture [14] as well as to the 2,2′,4,4′-BDE congener (BDE-47) [18]. In addition, it was found that PBDEs after metabolic activation compete with the thyroid hormone (T4) for binding to transthyretin, the T4 transporting protein [29]. Following perinatal maternal exposure of rats to DE-71 (a commercial tetra- and penta-BDE mixture), reduced serum T4 was measured in the offspring showing its developmental toxicity [51]. Neonatal exposure to BDE-47 and BDE-99 has been found to induce neurotoxic effects in the adult animal [12]. In mice, the penta-BDE mixture also produced a decrease in the thymus/body weight ratio and in the antibody response to sheep red blood cells, and increased the activity of the hepatic cytochrome P450 mixed function oxidase system [14].

Using the in vitro CALUX-assay, pure PBDE-congeners appeared to act via the Ah-receptor signal transduction pathway as agonists, but mainly as antagonists [28]. A recent in vivo study with rats and commercial PBDE mixtures also indicated that hepatic induction of CYP1A1 and CYP2B activities could occur [50]. The former activity is of special relevance as this is an Ah-receptor-mediated process, which is common for dioxin-like compounds and PCBs, and most of the toxic responses (including the immunotoxicity) of dioxin-like compounds are mediated through binding to this receptor [34,35,46]. Persistent compounds with this type of mechanism are included in the toxic equivalency concept (TEF) and are now generally used in risk assessment procedures [45]. The CYP2B induction found in in vivo studies is also of toxicological interest, as this indicates the activation of multiple genes (e.g., glucocorticoid) associated with the phenobarbital responsive unit [50]. Finally, limited in vitro data indicate that some PBDEs and their hydroxylated metabolites can act as estrogenic compounds—data that suggest that in vivo metabolism of PBDEs might produce more potent pseudoestrogens [30]. The information about the toxicological effects of TBBP-A and HBCD is even more limited [25]. In vivo studies with TBBP-A and rats indicated that this compound can cause hepatotoxicity and disturbance of the haem synthesis [40]. In addition, it was shown that TBBP-A and lower brominated analogs can be potent competitors with T4 for binding to transthyretin (TTR) in vitro [30].

DISCUSSION

The toxicological profile of many BFRs is too incomplete and insufficient to perform an adequate human and ecological risk assessment. For a selected number of BFRs (including PBDEs and TBBPA), interactions with thyroid hormone homeostasis, estrogen, and Ah (dioxin) receptor have been reported. However, these studies are based only on in vitro or short-term experiments; therefore, significant gaps in knowledge exist for the situation of chronic and low-level exposure of humans and wildlife. Most notably, the PBDEs exhibit a high variety of biological effects, depending on the bromine substitution pattern. As these PBDEs occur in the environment in complex mixtures, the identification of biological and toxicological structure–activity relationships (SARs) is of great importance for understanding the mixture toxicity of this group of compounds. In addition, there is very little information available regarding useful biological or toxicological markers of low-level exposure to these compounds. Because of this lack of information and the apparently similar toxicity of structurally related PCBs and dioxins (partial Ah-receptor agonist and antagonist activity in vitro, thyroid toxicity, and immune effects) the European Union (EU) Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE)

concluded that further information is required regarding the potential of (PeBDE) for endocrine disruption and/or dioxin-like effects. This was concluded for both human and environmental risk assessment [5,6]. In response to the need for research on endocrine disruptors, the European Union allocated a budget of €20 million, and proposed four projects for funding, including a project on BFRs [13].

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