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Toxic effects of brominated flame retardants in man and in wildlife

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Abstract

Brominated flame retardants (BFRs) are ubiquitous industrial chemicals, and many of them are produced in large volumes. Due to this fact, several BFRs are found in quantifiable levels in wildlife, as well as in humans. However, we are still lacking information on the effects of BFR in wildlife and, especially, in man. This review summarises the biological effects of polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and derivates, hexabromocyclododecane (HBCD) and polybrominated biphenyls (PBBs), however excluding other aspects such as environmental levels. These BFR groups were selected because of a large volume production (PBDEs, TBBPA and derivates), and availability of some toxicity data in spite of much lower production volumes (HBCD and PBBs). In addition, the increase in levels of PBDEs in human (breast milk) and wildlife samples during later time made it especially interesting to include this BFR group. *PBDEs:* The commercial PBDE products predominantly consist of so-called penta-, octa- and decabromodiphenyl ether products. Each product consists of a rather narrow range of congeners and is named after the dominating congener as regards the bromination pattern. Generally, the PentaBDEs seem to cause adverse effects at the comparably lowest dose, whereas much higher doses were needed for effects of the DecaBDEs. The critical effects of PentaBDEs are those on neurobehavioural development (from 0.6 mg/kg body weight) and, at somewhat higher dose, thyroid hormone levels in rats and mice, of OctaBDEs on fetal toxicity/teratogenicity in rats and rabbits (from 2 mg/kg body weight), and of DecaBDEs on thyroid, liver and kidney morphology in adult animals (from 80 mg/kg body weight). Carcinogenicity studies, only performed for DecaBDEs, show some effects at very high levels, and IARC (1990) evaluates DecaBDEs not classifiable as to its carcinogenicity to humans. *TBBPA:* The toxicity of TBBPA in the experimental in vivo studies is suggested to be low. In most reported studies, only doses in g/kg body weight were effective, but at least one study suggested renal effects at around 250 mg/kg body weight. Although difficult to include and interpret in a quantitative risk assessment, the in vitro effects on immunological and thyroid hormones, as well as binding to erythrocytes should be noted. Before a solid standpoint could be reached on TBBPA toxicity additional studies must be performed. This statement is even more valid regarding the TBBPA derivates, where there is an almost complete lack of toxicity data. *HBCD:* Also in the case of HBCD, relevant toxicity studies are lacking. Based on the present animal studies, a critical effect is seen in the liver and on thyroid hormones (LOAEL 100 mg/kg body weight/day). However, in a recent short paper behavioural effects in mice pups were observed already at 0.9 mg/kg body weight, and behavioural effects may be a sensitive endpoint for HBCD, as well as for other BFRs. *PBBs:* Due to the Michigan accident in 1973–1974, many toxicity studies on PBBs are available. The critical experimental effects are those on reproduction and carcinogenicity, and a NOAEL of 0.15 mg/kg body weight/day could be suggested based on the cancer effects. In man no unequivocal effects have been observed, although in some studies neurological and musculoskeletal symptoms were suggested. Based on the carcinogenic effects in animals, a human TDI of 0.15 μg/kg body weight has been presented.

To conclude, the toxicity data are almost entirely based on experimental models. There are differences among the BFR groups, as well as within these groups, both regarding type of toxic effect and at what dose it appears. As BFRs will continue to appear both in industrial applications and, even if the production has ceased, in our environment, there is a continued need for effects studies on BFRs.
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1. Overview

Brominated flame retardants (BFRs) are ubiquitous chemicals with large and global industrial use, and many of them are still produced in large volumes. Due to this fact, several BFRs are found in quantifiable levels in wildlife as well as in humans (e.g. De Wit, 2002). However, we still know little about the effects of BFRs in wildlife and in man. Among the BFRs, the best environmental and human risk assessment data are available for polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs). The interest for PBBs stems mainly from the contamination incident in Michigan 1974, where PBBs by accident were

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given to farm animals. As a result, individuals living on affected farms and consumers of contaminated farm products were exposed to these compounds for months before the mistake was discovered. Regarding PBDEs, the high production volume and the structural resemblance to other well-known environmental contaminants such as polychlorinated biphenyls (PCBs) are two main reasons for environmental and health concern. Several BFRs are accumulated in biota, and in many cases the highest levels in wildlife are found in the aquatic environment. In the PBDE example, water-living mammals (e.g. whales), fatty fishes and/or fishes near point sources of contamination could reach very high levels. PBDEs and occasionally also other BFRs are found in human breast milk and adipose tissues in several western countries, and the PBDE levels in both biota and in breast milk have increased in later time. This article will give a brief overview of the effects that have been observed or proposed to be related to BFR exposure, and will focus on data relevant for human risk assessment.

2. Definition of study area

BFRs are produced in a volume of ca. 150 000 tons/year (OECD, 1994). Of the total BFR volume produced, about one-third consist of PBDEs, another third consist of tetrabromobisphenol A (TBBPA) and derivatives, and the last third contain various other brominated compounds, two examples being PBBs and hexabromocyclododecane (HBCD). In this last group, IPCS have registered over 30 brominated compounds with flame-retardant usage (IPCS, 1993). Of these, most of them have an aromatic structure, but also aliphatic, cycloaliphatic, heterocyclic and bromophosphorous compounds are listed. However, the majority of the compounds in the latter group are used, if at all, in small quantities and little is known of their possible effects in biological systems. Because of earlier usage and the Michigan contamination accident, the PBBs are rather well studied. As regards the HBCD, high levels (compared to other BFRs) have been found in aquatic biota from polluted areas (e.g. Sellström et al., 1998).

This article summarises the biological effects of PBDEs, TBBPA and derivatives, PBBs and HBCD. The decision for selecting these BFR compounds for review was made based on large volume production (PBDEs, TBBPA and derivates), and availability of exposure and toxicity data in spite of much lower production volumes (PBBs and HBCD). In addition, the increase in levels of PBDEs in human (breast milk; Meironyté Guvenius, 2002) and wildlife (Ikonomou et al., 2002) samples during later time made this BFR group of special interest. It should be noted that only data on the *toxic effects* of the mentioned substances will be discussed in this chapter, and not environmental levels, toxicokinetic properties, or some other aspects of them. Moreover, there will be a focus on effects that are of importance for *human risk assessment*, i.e. mainly mammalian toxicity studies, and nonmammalian effect data will be reviewed in less detail. Lastly, the present compilation will not try to include all the published articles in this area, but will primarily concentrate on those critical studies that will be of main use in the risk assessment of these chemicals. In case of enzyme induction, it is doubtful if these effects could be considered as adverse, and microsomal enzyme induction will therefore not be considered to be an important critical effect in the risk assessment of PBDEs.

3. Data search methods

In this review, I have compiled data and used references from the available IPCS documents for each flame retardant group (PBDE—IPCS, 1994a; TBBPA—IPCS, 1995; PBB—IPCS, 1994b).The KEMI draft document on HBCD (KEMI, 2002) has also been very valuable. In addition, other available reviews on flame retardants (Darnerud et al., 2001; Peltola and Ylä-Mononen, 2001; De Wit, 2002; Hardy, 2002) have been used. New studies have been found by the selected searching in useful databases, e.g. the National Library of Medicine PubMed Service and iNFOTRIEVE®.

4. PBDE

The commercial PBDE products predominantly consist of so-called penta-, octa- and decabromodiphenyl ether products. Each product consists of a rather narrow range of congeners and is named after the dominating congener as regarding the bromination pattern. PBDE congeners are often identified by the IUPAC nomenclature originally invented for denomination of PCB congeners (Ballschmiter and Zell, 1980). Today, decabromodiphenyl ether (DecaBDE) is the largest product on the market and makes up over 80% of the total production of PBDEs, whereas pentabromodiphenyl ether (PentaBDE) and octabromodiphenyl ether (OctaBDE) products constitute about 12% and 6%, respectively, of the total PBDE production (www.bsef.com; De Wit, 2002). Examples of products containing PBDEs are various plastic components in electronic devices (e.g. cabinets, circuit boards, cables, switches, capacitors) and in cars and in building materials, and textiles.

Most of the toxicological effect studies in experimental systems have used the commercial PBDE mixtures, but there are also examples of studies performed on single congeners. A general problem with the use of commercial PBDE product mixtures, as well as with many other commercial organohalogen products, is the comparably low purity of the mixture and the lack of knowledge on the nature of possible interfering compounds. Another problem is the possibility of transformation of PBDEs during combustion, etc. into other products of which some

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are more toxic than the original products (e.g. brominated dibensofurans and dioxins). Transformation as well as toxicokinetic aspects will however not be dealt with in this particular review.

Below are summaries of the data on toxicity and similar effects (e.g. enzyme induction) from studies on commercial PentaBDE (tetra- to hexa-congeners), OctaBDE (hexa- to nona-congeners) and DecaBDE (nona- and deca-congeners) products. Many of these results are described more in detail in earlier reviews. The reader is referred to these reviews, or further to the original articles, to obtain more details (e.g. IPCS, 1994a; Darnerud et al., 2001; Peltola and Ylä-Mononen, 2001; De Wit, 2002; Hardy, 2002).

4.1. Effects in mammals and related experimental systems

4.1.1. PentaBDE

PentaBDE gave a low acute toxicity in experimental animals (rats, rodents) and the oral LD-50 in rat was in the range 0.5–5 g/kg body wt. (IPCS, 1994a). The clinical signs were reduced growth, diarrhoea, piloerection, reduced activity, tremors of forelimbs, red staining around eyes and nose, and continuous chewing. The porphyrogenic activity was relatively high according to studies in which the concentration of porphyrins increased considerably after oral dosing with the commercial pentaBDE product DE-71 (mixture of tetra-, penta- and hexaBDE) at 100 mg/kg body wt./day for 13 weeks (IPCS, 1994a). No mutagenic potency was observed in Ames test models using several different *Salmonella* strains with and without microsomal activation (IPCS, 1994a).

After repeated dosage with PentaBDE products, several morphological effects were observed, such as changes in hepatic and thyroid size and histology. In two studies of commercial PentaBDE mixtures in rats, these effects appeared at the 10 mg/kg body wt. dose (Great Lakes Chem.; IPCS, 1994a). Immunological effects were suggested in mice after exposure to commercial DE-71 mixture (72 mg/kg body wt. for 14 days); suppression of the anti-SRBC response was observed, as well as a decreased thymus weight (Fowles et al., 1994). The PBDE congener BDE 47 markedly reduced the splenocyte numbers in mice (C57BL) after daily oral administrations of 18 mg/kg body wt. for 14 days (Darnerud and Thuvander, 1999). In the same study, Bromkal 70 reduced IgG antibody production from pokeweed-stimulated mouse splenocyte cultures ex vivo, whereas no immunological effects were seen in rats.

Commercial PeBDEs affected thyroid hormone homeostasis, and both technical products and pure tetra- and penta-congeners (the latter at doses of 10–18 mg/kg body wt./day for 2 weeks) produced effects on serum thyroxin levels in rats and mice (Great Lakes Chem., IPCS, 1994a; Hallgren et al., 2001; Zhou et al., 2001; Hallgren and Darnerud, 2002). In one study on mice, effects on thyroxin were observed already at single dose of 0.8 mg/kg (Fowles et al., 1994), although with lack of dose–response effects relationship.

Microsomal enzyme induction was seen in several studies after administration of pentaBDE products. Induction of several CYP isozymes was indicated by use of substrates for specific enzymes, and increases in EROD, MROD and PROD activities were suggested at BDE 47 doses from 6 to 10 mg/kg body wt./day (Zhou et al., 2001; Hallgren and Darnerud, 2002). In a rat hepatoma cell line (H4IIE), some of the pure PBDE congeners acted via the AhR signal transduction pathway as agonists, antagonists, or both. Their potencies were approximately six orders of magnitude lower than that of TCDD but comparable to those of some mono-ortho PCBs such as PCB 105 and PCB 118 (Sanderson et al., 1996). In studies by Chen et al. (2001), pure PBDE congeners and commercial PBDE mixtures had Ah receptor binding affinities 10^{-2} to 10^{-5} times that of 2,3,7,8-TCDD. Interestingly, binding affinities for PBDEs could not be related to the planarity of the molecule, possibly because of sterical reasons.

A commercial PentaBDE gave rise to maternal and fetal toxicity (chiefly manifested as a weight decrease) in rats at rather high doses (100 and 200 mg/kg body wt., respectively, on gestation days 6–15) (BFRIP; IPCS, 1994b). The effects on thyroid hormones, mentioned above in adult animals after PBDE exposure, could also be seen in offspring to PBDE-dosed dams: In rat pups to DE-71-exposed dams, decreased thyroxine levels were seen at 10 mg/kg body wt. upon gavage on gestational day 6 to postnatal day 21 (Zhou et al., 2002). The effects were seen at PND 4 and 14, but a reduction in thyroxin was also seen in fetuses on GD 20. At lower doses (from 0.6 to 0.8 mg/kg body wt.), the pure pentaBDE congener BDE 99 caused impaired habituation and impaired learning and memory functions in mice pups after oral administration (to pups) at day 10 after partus (Eriksson et al., 2001). At a higher dose, BDE 47 also caused similar effects. Branchi et al. (2002) showed similar effects on spontaneous motor activity in mice after perinatal exposure to PBDE 99 (from 0.6 mg/kg body wt., GD 6-PND 21). Also in adult mice, behavioural effects were observed, following neonatal exposure to BDE 99 during a critical period (Eriksson et al., 2002a).

No cancer study has been performed on PentaBDE.

4.1.1.1. Critical effects of PentaBDEs. For PentaBDEs, the critical effects among the available studies seem to be developmental neurotoxicity and, generally at somewhat higher doses, altered thyroid hormone homeostasis. Regarding the neurotoxicity in mice, no clear mechanism could be defined but effects of the PentaBDEs both via thyroid hormone disruption and directly on signal transmission in brain have been discussed. For example, PBDEs as well as other BFRs, were capable to induce cell death of cerebellar granule cells in culture (Reistad et al., 2002). PBDEs were also shown to release arachidonic acid in cerebellar granule cells via a phospholipase A_2 pathway, and PLA_2 has been associated with learning and memory (Kodavanti and Derr-Yellin, 2002). As concerns the thyroid hormone effects

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observed in the rodent model, a suggested mechanism is binding of PBDE metabolites to the thyroxin-transporting protein TTR, thereby decreasing the thyroxin levels in the blood and peripheral organs (Brouwer et al., 1988, 1998). An additional explanation to the hormonal effects is that thyroxin will be degraded faster due to PBDE-induction of the phase II enzyme UDP-GT (Bastomsky, 1974; Zhou et al., 2001) and therefore excreted at a higher speed. The thyroid effects seem to occur at lower PBDE exposure levels during early developmental stages. During these stages, thyroid hormones play an important role in the development of vital organs, including the brain.

To summarise, the LOAEL value for PentaBDE could be set to 0.6–0.8 mg/kg body wt., based on the most sensitive effect observed, neurobehavioural effects during early development. However, it is not known what these observations of altered spontaneous activity in neonatal mice means in terms of human risk assessment. Also, gaps in our knowledge make this evaluation only preliminary. For example, the lack of carcinogenicity data is unsatisfactory, and more should be learnt about reproductive and immunological effects. For the future, such studies should be given high priority, especially as the tetra- and pentabrominated congeners in most cases are the main PBDE congeners found in biota and in man.

4.1.2. OctaBDEs

Similar to the pentaBDEs, the acute toxicity of the OctaBDEs preparations is low. The dermal (rabbit) and oral (rat) LD-50 values range between >2 and >28 g/kg body wt. (IPCS, 1994a). Low skin and eye irritation are reported (IPCS, 1994a). Although being a nonmammalian model, the porphyrinogenic potential was reported strong in cultured chick embryo liver cells after incubation at 10 μg/ml for 24 h (Koster et al., 1980). Regarding genotoxicity, OctaBDE caused no effects, either in *Salmonella* mutagenicity tests or in unscheduled DNA synthesis assay (IPCS, 1994a). Moreover, no effect on sister chromatic exchange in Chinese hamster ovary cells was observed.

In subacute toxicity studies in rats with a commercial OctaBDE, morphological effects on the liver (enlarged with eosinophilic round bodies) were observed at the 10 mg/kg body wt. level (estimated from dietary OctaBDE concentrations) (Great Lakes Chem.; IPCS, 1994a). Effects on the thyroid as well as on the liver (necrosis) was observed at higher levels. A subchronic (13 weeks) toxicity study in rats revealed a similar liver effect at 10 mg/kg body wt. and at higher doses effects also sere observed in the thyroid, kidney and haemological system. Similarly to PentaBDEs, no carcinogenicity study has been reported on OctaBDEs.

In the rat, fetal toxicity was seen after administration of OctaBDE preparations (DE-79 and Saytex 111) by gavage to the mother (IPCS, 1994a; US EPA, 1986). The fetal effects, namely late resorptions, weight decrease, reduced ossification, bent ribs and limp bones, and rear limb malformations, started to appear at 10–25 mg/kg body wt., whereas maternal toxicity (weight decrease, effects on cholesterol levels) were seen at a higher dose. In rabbits, similar foetal toxic effects were seen after Saytex 111 administration, however in this case effects were seen at lower doses; delayed ossification occurred at 2 mg/body wt., and weight decrease and fused sternebrae at 5 mg/kg body wt. Also in the rabbit, maternal toxicity was observed at OctaBDE doses higher than those giving fetal effects (maternal body weight gain decrease and liver enlargement at 15 mg/kg body wt.) (Breslin et al., 1989; commented in Darnerud et al., 2001).

4.1.2.1. Critical effects of OctaBDEs. Morphological effects in the liver of adult rats were seen after dietary OctaBDE administration at 10 mg/kg body wt. Higher doses also affected the thyroid gland, kidney and the haemological system. Fetal toxicity of OctaBDE was manifested as weight decrease, reduced ossification, bent ribs and limp bones/fused sternebrae, in the rat and the rabbit, and in the rabbit these effects began to appear at 2 mg/kg body wt. (Breslin et al., 1989). The maternal effects in the rabbit started at 15 mg/kg body wt.

Thus, it could be concluded that OctaBDE toxicity is first seen at early developmental stages, and that the effects are suggested to appear at 2 mg/kg body wt. (=LOAEL) in rabbits, and at somewhat higher doses in the rat. The correspondence in effects in the rat and the rabbit study increase the impact of these results. As noted for the PentaBDEs, no carcinogenicity study has been performed on OctaBDEs, and there is also a lack of data on many other endpoints.

4.1.3. DecaBDE

The acute toxicity of DecaBDE products is low, oral and dermal LD-50 values varying between 2 and 5 g/kg body wt. (IPCS, 1994a; Norris et al., 1975a,b). Skin irritation and chloracnegenic activity were negative, whereas a transient eye irritation (redness and chemosis) was observed after Saytex 102 application. Studies of mutagenicity and chromosomal aberration were all negative. The porphyrogenic activity was also negative.

In the subacute/subchronic studies performed, effects of DecaBDE were first seen at 80 mg/kg body wt. (thyroid hyperplasia, liver enlargement and hyalin degeneration in kidney in rats; dose estimated from dietary intake), whereas hematocrit and red cell count were affected first at 800 mg/kg body wt. (IPCS, 1994a; Norris et al., 1975a,b).

In chronic toxicity studies (103 weeks) in rats and mice, the tumour incidence was observed after DecaBDE (commercial, 94–99% pure) exposure via the diet (NTP, 1986). At the doses (ca. 1200 and 2500 mg/kg body wt./day) given in rats, a dose-related increase in hepatic adenomas and an increase in pancreatic adenomas at the high dose were observed. In mice, the combined incidence of hepatocellular adenomas and carcinomas was increased, although not dose-related (doses ca. 3500 and 7000 mg/kg body wt./day).

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Also, the combined incidence of thyroid gland follicular-cell adenomas and carcinomas was slightly increased. In an additional cancer study in rats, no effects were observed (Kociba et al., 1975). Regarding the latter study, the IARC Working Group pointed out that the dose levels (corresponding to 0–1 mg/kg body wt./day) were very low.

No reduction in reproductive performance was seen after DecaBDE exposure in the diet (DecaBDE product: 77% decaBDE, 22% nonaBDE, 1% octaBDE). In a teratogenicity study in rats, the same DecaBDE substance was given by gavage at gestation days 6–15; at 100 mg/kg body wt. resorptions were observed, and at 1000 mg/kg body wt. foetal subcutaneous edema and delayed ossification were registered (both studies: IPCS, 1994a; Norris et al., 1975a,b).

4.1.3.1. Critical effects of DecaBDE. The effects of DecaBDE products in mammalian models seem rather modest. Effects are first seen in a subacute study in rats at about 80 mg/kg body wt. (=LOAEL) (thyroid hyperplasia, liver enlargement and hyaline degeneration in kidney). At 100 mg/kg body wt., foetal resorptions were registered in rats.

The carcinogenicity study of DecaBDE in rats and mice is important, being the only study of tumour induction performed on PBDE. In this study, adenomas and carcinomas are indeed observed, but at very high doses (1200 mg/kg body wt./day and above). Hypothetically, another dosing regimen (narrower dosing intervals) might have resulted in carcinogenic effects at lower doses.

4.2. Effects in other animals/in wildlife

Effects of PBDEs have been reported in algae, invertebrates and in fish. In fish, Bromkal 70-5 DE induced CYP enzymes (EROD), generated fatty liver and reduced spawning success (Holm et al., 1993). Hornung et al. (1996) tested pure PBDE congeners on fish eggs (by microinjection) and saw no effects. In a study on rainbow trout, BDE-47 and -99 were given in the feed to rainbow trout (Tjärnlund et al., 1998). The result was a reduction in GSH reductase, haematocrit and blood glucose values. The effects of the congener BDE-47 on the calanoid *Acartia tonsa* were studied by Breitholz et al. (2001). In the 48-h acute toxicity test and larval developmental test, the 2- and 5-days LC-50 values were 2.4 and 0.013 mg/l, respectively. In addition, in reports not generally available, toxic effects of a tetra- to hexa-BDE mixture induced toxicity in a *Daphnia* test model. The NOEC values in a 48-h acute toxicity test and a 21-day life-cycle study were in both cases about 5 μg/l (CITI, 1882; Dottar and Kreuger, 1998; both in Peltola and Ylä-Mononen, 2001).

4.3. Effects in man

Few studies have been performed where effects of PBDE have been studied in humans.

In two separate studies, the skin sensitisation potential of commercial DecaBDE products was followed in human volunteers (Norris et al., 1975a,b; IPCS, 1994a). Neither of these studies revealed any evidence of skin sensitisation.

Four epidemiologic studies have been performed in working places where flame retardants were used (IPCS, 1994a). The workers were potentially exposed to brominated flame retardants, including PBDEs and possibly also to PBDDs and PBDFs; the quality of the studies was not assessed. According to these studies, no adverse effects could be related to exposure to these chemicals. In one occupational study, where workers were exposed to PBBs and PBDEs during manufacture, higher-than-normal prevalency of primary hypothyroidism and significant reductions in conducting velocities in sensory and motor neurons were reported (Bahn et al., 1980). Apart from these findings, no other neurologic or dermatologic changes were seen. No decaBDE could be detected in the serum of exposed workers, and it could not be concluded that the observed effects were caused by the PBB and PBDE exposure.

In a study of male fish-eaters from the Baltic region, consuming 0–32 meals/month, a number of hormones were measured in the blood and compared to the levels on some selected environmental contaminants, including the PBDE congener BDE 47 (Hagmar et al., 2001). After adjustment for age, there was a significant association (negative correlation) between plasma BDE-47 and TSH. The authors stated that some significant correlation will occur from pure chance, and it was concluded that high consumption of organohalogen-polluted fish may not appear to affect plasma levels concentrations of pituitary, thyroid, or testosterone hormone levels in male adults.

4.4. Levels in man

Apart from these few reported effect studies, many observations of PBDE levels in human have been made. In occupationally exposed workers, PBDEs were detected, and significantly higher levels were recorded in workers exposed to these compounds during computer dismantling (Sjödin et al., 1999; Thomsen et al., 2001) and rubber manufacturing (Thuresson et al., 2002) and in computer technicians (Jakobsson et al., 2002). However, also in humans with no occupational exposure, detectable PBDE levels in serum have been observed (Sjödin et al., 2000; Van Bavel et al., 2002; Petreas et al., 2002; Lee et al., 2002). PBDEs have been detected also in adipose tissues (Meironyté Guvenius et al., 2001; Choi et al., 2002; Covaci et al., 2002; Crhova et al., 2002; She et al., 2002). In several studies, PBDEs have been found in breast milk from the mothers representing the general population (Meironyté et al., 1999; Lind et al., 2003; Ohta et al., 2002; Ryan et al., 2002), and very high PBDE levels were registered in a pooled breast milk sample from USA (Päpke et al., 2001). However, human PBDE levels, and more specifically time

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trends and spatial trends in breast milk, will be discussed in other parts of this issue.

4.5. General PBDE conclusion

To conclude, exposure to PBDEs gives rise to adverse effects in experimental in vivo models, and depending on type of product different effects are seen, occurring at varying dose levels. Generally, the technical PentaBDE products seem to cause effects at the comparably lowest dose, whereas much higher doses were needed for effects of the DecaBDEs. Indeed, DecaBDES are generally considered to have the lowest toxicity of these three compound groups. The critical effects of PentaBDEs are those on neurobehavioural development and, although somewhat less sensitive, thyroid hormones in offspring (from 0.6 to 0.8 and 6 to 10 mg/kg body wt., respectively), whereas OctaBDEs primarily give rise to fetal toxicity/teratogenicity in rats and rabbits (from 2 mg/kg body wt.) and DecaBDEs cause certain morphological effects in the thyroid, liver and kidney of adult animals (from 80 mg/kg body wt.). Carcinogenicity studies on decaBDE, revealing some effects at high very high doses, have resulted in an IARC classification stating limited evidence for carcinogenicity of decaBDE in experimental animals (IARC, 1990). The overall IARC evaluation says decaBDE is not classifiable as to its carcinogenicity to humans (Group 3). We know very little about human effects of PBDEs, and have to base our risk assessment chiefly on animal models. What we know is that humans in general, at least in Western countries, are exposed to PBDEs and that human tissues contain measurable PBDE levels. If these levels are high enough to cause adverse human effects is unknown, but we know that the lowest body weight-related dose levels that cause effects in animals are much higher than available estimations of human dietary intake. Thus, a factor of 10×6 differs between these two exposure levels, based on Nordic and Canadian human intake data (Darnerud et al., 2000; oral information from Dr. Ryan, Canada and Dr. Kiviranta, Finland, at the BFR Workshop in Stockholm 2001). However, we know very little of PBDE toxicokinetics in man, and the actual margin of safety may be much smaller if based on body burden levels or concentrations in target organs. Also other data gaps in our knowledge of PBDE toxicity make this conclusion preliminary. Toxicity gaps that should be filled are, e.g. the carcinogenic potential of other PBDE compounds than DecaBDEs, more data on reproductive and immunologic effects, the mechanism of PentaBDE neurotoxicity and the possible relation between the observed thyroxin effects and other endpoints of toxicity. Another area where data is missing and which has purposely been omitted in this review is the degradation of PBDEs to lower brominated PBDE or other bromoorganic compounds. This transformation could in some case produce products with a higher toxic potency than the initial compounds.

5. Tetrabromobisphenol A (TBBPA)

5.1. Effects in mammals and related experimental systems

The acute oral toxicity of TBBPA for laboratory animals is low. The oral LD-50 for the rat and mouse and rabbit was >5 and 10 g/kg body wt., and the dermal LD-50 in rabbits was >2 g/kg body wt. (IPCS, 1995). TBBPA was not irritating and gave no sensitization reaction in animals tests, and only upon dermal exposure on abraded skin up to 2500 mg TBBPA/kg body wt. a slight skin erythema was seen in rabbits (Goldenthal et al., 1979; IPCS, 1995). After a single-dose TBBPA, moderate microsomal enzyme induction was observed in liver (Gustafsson and Wallén, 1988).

TBBPA was not mutagenic in various studies with *Salmonella typhimurium* strains, with metabolic activation by an S9 mix of Aroclor-induced rats and hamsters (IPCS, 1995). TBBPA caused no effect on induction of intragenic recombination in two in vitro mammalian cell assays (Helleday et al., 1999). In an in vitro model for immunotoxicity, TBBPA and also TBBPA bisallylether reduced CD25 (IL-2 receptor-alfa-chain), an inducible receptor chain essential for proliferation of activated T cells. The immunosuppressive effect was suggested not to be mediated via the Ah receptor (Pullen and Thiegs, 2001).

TBBPA was shown to be an effective binder to human transthyretin (TTR) in vitro, with ca. 10 time higher potency than thyroxin, the natural ligand (Meerts et al., 2000). In the same system, pentabromophenol also bound effectively to TTR (7 times T4). On the other hand, PBDE congeners as such did not compete with T4 for TTR binding, but were active only after microsomal biotransformation to their hydroxylated counterparts. When Meerts et al. (1999) studied the effects of TBBPA in an in vivo model, no effect of this compound on thyroid hormones in pregnant mice could be seen (see below).

An in vitro study of TBBPA on the function of biological membranes resulted in haemolysis of human erythrocytes and uncoupling of the oxidative phosphorylation in rat mitochondria, suggesting that TBBPA primarily alters the permeability of biological membranes (Inouye et al., 1979; IPCS, 1995). In study on the disposition of TBBPA in rats, it was seen that the level of ^{14}C-TBBPA radioactivity was 10 times higher in erythrocytes than in plasma 72 h after the administration (Szymanska et al., 2001). The authors suggest that the erythrocyte labelling represents TBBPA metabolite(s).

In several subacute or chronic exposure studies (oral, dermal, inhalation) of TBBPA in rats, no effects were observed (including body weight, haematology, clinical chemistry, urinalysis, organ weights, and gross and microscopic examination). In the dermal study, only slight erythema was noticed in rabbits. In an oral 90-day study on mice, 700 mg/kg body wt. did not cause any detectable adverse effects, whereas 2200 mg/kg body wt. resulted in decreased body weight, increased spleen weight, and re-

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duced concentration of red blood cells, serum proteins, and serum triglycerides (Tobe et al., 1986; IPCS, 1995). In a study on rats, which were orally administered TBBPA in daily doses up to 250 mg/kg body wt. for 1 to 4 weeks, certain parameters suggest a slight renal impairment (significantly increased elimination of renal epithelial remnants in urine) (Frydrych and Szymanska, 2001). However, the results of this study are somewhat difficult to interpret. No carcinogenicity or long-term toxicity studies on TBBPA were reported.

In two teratogenicity studies in rats, no teratogenic effects were observed. However, in one study, three of five dams died in the highest (10 g/kg body wt. during day 6–16 during gestation) dose group (IPCS, 1995). In another study, TBBPA was given to pregnant rats on days 10–16 of gestation (Meerts et al., 1999), and effects on thyroid hormones (incl. TSH), and on competitive binding to fetal and maternal transthyretin (TTR) were studied. No effect was seen on T4 and T3 levels in dams and fetuses, whereas TSH levels were significantly increased in fetuses but not in dams. Result from the ^{125}I-T4-binding study showed no shift in binding, suggesting no TBBPA-related binding to TTR. Consequently, TBBPA was concluded not to bind to TTR in vivo. The difference between in vitro and in vivo effects (a strong effect observed of TBBPA on TTR in vitro) may have several explanations, and may well include toxicokinetic factors; a rapid excretion of TBBPA would prevent the formation of high enough plasma levels to have effects on the T4–TTR complex.

5.2. Effects in other animals/in wildlife

In fish, the acute 96-h LC-50 values of TBBPA for three species of fish was about 0.5 mg/l. Effects observed during the experiments were irritation, twitching and erratic swimming (bluegill sunfish, rainbow trout) and reduced survival and reduced growth of young individuals (fathead minnow) (IPCS, 1995). In effect studies in marine and freshwater algae, TBBPA was toxic in some marine species. TBBPA affected the reproduction of *Daphnia magna* and was toxic to Mysid shrimps (LC-50 about 1 mg/l).

TBBPA had no estrogenic activity in quail and chicken embryos, but resulted in embryolethality at high doses (Berg et al., 2001).

5.3. Effects in man

In humans, no skin irritation of sensitisation was observed in 54 human volunteers (Dean et al., 1978a; IPCS, 1995). Apart from that, no epidemiological or other data on effects of TBBPA of humans are available.

5.4. TBBPA derivates

Concerning TBBPA derivates, very few toxicity studies are available, but there is also a lack of other important data concerning their physical and chemical properties, production and use, environmental transport, etc. Because of this lack of data, these compounds were not evaluated by IPCS (1995). The TBBPA derivates (mentioned in IPCS, 1995) are dimethylether, dibromopropylether, bis(allylether), bis(2-hydroxyethyl ether), brominated epoxy oligomer, and carbonate oligomers. Where acute toxicity data were present, the derivates had only weak effects. Mutagenicity tests (*S. typhimurium* strains without and with metabolic activation) were mostly negative but in one case, TBBPA dibromopropylether, positive in *S. typhimurium* strains TA 100 and TA 135 (IPCS, 1995). However, using the same substance the results of an unscheduled DNA synthesis and an in vitro sister chromatid exchange were negative.

5.5. TBBPA conclusion

The toxicity of TBBPA in the tested experimental systems is suggested to be low. In most of the reported mammalian studies, only doses in gram/kg body wt. were effective. However, studies by Frydrych and Szymanska (2001) suggested that lower doses (250 mg/kg body wt. and lower) could result in a slight renal impairment in rats, although the study was difficult to interpret and should be repeated. Some of the in vitro studies could also be of interest in risk assessment aspects, and both the immunosuppressive effect, the in vitro binding to TTR (a T4 transporter in blood) and the binding to the erythrocytes should be noted. Before a definite standpoint could be reached on TBBPA toxicity, additional toxicity studies must be performed, including those on reproductive, immuno-, neurobehavioural and kidney toxicity. Because of the lack of toxicity data on the TBBPA derivates, little can be concluded on the possible risk from exposure to these compounds.

6. HBCD

Hexabromocyclododecane (HBCD) is an additive flame retardant used in the polymer and textiles industries. The major use of HBCD is in polystyrene, which is largely used in insulation panels and blocks for building constructions. HBCD could reach the environment by these products being incinerated, recycled or dumped at waste sites.

HBCD is reported to be absorbed from the gastrointestinal tract and it could be hypothesised that food intake is the largest single source of human exposure to HBCD. In experimental studies, HBCD has been found in several organs after oral administration, and the substance accumulates in adipose tissue after administration. Several (unidentified) metabolites are also shown in experimental studies (Yu and Atallah, 1980; KEMI, 2002).

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6.1. Effects in mammals and related experimental systems

Toxicological effects of HBCD have been investigated in several studies, of which many are internal reports. According to KEMI (2002), the acute toxicity have been studied after dermal (rabbit), oral, (rat and mouse) and inhalation (rat) exposure. In the dermal studies, essentially no effects were seen after application of up to 20 g/kg body wt. In the oral studies, no increased death rate could be observed, and the LD-50 was defined to >6400 mg/kg body wt. in mice and >10 000 mg/kg body wt. in rats (EPA, 1990a; Wilson and Leong, 1977; both in KEMI, 2002). In some studies, at higher levels the animals showed some toxic signs, i.e. hypoactivity, corneal opacity, ptosis, and diarrhoea, as well as some decrease in body weight gain. After inhalation, a slight dyspnea was seen in rats at 200 mg/l air (Wilson and Leong, 1977; KEMI, 2002). To conclude, the acute toxicity of HBCD seems low.

In a number of eye and skin irritation studies on rabbits and guinea pigs, the substance was concluded not to be irritative or corrosive to the skin, and a very mild eye irritant. However, two of three studies showed that HBCD induced a dose-related sensitisation at higher doses after intra-dermal and topical application on guinea pigs. Mutagenicity studies (Ames test and in vitro test of chromosomal aberrations) showed no mutagenic potency of HBCD.

Regarding repeated dose toxicity of HBCD, two 28-day and two 90-day studies have been presented (Chengelis, 1997; Zeller and Kirsch, 1969, 1970; Chengelis, 2001; KEMI, 2002). In all these studies, the liver was defined as a target organ, and the effects observed were increased liver weight, microfoliar hyperplasia, and lipoid phanerosis. Based on the 90-day study by Chengelis et al., a LOAEL of 100 mg/kg body wt. was proposed based mainly on increased liver weight. In the same study, serum concentrations of thyroid hormones (T4 and TSH) were also affected at the 100 mg/kg dose. In addition, in the 28-day study by Zeller and Kirsch (1969) thyroid hyperplasia and inhibition of oogenesis was seen, although at higher doses (effects seen at 500 and 2500 mg/kg body wt. dose, respectively).

In an 18-month study carcinogenicity on mice, a large number of organs and tissues were monitored for possible tumours or neoplastic changes (Kurokawa et al.; cited in KEMI, 2002). Certain changes were seen in the liver only, and both gross findings (liver nodules) and histopathology (necrosis, fatty infiltration, altered foci and hepatocellular tumour) were generally most pronounced in the medium-dosed group (130 mg/kg body wt.; compared to 13 and 1300 mg/kg body wt., and control). In spite of inconsistencies in the dose–effect relationship in the cancer study, available data suggest that the carcinogenic risk of HBCD should not be overlooked. However, the lack of mutagenic effects suggests an epigenetic factor behind the increased tumour incidence, and an effect threshold could thus be proposed. From the tabulated data of the carcinogenicity study on mice, one of the observed effects seems to occur more frequent already at the 13 mg/kg-dose, although no statistical evaluation was presented. At the highest dose, 1300 mg/kg body wt., the levels of all these parameter decreased. To conclude, the carcinogenic potency of HBCD on the liver should not be disregarded but several factors (lack of strict dose–effect relationship, lack of effects in female mice, the studied mice strain, B6C3F1, is a sensitive strain for development of liver neoplasms) make this study questionable as a tool for carcinogenicity assessment.

In a 28-day study on reproductive effects of HBCD, high doses were shown to inhibit oogenesis in rats (Zeller and Kirsch, 1969; KEMI, 2002). In the males, no effects of high HBCD doses were observed on testes and epididymis. Based on the oogenesis effects, a NOAEL was set to 2500 mg/kg body wt./day. Studies on the developmental toxicity in rats, administering HBCD on days 0–20 of gestation in doses up to 750 mg/kg body wt./day showed a slight suppression of maternal food intake, and a certain increase in maternal liver weight. Based on these effects, a maternal NOAEL of 75 mg/kg body wt./day was obtained. However, no foetal abnormalities were seen and the number of live-born was unaltered. To conclude, available HBCD studies indicate a low foetotoxicity and teratogenicity, but that there is a need for further studies.

In a recent extended abstract, Eriksson et al. (2002b) exposed neonatal NMRI mice for HBCD on day 10, as a single oral gavage dose (0.9 or 13.5 mg/kg body wt.). At a later timepoint (3 months), behavioural studies were conducted in which locomotion, rearing, and total activity were recorded. The mice in the exposed groups were initially less active but became at later measurement periods more active than the control groups, and these effects were dose–response related. Based on this short paper, a preliminary LOAEL of 0.9 mg/kg body wt. may be set for these effects.

6.2. Effects in other animals/in wildlife

In general, toxic effects in the aquatic systems tested were hard to find: No toxic effects were seen in algae, in Daphnia (short-term test), and in fish. However, in a chronic study on Daphnia (21 days of exposure) the LOEC value was quite low (5.6 μl/l) (Dottar and Kreuger, 1997).

6.3. Effects in man

No human data are available except for a patch test in which patches with 10% HBCD were applied for 48 h, with no skin reactions on any subject (EPA, 1990b; KEMI, 2002).

6.4. HBCD conclusion

To summarise the HBCD data, there is a lack of relevant studies of high quality that could form a basis for a risk assessment for this compound. In a human test, HBCD

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induced no skin reactions in a patch test. Based on available animal data, the critical effects are found in the liver: There was an increased liver weight and hepatic "lipoid phanerosis" in a 90-day feeding study on rats (LOAEL 100 mg/kg body wt./day), and effects on thyroid hormones were observed at the same dose level. Due to the many shortcomings of the carcinogenicity study on mice by Kurokawa et al., this study is of limited value and must be repeated. However, mutagenicity studies are negative which suggest that the carcinogenic effect, if any, has an epigenetic mechanism. In a recent short paper, a behavioural study in mice showed effects already at 0.9 mg/kg body wt., when HBCD was given on day 10 and testing was performed at 3 months after birth. Thus, behavioural effects may be a sensitive endpoint for HBCD, as have been shown for other flame retardant substances. Other types of behavioural tests should therefore be conducted on HBCD.

7. PBB

Polybrominated biphenyls (PBB) are identical to their chlorinated counterpart PCB, except for type of halogen atom present in the molecule. Thus, theoretically PBB should have a similar pattern of toxicity compared to PCB, apart from the change in effects that the chlorine–bromine substitution brings about. Consequently, the planar PBBs are most toxic (as they bind to the Ah receptor), whereas mono-ortho congeners are intermediate and di-ortho congeners least toxic. Indeed, 3,3′,4,4′,5,5′-hexabromobiphenyl was found to be the most toxic PBB congener in several systems, but this congener is present in low concentrations in technical PBB mixtures. Generally, the number of congeners in commercial mixtures is smaller in comparison to PCB, and most of the reported studies have been performed with use of the commercial mixture FireMaster (FM), or with similar hexabromobiphenyl mixtures. The cause for the comparably large number of studies on FM is the accident in Michigan 1973–1974, when FM was inadvertently added to animal feed. FM contained (in average) 60–80% 2,2′,4,4′,5,5′-hexaBB, 12–25% 2,2′,3,4,4′,5,5′-heptaBB, and smaller amounts of lower brominated compounds (IPCS, 1994b). Therefore, when nothing else is stated, in the present text the term PBB is equal to FM/hexaBB. Today, with the recent closure of the decaBB production in France, the PBB production in the world has ceased.

Much of the toxicological data gathered on PBB up to the early 1990s is compiled in IPCS health criteria document on PBB (IPCS, 1994b).

7.1. Effects in mammals and related experimental systems

The acute toxicity of commercial PBB mixtures is low (LD-50>1–21 g/kg body wt.) in rats, rabbits and quails, following oral or dermal administration (rats: e.g. Gupta and Moore, 1979). Generally, repeated dosing induced toxic effects at a lower dose compared to single (bolus) dosing. Effects, including death, were delayed after PBB (hexabromobiphenyl) administration, and signs of toxicity include reductions in feed consumption. Thus, a "wasting syndrome" is developed as an early indication of toxicity, and at death, the loss in body weight can be 30–40%. These effects are not seen in the few studies performed on octa- and deca-BB.

Eye and skin irritation tests/sensitization tests gave no, or only mild, reactions with use of the OctaBB and DecaBB preparations. Various assays for the detection of mutagenicity or genotoxicity generally failed to show any effect with individual PBB congeners or commercial mixtures. However, in some tumour-promotion models, FM and certain pure PBB isomers were effective, but the results from different models were somewhat contradictory.

Rhesus monkeys are among the species most sensitive to FM, and at long-time exposures of 1.3–300 mg FM/kg feed, they developed a number of symptoms, including weight loss, clinical chemistry changes, hair loss, skin lesions, oedema, etc. (Allen et al., 1978). In rats, repeated PBB (OctaBB and FM) exposure to low doses increased the liver weight, whereas a decrease in thymus weight was seen after FM exposure. Histopathologic changes in these organs were also noted. The morphological effects of PBB were most prominent in the liver, and were shown as liver enlargement, hepatocyte swelling and vacoulation, proliferation of ER and single-cell necrosis (e.g. Gupta et al., 1983). Histopathological effects were also seen in thymus, and it seems to be more toxic PBB congeners that give rise to the most severe effects, observed as body, thymus (decrease) and liver (increase) weight chances as well as morphological changes in liver and thymus. Atrophy of the thymus is a frequent observation following PBB exposure. In the liver, induction of mixed function oxidase enzymes has been much studied, and FM is considered to be a mixed-type inducer of hepatic microsomal enzymes.

PBBs interact with the endocrine system, and exposure resulted in decreases in serum T3 and T4 in rats and pigs (Byrne et al., 1987; Werner and Sleight, 1981). Vitamin A levels were shown to be strongly influenced by the PBB exposure, and also steroid hormone levels were reported to be altered (e.g. Bonhaus et al., 1981). PBB resulted in porphyria in rats and mice at 0.3 mg/kg body wt. (NOEL 0.1 mg/kg body wt./day) (e.g. Gupta et al., 1983).

In in vivo long-term toxicity studies, the liver was shown to be the principal site of tumour formation after PBB exposure. The incidence of hepatocellular carcinoma was increased in both rats and mice receiving PBB (FM and technical NonaBB) in doses from 0.5 and 5 mg/kg body wt./day for 2 years and 18 months, respectively (NTP, 1993; Momma, 1986; IPCS, 1994b).

Adverse effects of PBB on reproduction, such as resorptions and decrease viability of offspring, were observed in many species, and in the mink they were seen at a dietary

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concentration of 1 mg/kg (Aulerich and Ringer, 1979). In Rhesus monkeys, decreases in the viability of the offspring were observed following a 12.5-month exposure via the diet, corresponding to an approximate daily dose of 0.01 mg/kg body wt. (Allen et al., 1979).

7.2. Effects in other animals/in wildlife

In short-term tests, the immobilization of *D. magna* by decabromobiphenyl was investigated. The EC-50 (24 h) value was reported to be 66 mg/l, but could be questioned because of low solubility of the substance (Atochem, 1990; IPCS, 1994b).

In hens, egg production and hatchability were affected at 30 mg PBB/kg feed (Ringer and Polin, 1977). In the same species, PBB resulted in increased mortality and reduced growth rates (Cecil and Bitman, 1978), and embryonic death. Japanese quail seemed somewhat less sensitive to these effects.

7.3. Effects in man

Human effects have been studied mainly in two separate epidemiological studies (reviewed in IPCS, 1994b), in which a number of endpoints were studied, e.g. cutaneous effects, liver function, porphyrin production, neurological effects, immune function and pediatric aspects. In the Michigan study (Michigan Department of Public Health), there were no general pattern of differences between "contaminated" and "noncontaminated" farms, and no unusual abnormalities of a number of examined organs or tissues were noticed. When comparing groups with different levels of exposure, there was no positive association between serum concentration of PBB and reported symptoms/disease frequencies. In the other study, from Wisconsin (Environmental Science Laboratory), the incidence of symptoms was greater and the greatest differences were in the classification of neurological and musculoskeletal symptoms. In spite of that the two studies could be interpreted somewhat differently, both studies showed that there were no positive dose–response relationship between the PBB levels in serum and adipose tissue, and the prevalence of symptoms. In one case, neurological performance tests gave a negative correlation between serum PBB levels and performance test scores, and subtle neuropsychological effects in the offspring to exposed individuals were also suggested; however, these effects have been questioned by other experts. In a recent study, the cancer risk in the MDPH cohort was followed 1973–1993 (Hoque et al., 1998). The authors found a serum PBB dose–response-related cancer risk of the digestive system, after adjustment for several possible confounders, and also the risk for lymphoma showed a dose–response relation. However, there was no increased overall cancer risk related to higher PBB serum levels.

7.4. PBB conclusion

Results from animal studies have shown that the reproductive effects in monkeys and the carcinogenic effects are those seen at the lowest administered dose. In the 2-year NTP carcinogenicity study, a daily dose of 0.15 mg/kg body weight did not result in any adverse effect, whereas higher doses induces tumours. Thus, a NOAEL of 0.15 mg/kg body wt./day could be suggested on the basis of this study. As PBB probably cause cancer by an epigenetic mechanism, an uncertainty factor (1000) was used to obtain a tolerable daily intake; this will result in a TDI of 0.15 μg/kg body wt. (IPCS, 1994b). This could be compared to an estimated daily intake for adults in the general population, 2 ng PBB/kg body wt., and for infants receiving human milk, 10 ng/kg body wt. (IPCS, 1994b).

8. General conclusion

In this article, I have only discussed the toxic effects of the compounds and not the exposure. However, it must always be remembered that the risk for health effects from exposure to chemical compounds, in this case brominated flame retardants, is a combination of the intrinsic toxic potential of and the actual (target tissue) exposure for the compound.

The BFR compounds/compound groups discussed above do in most cases belong to a similar structural group, i.e. they contain two aromatic bromine-containing rings (with the exception of HBCD). Indeed, this structural resemblance also affects the toxic potential, and several congeners bind to the dioxin (or Ah) receptor. This is for instance the case with the hexabromobiphenyl (3,3′,4,4′,5,5′ -HBB). In practice, these "highly toxic" congeners play a little role, as they often are present in low levels. However, in the case of HBB the observed carcinogenicity could very well be Ah-receptor mediated. Other similarities in effects of the BFRs, that could in some cases be structure related, are the neurobehavioral effects, the effects on thyroid hormone homeostasis and the effects on the liver. There are however also rather distinct differences between the members of the BFR groups, and TBBPA seems to have a comparatively low toxic potential, compared to the other groups. There are also differences within each BFR group, regarding both target organs/tissues and effective dose, and one example is the PBDEs. The differences could partly be caused by the differences in uptake, distribution and elimination, parameters that will not be discussed in this presentation.

Lastly, there are several and important data gaps that have to be filled before we could perform solid risk assessments of the different members of the BFR. These gaps include, among other, carcinogenicity, neurotoxicity, immunotoxicity and reproduction toxicity studies. As stressed in the Summary session of the Dioxin 2002 Conference in Barcelona, effect studies are highly needed.

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