

The EHC 152 (IPCS, 1994) refers to laboratory experiments in methanol, showing rapid photodegradation of 2,2',4,4',5,5'-hexabromobiphenyl (90% degradation after 9 minutes) and resulting in mainly lower brominated PBBs. However, in the US ATSDR (2004), it is questioned whether this photolysis could take place in water due to the lack of active groups. Therefore it is questionable whether hexabromobiphenyl can be degraded rapidly in air.

Biodegradation in water under aerobic conditions is low, although the lower substituted biphenyls might biodegrade in aerobic water and sediment (Kong and Sayler, 1983; Sugiura, 1992; Yagi, and Sudo, 1980), the higher substituted biphenyls are resistant to aerobic biodegradation (Kawasaki, 1980; Sasaki, 1978; Shelton and Tiedje, 1981) (quoted from US ATSDR, 2004). This is further supported by the measurement (by GC) of negligible biodegradation of hexabromobiphenyl in a four week ready biodegradability test (OECD TG 301C), resulting in 4% reduction in total concentration as measured by GC (Governmental Japanese database NITE, 2006) resulting in an extrapolated half-life in water >2 months.

Under anaerobic conditions, it has been shown that microorganisms in river sediments obtained from populated areas can biodegrade higher substituted PBBs, including FireMaster mixtures (Morris *et al.* 1992) to form lower brominated products (quoted from US ATSDR, 2004). However, the potential of sediment microflora from remote areas has not been investigated, so it cannot be evaluated whether anaerobic debromination may be a considerable cause for degradation under anaerobic conditions.

PBBs have been reported to be persistent under field conditions. The information on the fate of PBBs in soil is limited. Soil samples from a former PBB manufacturing site, analysed several years after accidental release, still contained PBBs. However, the congener composition differed from the original PBB mixture, indicating partial degradation of the PBB residue in the soil samples. According to the 1994 EHC Review, follow-up surveys over a three-year period following the termination of PBB production showed no significant decline in PBB levels in sediments from a river. In laboratory investigations, mixtures of PBBs appear to be fairly resistant to microbial degradation. (Quoted from EHC 152 (IPCS, 1994)) This implies that the degradation half-life in soil and sediment is >6 months.

The US ATSDR (2004), refers to studies in soils with high levels of FireMaster, in which degradation of hexabromobiphenyl was "significant" during a period of several years but it was not complete. However in other soils, in which the concentrations were lower, or to which manure was added, degradation was even slower. The degradation was attributed to photodegradation even if this process will only take place at the soil surface (US ATSDR, 2004).

Conclusion

In spite of photodegradation in methanol, it is questionable whether hexabromobiphenyl can be degraded rapidly in air. There is evidence of low or no degradation in water ($DT_{50} > 2$ months), soil and sediment ($DT_{50} > 6$ months) in the laboratory as well as in the field. Therefore, hexabromobiphenyl is considered to be highly persistent.

2.2.2 Bioaccumulation

The EHC review states that PBBs are lipophilic and able to bioaccumulate. This is also supported by monitoring results from wildlife studies. For example, fathead minnows (*Pimephales promelas*) caged in a river where water levels of PBB remained consistently at less than 0.1 µg/l concentrated these contaminants in their bodies more than 10,000 fold in two weeks of exposure (EHC 152 (IPCS, 1994)).

As expected from their lipophilicity, PBBs show a marked tendency to accumulate in animals. US ATSDR, (2004), states that PBBs may also be transported from water to aquatic organisms in which bioconcentration may take place. Data from different laboratories on the bioconcentration of

PBBs in fish show wide variation. The experimentally determined bioconcentration factor (BCF) for hexabromobiphenyl (mixtures of unspecified congeners) in the whole body of fathead minnows (*Pimephales promelas*) was 18,100 in a 32-day exposure (Veith *et al.*, 1979). In fillet of fathead minnow, the estimated BCF was >10,000 (Hesse and Powers, 1978). Weight-based BCF values in the range 4,700-16,000 were recorded in a 60 day test with the carp *Cyprinus carpio* placed in concentrations of hexabromobiphenyl of 0.1-1 µg/L respectively (Governmental Japanese database NITE, 2006).

Furthermore, a potential for biomagnification has been demonstrated by Jansson *et al.*, (1993), who reported a biomagnification factor (BMF) for 2,2',4,4',5,5'-hexabromobiphenyl (PBB congener 153) of about 175 comparing lipid-based concentrations in prey (herring) and predator (Baltic seal). This BMF was at the same level as that of the PCB congener 153. These findings were supported by Vorkamp *et al.*, (2004)⁶, who found lipid-based concentrations of hexabromobiphenyl (PBB 153) in polar bear to be a factor of about 100 higher than in ringed seal from East Greenland. They conclude further, that the PBBs (and PBDEs) seem to biomagnify along the marine food chain in a manner similar to PCBs and that PBBs show indications of a higher biomagnification potential than PBDEs (Vorkamp *et al.*, 2004).

Conclusion

With measured weight-based BCF values in the range 4,700-18,100 (most of which exceed 5,000) and demonstrated biomagnification in the aquatic food chain, hexabromobiphenyl is considered to be highly bioaccumulative and to have a high potential for biomagnification. These properties are demonstrated by several authors to be comparable to those of hexachlorobiphenyl, for which the bioaccumulative properties are well documented. Evidence appears to be satisfactory to conclude high bioaccumulation and biomagnification.

2.2.3 Potential for Long Range Environmental Transport

The partitioning of hexabromobiphenyl in the environment will be governed by its high log K_{ow} (6.39) and low water solubility (3 µg/L) resulting in sorption to particulate matter (dust, soil and sediment) and organic material (including living organisms). Furthermore, the combination of these properties and the relatively low vapour pressure (6.9×10^{-6} to 7.5×10^{-4} Pa) of hexabromobiphenyl, results in a low potential for volatilisation. The latter is specified in US ATSDR (2004) as follows: Based on an estimated Henry's law constant of 3.95×10^{-1} Pa m³/mol (where Henry's law constant = vapor pressure/water solubility) and an estimation method (Thomas, 1990), the estimated volatilization half-life of hexabromobiphenyl is 23 days. Therefore, the transport of PBBs from water to the atmosphere by volatilization is not expected to be important.

The assessment of the potential for long-range transport of hexabromobiphenyl could be done by comparing the properties of hexabromobiphenyl to those of the currently listed POPs. As a starting point for the assessment of hexabromobiphenyl, the highest and lowest of the values in Table 1.1 were used (for vapour pressure, only the value at 25 °C) and, for comparison, the information on the UNEP-POPs homepage. Among the currently listed POPs, most of the relevant properties were available for aldrin, chlordane, dieldrin, DDT, hexachlorobenzene, mirex, toxaphene, endrin and heptachlor. Missing information (water solubility of mirex) was sought in US ATSDR (1995), so as not to introduce what seems to be an outlier in the comparison by using the value of 6.5×10^{-5} mg/L from AMAP (2004).

⁶ These investigations are part of the Arctic Monitoring and Assessment Programme (AMAP).

The water solubility and vapour pressure as well as Henry's Law Constants calculated from these values of the currently listed POPs are summarised in Table 2.1 together with information on hexabromobiphenyl from Table 2.1.

Table 2.1 Water solubility (WS), vapour pressure (VP) and (calculated) Henry's Law Constant (HLC) (at 25 °C) for hexabromobiphenyl and currently listed POPs.

| Substance | WS mg/L | VP Pa | HLC Pa m ³ /mol |
|-------------------------|-----------------|----------------------------|----------------------------|
| Hexabromobiphenyl-min | 0.011 | 6.9x10 ⁻⁶ | 0.39 |
| Hexabromobiphenyl-max | 0.003 | 6.9x10 ⁻⁶ | 1.44 |
| POP-min | 0.0012 (DDT) | 2.5x10 ⁻⁵ (DDT) | 0.04 (endrin) |
| POP-max | 3.0 (toxaphene) | 27 (toxaphene) | 3726 (toxaphene) |
| POP-2 nd max | 0.5 (dieldrin) | 0.04 (heptachlor) | 267 (heptachlor) |

Table 2.1 shows that the water solubility of hexabromobiphenyl is at the level of the least water soluble among the currently listed POPs (DDT), while the vapour pressure of HBB is one order of magnitude lower than that of DDT. The two Henry's Law Constants calculated for hexabromobiphenyl are well inside the range marked by the currently listed POPs, being at least one order of magnitude higher than the lowest (endrin). It should be noted that in presenting the data in table 2.1 it is not inferred that a chemical (in this case hexabromobiphenyl) is considered to meet the long-range environmental transport criterion just because it fits within the range of values of currently listed POPs.

Based on the vapour pressure alone, the potential for long-range airborne transport of hexabromobiphenyl is low compared to most of the currently listed POPs, while a comparison of the Henry's Law Constants places hexabromobiphenyl in a position close to endrin.

The EHC 152 (1994), argues that the vapour pressure of hexabromobiphenyl is 6.9x10⁻⁶ Pa and, thereby the potential for volatilisation is low. There is no information available about measured half-life of hexabromobiphenyl in the atmosphere. In the laboratory photodegradation of 2,2',4,4',5,5'-hexabromobiphenyl was rapid (90% degradation after 9 minutes) mainly resulting in lower brominated PBBs (EHC 152 (IPCS, 1994)). On the other hand, the rates and extent of photolytic reactions of PBBs in the environment have not been determined in detail. The few field observations available indicate a high persistence of the original PBBs or a partial degradation to less brominated, and often more toxic, photoproducts.

In support of the assessment of the potential for long-range environmental transport, monitoring data demonstrate that this substance has managed to reach remote areas like the Barents Sea and Greenland. In the Arctic, hexabromobiphenyl has been measured in samples of animals in several investigations. The results are summarised in Annex A, Table A.1.

In whitefish from Lapland (North Scandinavia) and ringed seal from Svalbard, concentrations of 0.29 and 0.42 µg/kg lipid, respectively, were reported by Jansson *et. al.*, (1993). In another paper, Jansson *et. al.*, (1987) reported concentrations of hexabromobiphenyl (Firemaster BP-6) in ringed seal from Svalbard to be 4 µg/kg lipid and concentrations in guillemot muscle of 50 µg/kg lipid. It is not clear whether these results are from different investigations. For comparison, Krüger (1988), measured 0.8 µg/kg of PBB 153 in unspecified seal samples from the same area (Quoted from US ATSDR, 2004).

In samples of large char collected in 1999-2001 from one of two lakes in Bear Island in the Barents Sea, Evenset *et al.*, (2005) measured concentrations of 4.11-51.5 µg/kg lipid of hexabromobiphenyl (PBB 153). These figures should be used with some caution since levels of other POPs are always very high in char from this lake, maybe due to a local biotransfer process through neighbouring bird species. These levels are the same as or higher than levels of PBB 153 (0.2-9.4 µg/kg lipid) in lake trout sampled in 1997 from Lakes Ontario, Erie, Huron and Superior, which were measured by Luross *et al.*, (2002) (Table 2.2).

Vorkamp *et al.* (2004), measured concentrations of PBDEs in samples from Greenland and the Faroe Islands of sediment and seven species of animals representing different trophic levels of the food chain. As a pilot investigation, analyses for five PBBs including PBB 153 were made in selected samples of blubber or fat from ringed seal, mink whale and polar bear from Greenland as well as pilot whale and fulmar from the Faroe Islands. PBBs were detected in all samples, except sediment samples, shorthorn-sculpin samples and samples of ringed seal from West Greenland. In all other samples, PBB 153 was generally the dominant congener. The concentrations measured in samples from (East) Greenland were in the range 0.34-44.26 µg/kg lipid with the lowest values found in the seal and the highest in polar bear. In the Faroese samples, the range of concentrations of PBB 153 was 8.71-25.54 µg/kg lipid weight with the highest values found in fulmar, a fish predator (Vorkamp *et al.*, 2004).

For comparison, concentrations of PBB 153 in grey seal and osprey from the Baltic Sea were 26 and 22 µg/kg lipid weight, respectively (Jansson *et al.*, 1993). Thus, concentrations of PBB 153 as µg/kg lipid weight in seals from the Arctic (0.34-0.74) are considerably lower than in seals from the Baltic Sea (26 µg/kg lipid weight), while concentrations in predatory birds from the two areas (fulmar and osprey) are of the same order of magnitude, being 25 and 22 µg/kg lipid weight, respectively.

Vorkamp *et al.*, (2004), conclude that PBBs and PBDEs seem to biomagnify along the marine food chain in a similar manner to PCBs. PBBs show indications of a higher biomagnification potential than PBDEs. Even though their absolute concentrations are lower than those of PBDEs, the PBDE/PBB ratio increases in the order ringed seal<pilot whale<mink whale<fulmar<polar bear, leading to almost equal concentrations of PBDEs and PBBs in polar bear. Apparently, the compounds follow the same spatial trend as previously observed for organochlorine compounds, with higher concentrations in East Greenland than in West Greenland (Vorkamp *et al.*, 2004). This indicates that the long-range transport of hexabromobiphenyl may be slow.

Monitoring information on PBBs from areas outside the Arctic, Northern Europe and America is scarce, as only one reference has been found. Hexabromobiphenyl (PBB 153) was not detected (LOD between 0.02 and 0.1 µg/kg wet weights) in samples of muscle and liver from several species of fish from the eastern Mediterranean region of Turkey (Erdogru *et al.*, 2005).

In summary, the 1994 EHC, review concludes that long-range transport of PBBs in the atmosphere has not been proven, but that the presence of these compounds in Arctic seal samples indicates a wide geographical distribution (EHC 152 (IPCS, 1994)). Several authors report levels of hexabromobiphenyl (and other brominated biphenyls) in arctic animals, especially in fish eating predators and predators at higher trophic levels.

In a recent modelling study, Scheringer *et al.*, (2006), investigated the persistence and long range transport potential of four potential POPs, including chlordecone and hexabromobiphenyl. They concluded that these POP candidates have persistence and long range transport potential properties similar to those of several known POPs. Furthermore, they included the uncertainty regarding the data quality in a Monte Carlo analysis, which indicated that the result is valid although there are considerable uncertainties in the chemical properties of the four POP candidates.

Conclusion

Although hexabromobiphenyl is less volatile than any of the currently listed POPs, it is found throughout the Arctic wildlife, demonstrating that it does have a high potential for long range environmental transport. The potential for long range environmental transport of hexabromobiphenyl is further supported by the modelling study of Scheringer *et al.*, 2006.

2.3 Exposure

Because production of hexabromobiphenyl is assumed to have ceased (section 2.1.2) the assessment of the exposure will focus on general exposure instead of current production sites.

2.3.1 Concentrations in abiotic environmental media

Recent monitoring data in soil, water and sediments for PBBs are limited. Historical monitoring data from the United States indicate that environmental PBB concentrations are confined to areas near former manufacturing facilities and regions of Michigan affected by the farm accident of the early 1970's (see Section 2.2.3) (US ATSDR, 2004).

The only available data for environmental concentrations of PBBs in areas outside the vicinity of former production sites are those from sediment samples from Greenland (Vorkamp *et al.*, 2004), where PBBs (including PBB 153) were not detected in any sample (the limits of detection/quantification are, however, not well defined in the paper).

2.3.2 Concentrations in biota

In the vicinity of Michigan

Concentrations in biota in the vicinity of the Michigan production and contamination accident sites were measured in a multitude of samples during the decade following the cessation of production. The US ATSDR (2004) includes the following: In the late 1980's, PBBs were detected in the concentration range of 15–15,000 µg/kg (lipid basis) in fish from embayments and tributaries of Lake Huron, but not from Lake Superior. Recently, Luross *et al.* (2002) determined the concentrations of several PBB congeners in lake trout from Lakes Huron, Superior, Erie, and Ontario. 2,2',4,4',5,5'-Hexabromobiphenyl (PBB-153) and 2,2',4,5,5'-pentabromobiphenyl (PBB-101) were found at the highest levels at concentrations ranging from 0.189 to 2.083 µg/kg wet weight and from 0.042 to 0.633 µg/kg wet weight, respectively. Several other congeners were also detected in these lake trout samples (Quoted from US ATSDR, 2004). The concentrations of PBBs in eggs of fish-eating birds (common tern, little gull, herring gull, and red-breasted mergansers) collected during 1975–1980 from nesting islands in northwestern Lake Michigan and Green Bay contained PBBs in the concentration range of 0.02–0.25 mg/kg (µg/g) wet weight (Heinz *et al.* 1983, 1985) (quoted from the US ATSDR, 2004).

Other areas

Monitoring data from areas outside the Arctic (see chapter 2.2.3) and the most exposed region of the US are summarised in Table A.2. in Annex A.

EHC 152 (1994) includes the following investigations on residues of (hexa)bromobiphenyl in biota:

- In Europe, 2,2',4,4',5,5'-hexabromobiphenyl (PBB 153) was found in fish from German and Swedish rivers at concentrations ranging from 0.3 to 0.6 µg/kg lipid (Krüger, 1988; Jansson *et al.*, 1992). A trout sample from a breeding farm contained much lower levels of PBBs than the fish samples from the rivers (Krüger, 1988).

- Swedish reindeers (pooled samples) showed PBB 153 levels as low as 0.04 µg/kg lipid (Jansson *et. al.*, 1992).
- PBBs (as a group) were not found in otters (*Lutra canadensis*) from a region relatively remote from industrial sites in north eastern Alberta (Canada) (Somers *et. al.*, 1987).
- Fish samples (freshwater and marine species) collected in 1983 from an industrial area of Japan (Osaka) did not contain "PBBs" (not specified) (Watanabe & Tatsukawa, 1990).
- In Europe, PBBs have been detected in seals (*Phoca vitulina*; *Pusa hispida*), guillemots (*Uria aalge*; *U. lomvi*), and white-tailed sea eagles (*Haliaeetus albicilla*). The concentrations (estimated by comparison with the technical product Firemaster BP-6) ranged from 3 to 280 µg/kg lipid (Jansson *et. al.*, 1987). The concentrations of PBBs in comparable samples from the Baltic Ocean were all higher than concentrations in samples from the Arctic Ocean. The same was true for polybrominated biphenyl ethers and PCBs (Jansson *et. al.*, 1987).
- Concentrations of PBB 153 determined in marine fish ranged from 0.2 to 2.4 µg/kg lipid (Krüger, 1988; Jansson *et. al.*, 1992). PBB 153 levels of 0.4-26 µg/kg lipid were found in seals (Krüger, 1988; Jansson *et. al.*, 1992).
- Detailed isomer-specific PBB analyses were carried out by Krüger (1988), in fish (several species) from the Baltic and North Seas and from sections of the Lippe and Rur rivers in North Rhine-Westphalia, Germany. Seal samples from Spitsbergen (Norway) were also included in this investigation. All samples contained PBBs. The smallest number of PBB congeners was found in seals (n=5) from an area remote from industrial sites. The main components were different hexabrominated isomers with 2,2',4,4',5,5'-hexabromobiphenyl reaching a mean concentration of 0.8 µg/kg fat. The mean concentrations of several PBB congeners and isomers (penta- to nonabrominated biphenyls) measured in fish (n=35) ranged, mostly, between 0.01 and 2 µg/kg fat. The pattern of PBB congeners found in fish differed in a characteristic manner, depending on the different capture sites. While relatively high amounts of nona- and octabromobiphenyls (besides polybrominated biphenyl ethers) were present in fish from German rivers (n=17; several species), hexabrominated biphenyls were predominant in fish from the North Sea and the Baltic Sea (n = 17; several species). In all samples from the Baltic Sea (n=6), 3,3',4,4',5,5'-hexabromobiphenyl was found in relatively high concentrations (maximum concentration: 36 µg/kg fat), but it was not detected in samples from the North Sea and from rivers. The concentrations of the other hexabrominated biphenyls were mostly higher in fish from the Baltic Sea than in fish from the North Sea.

(Quoted from EHC 152 (IPCS, 1994))

US ATSDR (2004) supplements with:

- Three bottlenose dolphins (*Tursiops truncatus*) collected during 1987–1988 from the U.S. mid-Atlantic contained PBBs at concentrations of 14–20 µg/kg lipid basis (Kuehl *et. al.*, 1991). The source of the PBBs in the dolphins was not given.
- The median concentrations of PBBs in carcass and brain of 10 specimens of bald eagles (*Haliaeetus leucocephalus*) collected from 29 states in 1977 were 0.07 and 0.05 mg/kg (µg/g), respectively (Kaiser *et. al.*, 1980). Twenty-two other specimens did not contain detectable levels (<0.03 mg/kg [µg/g]) of PBBs.
- In whitebeaked dolphins from the North Sea, the concentration of hexa-, penta-, and deca-BBs were 13, 8.3, and <0.9 µg/kg (µg/kg) wet weight, respectively. Tetra-, penta-, and deca-BBs concentration ranges were 1.1–1.9, 0.4–0.9, and <0.5 µg/kg wet weight, respectively, in sperm whales from the Atlantic Ocean (de Boer *et. al.*, 1999).

The German Baltic fish samples (as the only samples in that investigation) also contained PBB 169 at a concentration of 15.16 µg/kg lipid (EHC 152 (IPCS, 1994)).

In the Belgian samples from corpses of birds of prey, the variation in concentrations of hexabromobiphenyl was high. Thus, the maximum concentrations measured in muscle and liver were 150 and 180 µg/kg lipid; respectively (Jaspers *et al.*, 2006).

Jansson *et al.* (1993), measured hexabromobiphenyl (PBB 153) in samples of reindeer (a herbivore) from northern Sweden at a level of 0.037 µg/kg lipid. In two other herbivores (rabbit and moose) from Southern Sweden, PBBs were not detectable (level of detection not well defined).

2.3.3 Concentrations in human tissues and breast milk

Michigan

The human exposure to hexabromobiphenyl subsequent to the Michigan accident is discussed in EHC 152 (1994) as well as in US ATSDR (2004). The general trends of the findings are described as follows in EHC 152 (1994):

- Nearly 100% of the adipose samples randomly selected throughout the state had detectable PBB concentrations. Thus, statewide exposure of Michigan residents to PBBs can be demonstrated.
- Levels of PBBs in serum (Landrigan, 1980; Wolff *et al.*, 1982), breast-milk (Brilliant *et al.*, 1978; Miller *et al.*, 1984), and adipose tissue (Wolff *et al.*, 1982) were highest in the area of the accident (lower peninsula), and lowest in the upper peninsula, farthest from the source.
- Compared with residents of quarantined farms, direct consumers of products from quarantined farms, and PBB production workers, the tissue burdens among the general population of Michigan were 1-3 orders of magnitude lower. Moreover, for example, only 36% of the general population had serum PBB concentrations greater than 1 µg/L, compared with 78% among farmers (Anderson *et al.*, 1979; Wolff *et al.*, 1982).
- PBB levels appear to be higher in males than females (Meester & McCoy, 1976; Landrigan *et al.*, 1979; Landrigan, 1980; Wolff *et al.*, 1978; 1980; Kreiss *et al.*, 1982; Eyster *et al.*, 1983) and higher in children (below the age of 10 years) than in adults (Humphrey & Hayner, 1975; Landrigan *et al.*, 1979; Landrigan, 1980; Barr, 1980; Wolff *et al.*, 1982) (Quoted from EHS 152 (IPCS, 1994)).

The subsequent development is described in EHC 152 (1994):

- In most cases, PBB concentrations did not appear to be decreasing significantly over time. Wolff *et al.* (1979b), did not find any significant variation in the serum PBB levels of nine dairy farm residents during 18 month of observation.
- Paired serum samples, one collected in 1974 and the other in 1977, were also available for 148 members of the Michigan PBB cohort. The data indicate that levels were generally stable over the 3-year period with a mean change of 16 µg/litre (Landrigan *et al.*, 1979). In another study of the Michigan PBB-cohort, the decrements in median serum levels of PBBs between matched pairs over one (1977-78) and two (1977-79) year intervals were both only 1 µg/litre (Kreiss *et al.*, 1982). No significant change in blood plasma PBB levels was observed over a 5-month period in 41 residents of quarantined farms (Humphrey & Hayner, 1975). In contrast, Meester & McCoy (1976) reported a marked decline over 3 years (1974-76) in serum levels of PBBs. These authors also found that the average decrease in PBB concentrations in the fat of 16 individuals was about 40% in a period of 6 months. No changes in PBB levels were seen over an 11-year period (1976-87) in fat samples from a patient with long-term exposure to PBBs from the early 1970s as a result of the Michigan PBBs accident. The average fat level of PBBs was 0.8 mg/kg (Sherman, 1991).

- In 1981, PBBs were found in 13-21% of serum samples from 4-year-old Michigan children. Their mothers belonged to a group that was surveyed either with regard to the consumption of Lake Michigan sport fish (mean PBB level detected in children: 2.4 ng/ml) or with regard to former exposure to quarantined farm products (mean PBB level detected in children: 3.0 ng/ml) (Jacobson *et al.*, 1989) (Quoted from EHC 152 (IPCS, 1994)).

Other areas

The EHC 152 (1994), stresses the lack of available monitoring studies from areas outside Michigan, as few human monitoring data are available for the US population outside of Michigan. One study deals with the population in the vicinity of industrial areas involved in PBB production or use (Stratton & Whitlock, 1979), the other with farmers of the state of Wisconsin who were examined as control group in connection with the Michigan PBB studies (Wolff *et al.*, 1978).

PBBs were found in all studies, but, because of the limited data, the significance is unclear. The highest PBB levels were found in the hair of humans living near PBB industry. Of the nine samples analysed, five had detectable PBB levels. Both male and female hair samples contained PBBs (Stratton & Whitlock, 1979).

There is very little human monitoring data on PBBs in the populations of countries other than the United States. Krüger *et al.*, (1988) reported PBB contamination of breast-milk from women in Europe in a survey from North Rhine-Westphalia, Germany. The milk samples (n=25) contained a typical pattern of certain PBB congeners. It included penta- to octabromobiphenyls in concentrations ranging from 0.002 to 28 µg/kg, based on milk fat. The most abundant component was 2,2',4,4',5,5'-hexabromobiphenyl (PBB 153) followed by a peak consisting of two heptabromobiphenyl isomers (2,2',3,4',5,5',6- and 2,2',3,4,4',5,6'-heptabromobiphenyl, PBB 187 and 182 respectively). Differences in the pattern were only found in the milk given by a Chinese woman and in that given by a woman having been exposed to several fires in industry.

Concentrations of PBB 153 in human and cow's milk, both collected from the same region (North Rhine-Westphalia), were 1 µg/kg and 0.03 µg/kg, respectively, measured on a lipid basis (Krüger, 1988). (Quoted from EHC 152 (IPCS, 1994))

2.3.4 Human exposure

The US ATSDR (2004), considers the current human exposure to PBBs to be very low, because PBBs are no longer produced or used. Thus, the general population exposure to PBBs will only be from historical releases. For people residing in the lower peninsula of Michigan, especially in the immediate vicinity of the PBB contaminated areas of this region, exposure to PBBs may still be occurring today. However, environmental levels have decreased since the 1970s and current exposure, if any, will be at low levels. For other regions of the United States, the levels of exposure will either be very low or none (Quoted from US ATSDR, 2004).

In Arctic and North Atlantic regions, where the traditional diet includes top predators (*e. g.* seal in Greenland and pilot whale in the Faroe Islands), exposure has not ceased. Especially the level of PBBs in pilot whale blubber of up to 17 µg/kg lipid indicate the presence of hexabromobiphenyl in food. Pilot whale blubber is consumed as a delicacy in the Faroe Islands.

2.4 Hazard assessment for endpoints of concern

2.4.1 Toxicity

As described in Section 1.1.1, the descriptor "hexabromobiphenyl" covers 42 different hexabrominated biphenyls or congeners, as individually listed in Annex B. The EHC review (IPCS, 1994) indicates that the hexabrominated biphenyls are the most toxic of the chemical class

of polybrominated biphenyls (PBBs) and that the higher homologues (hepta-, octa-, nona- and decabrominated biphenyls) are of progressively lower toxicity. Toxicological studies on hexabromobiphenyl have been carried out mainly on the congener 2,2',4,4',5,5'-hexabromobiphenyl (PBB 153), which is the major component of the PBB mixture FireMaster[®], and on FireMaster[®] itself. The toxicity of FireMaster[®] appears to be primarily associated with the minor components 2,3,3',4,4',5-hexabromobiphenyl, 2,3',4,4',5,5'-hexabromobiphenyl, 3,3',4,4',5,5'-hexabromobiphenyl (PBB 169) and 2,3',4,4',5-pentabromobiphenyl (IPCS, 1994). The predominant congeners in FireMaster[®] (2,2',4,4',5,5'-hexabromobiphenyl and 2,2',3,4,4',5,5'-heptabromobiphenyl), are less toxic (IPCS, 1994). Other toxic contaminants in technical PBB mixtures include the polybrominated naphthalenes (HBNs). Hexabromonaphthalene has been identified as a toxic contaminant of Firemaster BP-6 or FF-1 at levels of approximately 150 ppm (Birnbaum *et al.*, 1983, as reported in US ATSDR, 2004). The toxicological effects of the PBBs in humans and in animal studies, as described in the scientific literature, are considered to be attributable mainly to exposure to hexabromobiphenyl congeners (EHC 152 (IPCS, 1994) and US ATSDR, 2004)), although a possible contribution of the HBNs to toxicity cannot be ignored.

Mechanism of action

Hexabromobiphenyl, in common with all PBBs, is a potent inducer of hepatic cytochrome P-450 metabolizing enzymes in the liver. The mechanism of action underlying a number of the toxicological effects of some of these compounds, including induction of metabolising enzymes, immunotoxicity, hepatotoxicity and reproductive toxicity, is considered to be due to interaction with the cellular Ah receptor (also the target of the polychlorinated dioxins, furans and dioxin-like PCBs), causing altered gene expression (Poland & Glover, 1977, 1980; Poland *et al.*, 1979; Goldstein, 1980; Moore *et al.*, 1980; McKinney & Singh, 1981; Parkinson & Safe, 1981; Bandiera *et al.*, 1982, 1983; McKinney & McConnell, 1982; Nebert *et al.*, 1982; Poland & Knutson, 1982; Robertson *et al.*, 1982b, 1984c,d; Safe *et al.*, 1982, 1985; Aust *et al.*, 1983; Dannan *et al.*, 1983; Lai, 1984; Safe, 1984, as quoted in IPCS, 1994).

Toxicokinetics

Hexabromobiphenyl is readily absorbed into the body, the primary route of human exposure being via food, due to accumulation and biomagnification in the food chain (IPCS, 1994; US ATSDR, 2004). The majority of animal toxicology studies have used the oral route of exposure and little information is available on exposure via the inhalation and dermal routes, although worker exposure is likely to occur mainly via these routes (Wolff *et al.*, 1979a, as quoted in IPCS, 1994). Following absorption, hexabromobiphenyl is widely distributed in the body and accumulates, with the highest concentrations found in adipose tissue and to a lesser extent the liver (IPCS, 1994).

Exposure *in utero* occurs via transfer of PBBs to offspring by placental transfer and infants are also exposed via milk. Human milk has been found to contain levels of 2,2',4,4',5,5'-hexabromobiphenyl 100 times higher than those found in maternal blood (Brilliant *et al.*, 1978; Landrigan *et al.* 1979; Eyster, 1983, as reported in IPCS, 1994).

Metabolism and excretion of the hexabromobiphenyls is low (IPCS, 1994; US ATSDR, 2004), and the compounds therefore show marked bioaccumulation and persistence in all species. Average half-lives for 2,2',4,4',5,5'-hexabromobiphenyl in humans have been estimated to be between 8 and 12 years (IPCS, 1994), while shorter half-lives have been reported in rats, monkeys, and other species (see Table 68 in IPCS, 1994). It has been suggested that humans may retain certain congeners to a greater degree than experimental animals (*e. g.* Fries (1985b, as quoted in IPCS, 1994), a phenomenon that is also found with the polychlorinated dioxins and furans.

Darnerud (2003), argues that the pattern of toxicity of PBBs should be similar to that of PCBs apart from the change in effects brought about by the chlorine-bromine substitution. Consequently, the planar PBBs are expected to be most toxic (as they bind to the Ah receptor) and toxicity to decrease through mono-ortho congeners to di-ortho congeners. This should be supported by experimental evidence, as 3,3',4,4',5,5' hexabromobiphenyl was found to be the most toxic PBB congener in several systems (Darnerud, 2003).

Toxicity of hexabromobiphenyl in animal studies

In experimental animal studies, hexabromobiphenyl shows relatively low acute toxicity ($LD_{50} > 1$ g/kg body weight) (see Table 70, IPCS, 1994). Toxicity is higher following repeated exposure (IPCS, 1994), due to progressive accumulation of the compounds and a characteristic delay in lethality after exposure is seen (Di Carlo *et al.*, 1978; Gupta & Moore, 1979, (as quoted in IPCS, 1994). At lethal doses, death is reported to be due to a "wasting syndrome" with marked loss in body weight rather than to specific organ pathology (Hutzinger *et al.*, 1985a; McConnell, 1985, as quoted in IPCS, 1994). However, prolonged exposure of laboratory animals to doses in the range of < 1 mg/kg bw/day to 100 mg/kg bw/day results in liver, kidney and thyroid changes, accompanied by effects in the nervous and immune systems, porphyria and skin disorders (IPCS, 1994).

A summary of outcomes of a number of the key toxicological studies on hexabromobiphenyl, including the NOAEL/LOAEL derived in each study is provided in Annex A, Table A.3 to this document. The studies included in Annex A, Table A.3 have been selected from the very large database on toxicological studies on hexabromobiphenyl, on the basis of the importance of the endpoint investigated (*e. g.* reproductive toxicity, carcinogenicity, other key target organ toxicity), robustness of the reported studies and the dose level (NOAEL/LOAEL) at which effects were reported. Table 2.2 below provides information on pivotal toxicological studies (also included in Annex A Table A.3) that provide information on the toxicity of hexabromobiphenyl at low levels of exposure, considered to be particularly relevant for characterisation of the toxicological risks of these compounds. Some of these studies have been used by US ATSDR to define Minimal Risk Levels (MRLs) for hexabromobiphenyl (US ATSDR, 2004).

Effects in toxicological studies included decreased circulating thyroid hormones in a 10-day gavage study in rats with a NOAEL of 1 mg/kg bw/day (Allen-Rowlands *et al.*, 1981, as quoted in US ATSDR, 2004), decreased lymphoproliferative responses in rats at a dose level of 3 mg/kg/day (LOAEL) (Luster *et al.*, 1980, as quoted in US ATSDR, 2004), and generalised toxicity in male Rhesus monkeys at 0.73 mg/kg bw/day (LOAEL) (Allen *et al.*, 1978; Lambrecht *et al.* 1978 (as quoted in US ATSDR, 2004)). PBBs produced porphyria in rats and male mice at doses as low as 0.3 mg/kg bw/day. The no-effect level was 0.1 mg/kg bw/day.

These results show that hexabromobiphenyl produced long-term toxicity in experimental animals at very low doses, a critical effect for the purposes of risk characterization being the effects seen in the thyroid in rats at doses as low as 0.05 mg/kg bw/day, comprising increased number and decreased size of follicles, accompanied by changes in levels of circulating T_3 and T_4 hormone (Akoso *et al.*, 1982, as quoted in US ATSDR, 2004).

Hepatocarcinogenicity of hexachlorobiphenyl has been demonstrated in a number of studies including repeated dose studies in Fischer-344/N rats and B6C3F1 mice (males and females) administered FireMaster^(R) FF-1 at dosages of 0, 0.1, 0.3, 1, 3, or 10 mg/kg bw/day (NTP 1983, NTP, 1992, as quoted in US ATSDR, 2004). Tumors included hepatocellular adenoma and carcinoma and, in female rats, cholangiocarcinoma. The lowest dose of FireMaster^(R) that produced tumors (primarily adenomas rather than carcinomas) in rats was 3.0 mg/kg bw/day for 2 years, and in mice the dose was 10 mg/kg bw/day (NTP 1983, as quoted in US ATSDR, 2004). Mice receiving 0.15 mg/kg bw/day in a study involving pre- and perinatal exposure in addition to lifetime exposure

did not suffer any adverse effects (NTP, 1992, as quoted in US ATSDR, 2004). The International Agency for Research on Cancer (IARC) in 1987 concluded that there was sufficient evidence that hexabromobiphenyl is carcinogenic in mice and rats and possibly carcinogenic to humans (Group 2B). Hexabromobiphenyl is not genotoxic in *in vitro* microbial and mammalian cell gene mutation assays (see Table 88 in IPCS, 1994), although it has been reported to interfere with cell-to-cell communication (Sleight, 1985 as quoted in IPCS, 1994). These results, coupled with the results of tumor promotion studies (*e. g.* Schwartz *et al.*, 1980; Jensen *et al.*, 1982, 1983, 1984; Jensen & Sleight, 1986; Rezabek *et al.*, 1987; Dixon *et al.*, 1988, as quoted in IPCS, 1994) indicate that these chemicals cause cancer by epigenetic mechanisms, involving both hepatic toxicity and hypertrophy, including cytochrome P-450 induction (IPCS, 1994).

Oral administration of hexabromobiphenyl was associated with adverse effects on reproductive parameters in a range of experimental animals (see Table 86 and 87 in IPCS, 1994). The most common adverse effects on reproduction were failure in implantation and decreases in pup viability of offspring. These effects were seen at a dose level of 28.6 mg/kg bw/day in a 15-day reproductive toxicity study in rats, with dosing between gestational day 0-14 (Beaudoin, 1979, as quoted in US ATSDR, 2004) and in mink at concentrations of 1 mg/kg diet (Aulerich and Ringer, 1979 as quoted in IPCS, 1994). Increased menstrual cycle duration and prolonged implantation bleeding were observed in female monkeys fed approximate daily dose levels of 0.012 mg/kg bw/day for 7 months before breeding and during pregnancy. Fetal deaths were also observed after approximately 1 year of exposure. Effects were attributed to decreases in serum progesterone (Lambrecht *et al.*, 1978; Allen *et al.*, 1978; 1979, (as quoted in US ATSDR, 2004).

Table 2.2 Pivotal toxicological studies on the toxicity of hexabromobiphenyl.

| Species | Study type | Effect | LOAEL/ NOAEL |
|---------------------|--|--|---|
| Rat | Short-term/acute toxicity 10 day repeat dose gavage study | decreased thyroid serum T4 hormones | 3 mg/kg bw/day (LOAEL) 1 mg/kg bw/day (NOAEL) |
| Rat, Sprague Dawley | 30-day dietary feeding study | increased number and decreased size of thyroid follicles | 0.05 mg/kg bw/day (LOAEL) |
| Mice B6C3F1 | In utero and post partum exposure from Gd 0-ppd 56 | hepatocellular adenoma and carcinoma in offspring | 1.5 mg/kg bw/day (LOAEL) 0.15 mg/kg bw/day (NOAEL) |
| Rhesus Monkey | 25-50 wk dietary feeding study | 34% weight loss in adult male, 0% weight gain in juvenile, proliferation of mucosal cells, chronic inflammation, severe ulcerative colitis, alopecia, keratinization of hair follicles and sebaceous glands, clinical chemical and hepatic changes | 0.73 mg/kg bw/day (LOAEL, males) |
| Rat, Sprague Dawley | 7 month dietary feeding study | decreased thyroid serum T3 and T4 hormones | 0.45 mg/kg bw/day (LOAEL) |
| Monkey, Rhesus | | increased menstrual cycle duration in 4/7; implantation bleeding in 2/7). 1/7 fetuses were aborted, 1/7 fetuses stillborn, 12% decreased birth weight and 22% decreased postnatal weight gain in 4/7 survivors | 0.012 mg/kg bw/day (LOAEL) |

Toxicity of hexabromobiphenyl in humans

Information on toxicological effects of PBBs (and by inference, hexabromobiphenyl) in humans has mainly been derived from the Michigan accident described in Section 2.1.4 of this draft Risk Profile (Carter (1976), Getty *et al.*, (1977), Kay (1977), Di Carlo *et al.*, (1978), Damstra *et al.*, (1982), Zabik (1982), and Fries (1985b), as quoted in EHC 152 (IPCS, 1994)). This accident resulted in widespread exposure of consumers for periods approaching 1 year, before the contamination of food by PBBs was identified and affected foodstuffs were removed from the food chain.

Adverse health effects reported included changes in liver enzymes, nausea, abdominal pain, loss of appetite, joint pain and fatigue (Anderson *et al.*, 1978b, 1979, as reported in IPCS, 1994), together with reports of skin disorders, including acne and hair loss, in the period following the contamination. (IPCS, 1994). Similar skin disorders have also been reported in workers with occupational exposure to PBBs (Anderson *et al.*, 1978a, as reported in IPCS, 1994), and also following exposure to the polychlorinated dioxins and furans.

Detailed epidemiological studies have been carried out on the health status of exposed individuals including immunological status, cancer incidence, reproductive effects and effects on development of young children. These studies have in the main failed to establish a definite link between any of these effects and exposure to PCBs, although some studies have reported decreased immune function in Michigan farm residents (Bekesi *et al.*, 1979, 1987) and effects have also been reported on pubertal development in young females (see endocrine-disrupting effects below).

There are no reports of acute hexabromobiphenyl intoxication in humans, and there is also no consistent epidemiological evidence for hepatocarcinogenicity in exposed humans. A relationship between increasing serum levels (>2 ppb) of PBBs and increasing risk of breast cancer was indicated in case-control studies of women exposed during the Michigan contamination episode (Henderson *et al.*, 1995; Hoque *et al.*, 1998), but according to US ATSDR, 2004 (and quoted from this source) the results are only suggestive due to factors such as the small number of cases, insufficient information on known breast cancer risk factors, and confounding exposures to other organochlorine chemicals.

Effects on endocrine systems

The PBBs (and by inference, hexabromobiphenyl) are considered to have effects on endocrine systems. They have been evaluated under the EU-Strategy for Endocrine Disrupters⁷ and have been placed in category 1 (evidence of endocrine-disrupting activity in at least one species using intact animals) in the priority list of chemicals established under the EU-Strategy. This categorisation is based on evidence of delayed vaginal opening in new-born rats, epidemiological evidence of hypothyroidism in workers exposed to polybrominated biphenyls and of increased incidence of breast cancer among women exposed to polybrominated biphenyls (as reported in BKH report, 2000). In an assessment (Blanck *et al.*, 2000) of pubertal development in girls and young women exposed in utero and via breast milk to high levels of PBBs (>7ppb), it was found that this population had an earlier age to menarche than a similar breastfed population exposed to lower levels of PBBs, or than a highly-exposed population who were not breastfed. Earlier pubic hair development was also seen in the more highly exposed population, suggesting an effect of PBBs on pubertal events (Blanck *et al.*, 2000).

⁷ http://europa.eu.int/comm/environment/endocrine/strategy/substances_en.htm