HEALTH EFFECTS OF BROMINATED FLAME RETARDANTS (BFRs)

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Abstract
Brominated flame retardant use has increased dramatically in order to provide fire safety to consumers. However, there is growing concern about widespread environmental contamination and potential health risks from some of these products. The most used products have been TBBPA, HBCD, and several PBDE mixtures, although the Penta- and Octa-PBDE commercial mixtures are no longer produced. TBBPA is relatively less persistent and bioaccumulative than most of the others, not acutely toxic, but does have potential to cause endocrine disruption. HBCD is persistent, bioaccumulative, induces enzymes, and alters thyroid homeostasis, among other responses. As for the PBDEs, the composition in the commercial mixture is different from that in biota. While the Deca-PBDE mixture is still made and used, BDE209 is less persistent and bioaccumulative than the lower brominated congeners, into which it can break down. However, Deca can cause cancer and developmental effects. The Penta and Octa mixtures, as well as several of the major congeners present in wildlife and people, can alter liver enzymes, affect thyroid levels, and are associated with developmental reproductive and neuro-toxicity. In North America, there is little margin of exposure between the most highly exposed people in the general population and the levels in animals where effects have been observed.

Introduction
Flammability standards exist for many consumer products and equipment in order to reduce fires. Due both to their efficiency and cost, flame retardants containing bromine have constituted the largest share of this market [1]. The three largest products have been TBBPA (tetrabromobisphenol A) (Figure 1); HBCD (hexabromocyclododecane) (Figure 2); and the PBDEs (polybrominated diphenyl ethers) (Figure 3).

N.*B.*For a general review of BFRs, see Birnbaum and Staskal, 2004 [2]

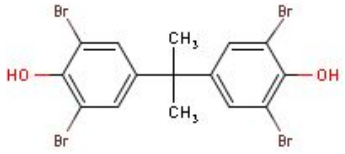

Figure 1

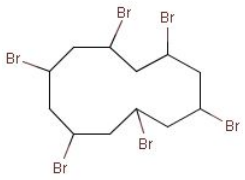

Figure 2

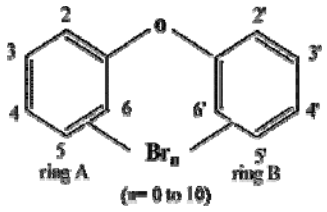

Figure 3

Literature Review
TBBPA is the largest volume product, primarily used in electronics, and mainly in a reactive mode. In contrast, HBCD and the PBDEs are strictly additive BFRs. The use of HBCD, a mixture of 3 stereoisomers, is growing in electronics and thermal insulation in buildings. There are potentially 209 BDE congeners; however, not all occur in the commercial products[3] (Guardia et al, 2006). While Deca production and use in hard plastics and textile backing continues, the Penta and Octa mixtures, used mainly in polyurethane foam and electronics, are no longer made,. The PBDEs are not dioxin-like, but the commercial products are contaminated with PBDDs/PBDFs[5]
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Widespread environmental contamination by these chemicals exists with increasing concentrations in air, water, soil, sediment, and wildlife: fish, birds, marine mammals. Many PBDEs and HBCD are persistent, bioaccumulative, and biomagnify up the food chain. They are also present in people[6,7]. The relative congener profiles in biota are usually different from those in the commercial products, suggesting a key role for environmental fate and transport as well as metabolism[8,9]. The lowest biotic concentrations are reported for TBBPA, followed by HBCD, and then the sum of the PBDEs. Concentrations of ΣBDEs, especially in people, are much higher in North American than in Europe or Asia, and have been reported to reach levels in the ppm lipid range.

In contrast to the PBDEs and HBCD, TBBPA is only moderately persistent and bioaccumulative. It is relatively non-toxic following acute exposures [10]. However, TBBA disrupts thyroid homeostasis and can alter estrogenic signaling. There are also *in vitro* studies suggesting hepatotoxicity, immunotoxicity, and neurotoxicity [11]. TBBPA is metabolized both oxidatively and by conjugation [12] but does not induce metabolizing enzymes [13]. It has not been tested in long term studies.

HBCD is slightly irritating, and repeated dose toxicity involves primarily the liver and thyroid. It can induce hepatic metabolizing enzymes [13] and has been shown to alter thyroid homeostasis[14]. It also has the potential to be developmentally neurotoxic. One of the stereoisomers appears to be more readily eliminated [15]. It has not been tested in chronic studies.

The greatest concern has centered on the PBDEs, due to their exponential rise in biota and people. While this rise may have peaked in Europe, levels continue to increase in North American samples. In fact, ∑BDEs has been reported to approach 10 ppm lipid in human adipose tissue [16], and exceeds 50 ppm lipid in bird eggs[17]. The sources of human exposure are not yet defined, and while diet is likely significant [18], indoor air [19] and house dust [20,21] are likely major contributors. The concentrations in human tissues in North America far exceed those measured in Europe. However, the congener profiles are similar, and while the BDEs present, and measured, are largely similar to those in the commercial Penta product, the ratios of the congeners are very different [22] with BDE47 being the major congener in most biotic samples, although certain recent studies have shown BDE153 to be the most common [23]. Whether this pattern change is due to fate and transport, metabolism up the food chain, differential stability of the different congeners, and/or differences in their pharmacokinetics remains to be determined.
In fact, recent pharmacokinetic studies have suggested that BDE99 is the most readily metabolized of the lower brominated congeners and PBDE 153 may be the most persistent [24]. BDE209 appears to have a relatively short half-life in people [25], and appears to undergo metabolic debromination as well as oxidation.

Acute toxicity studies have been conducted with the commercial PBDE mixtures and some of the major congeners, including BDE 47, 99, 153, and 209. Repeated dose studies have suggested that the mixtures, as well as some of the individual congeners, can be hepatotoxic at relatively high doses. The only mixture that has been subjected to chronic toxicity studies in rodents is Deca which caused an increase in hepatic and thyroid tumors following a high dose two year feeding study. In general, the lower brominated mixtures are more acutely toxic than the higher ones.

The presence of brominated dioxins and furans in the commercial products may explain the reported immunosuppression of the commercial PBDEs. The greatest concerns surround the issues of endocrine disruption, developmental reproductive toxicity, and developmental neurotoxicity. Disruption of thyroid homeostasis has been known for several years. The Penta mixture and several of the lower brominated congeners may be either estrogenic[26] or anti-estrogenic [27]. Several PBDEs are potent anti-androgens *in vitro* [28], and the commercial Penta product is anti-androgenic *in vivo* [29]. Low dose gestational exposure to BDE99 affects both male and female sexual development and leads to permanent changes in both testes and ovaries in the offspring [30, 31]. Postnatal exposure of male mice to BDE209 permanently alters sperm functions[32].

The developmental neurotoxicity of the PBDEs has raised the most concern. Commercial Penta as well as several individual congeners have been studied in rats and mice. Concern was initially raised by studies exposing infantile mice to BDE99 by Eriksson and coworkers [32]. This laboratory has shown that BDEs 47, 99, 153, 203, 206, and 209, among others, all cause permanent effects on learning, activity, and behaviors following exposure to the 10-day old rodent [33-35]. They hypothesize that the developmental neurotoxicity of BDE 209 is due to a metabolite[36]. Recently, Rice and co-workers confirmed the developmental neurotoxicity of BDE209 in mice[37]. Our laboratory has shown that the elimination of BDE 47 is much slower in pre-pubertal mice than in adults, resulting in elevated brain concentrations in pups compared to adults [38]. Effects on various neurobehavioral endpoints have also been shown by other laboratories [27,30,31,39,40]. Mechanistic studies have suggested that these effects could be related to effects on thyroid homeostasis, oxidative stress, or cell signaling processes, such as PKC and calcium mobilization [41-45].

Conclusions

To date, no epidemiological studies looking for effects have been published. There are several cohorts currently under investigation. However, a comparison of the body burdens in experimental animals, at which some of the sensitive developmental effects have been observed, and those in people at the high end of the general population in North America, suggest that there is little margin of exposure [46]. Whether levels in wildlife and people continue to rise given the cessation of production of Penta and Octa remains to be determined.

Disclaimer

This abstract does not reflect Agency policy.

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