Conclusion on effects assessment and toxicity of hexabromobiphenyl

Hexabromobiphenyl is readily absorbed into the body and accumulates following prolonged exposure. Although the acute toxicity of hexabromobiphenyl is low, a number of chronic toxic effects including hepatoxicity have been observed in experimental animals at doses around 1 mg/kg bw/day following long-term exposure, and effects are seen in the rat thyroid at doses as low as 0.05 mg/kg bw/day. Cancer was induced in animal studies at a dose of 0.5 mg/kg bw/day and the no-observed-effect level was 0.15 mg/kg bw/day. The International Agency for Research on Cancer has classified hexabromobiphenyl as a possible human carcinogen (IARC group 2B). The PBBs (and by inference, hexabromobiphenyl) are endocrine disrupting (ED) chemicals, and effects are seen on reproductive capacity in rats, mink and monkeys. Effects were seen in monkeys fed 0.012 mg/kg bw/day for 7 months before breeding and during pregnancy, the lowest effect level reported for hexabromobiphenyl in toxicology studies. There is epidemiological evidence of hypothyroidism in workers exposed to polybrominated biphenyls and of increased incidence of breast cancer in exposed women.

It can be concluded that hexabromobiphenyl is a bioaccumulative chemical with a range of potentially adverse effects on health, including carcinogenicity, reproductive toxicity, endocrine and other hormone-disrupting effects, at very low levels of exposure.

2.4.2 Ecotoxicity

Only few data are available on effects of PBBs on other organisms than mammals. Toxicity tests with technical decabromobiphenyl (Adine 0102) and bacteria (*Pseudomonas putida)* and the water flea *Daphnia magna* are quoted in EHS 152 (1994). The results were an EC10 of 53 mg/L for *Pseudomonas putida* (cell multiplication) and an EC50>66 mg/liter for *Daphnia magna* (immobilization, 24 hours). Because these concentrations exceed the solubility of HBB in water, the data may be of limited relevance to evaluating the environmental effects. However, the fact that the NOEC is reported to be <2 mg/L indicates that the water fleas were affected at the lowest concentration tested.

MacPhee & Ruelle (1969) and Applegate *et. al.*, (1957), report results from short term tests with hexabromobiphenyl (CAS No. 36355-01-8) and several species of fish in the range 5-10 mg/L (Quoted from the Ecotox data base (US EPA, 2006)). These concentrations are also above the water solubility and may also be of limited environmental relevance.

In a field study on water birds, correlations between behavioural effects and reproductive success were not unambiguously correlated to body burdens of PBBs. (EHS 152 (IPCS, 1994)).

In an untraditional fish early life stage test, Hornung *et al.*, (1996), injected halogenated organic contaminants into rainbow trout eggs. For 3,3',4,4',5,5'- hexabromobiphenyl they found an LD_{50} of 3,910 µg/kg. This result is not comparable to those of traditional fish tests, where exposure is via the water but it is comparable to results of other test with similar exposure. Hornung *et. al.* (1996), made such experiments to compare the toxicity of PBBs and PCBs and found that both 3,3',4,4'-tetrabromobiphenyl and 3,3',4,4',5,5'-hexabromobiphenyl were 10-fold more potent than identically substituted polychlorinated biphenyls.

Based on this, it seems to be relevant to expect the environmental toxicity of hexabromobiphenyl to be comparable to that of hexachlorobiphenyl.

3 SYNTHESIS OF THE INFORMATION

Hexabromobiphenyl belongs to a wider group of polybrominated biphenyls (PBBs). It has mainly been used as a fire retardant. Hexabromobiphenyl is already listed in Annex I of the UNECE Protocol on POPs.

According to available data, hexabromobiphenyl can be considered to be highly persistent in the environment. There is evidence of low or no degradation in water, soil and sediment, in the laboratory as well as in the field. Therefore, hexabromobiphenyl is considered to be highly persistent.

Hexabromobiphenyl is less volatile than many POP substances. However, extensive data on monitoring shows that it is found throughout the Arctic wildlife, demonstrating that it does have a high potential for long range environmental transport.

With measured weight-based BCF values in the range 4,700 - 18,100 and biomagnification factors in the aquatic food chain exceeding 100, 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 (a PCB compound), for which the bioaccumulative properties are well documented.

Hexabromobiphenyl is readily absorbed into the body and accumulates following prolonged exposure. Although the acute toxicity of hexabromobiphenyl is low, a number of chronic toxic effects including hepatotoxicity have been observed in experimental animals at doses around 1 mg/kg bw/day following long-term exposure, and effects are seen in the rat thyroid at doses as low as 0.05 mg/kg bw/day. The International Agency for Research on Cancer has classified hexabromobiphenyl as a possible human carcinogen (IARC group 2B). The PBBs are endocrine disrupting chemicals, and effects are seen on reproductive capacity in rats, mink and monkeys. There is epidemiological evidence of hypothyroidism in workers exposed to polybrominated biphenyls and of increased incidence of breast cancer in exposed women. Data on toxicity to other species than laboratory mammals is scarce but suggests the environmental toxicity of hexabromobiphenyl is comparable to that of hexachlorobiphenyl.

Based on the available data, hexabromobiphenyl should be considered as a POP warranting global action.

Production and use of hexabromobiphenyl has ceased over the last decades but it cannot be excluded that it is still produced or used in some countries. In addition to emissions during manufacture or use, hexabromobiphenyl can enter the environment from the widespread use of flame-retarded products. A considerable part of the substance produced will probably reach the environment sooner or later because of the high stability of these compounds. Furthermore, some of these chemicals may form toxic polybrominated dibenzofurans during combustion processes.

4 CONCLUDING STATEMENT

It has been demonstrated that hexabromobiphenyl clearly meets all the criteria laid down in Annex D of the Stockholm Convention: It is very persistent in the environment. It has a great potential for bioaccumulation and in addition there is clear evidence of its biomagnification. Due to its physical and chemical properties and based on findings in environmental samples, it is verified that hexabromobiphenyl can be transported long distances in air, far from its sources. Hexabromobiphenyl is a possible human carcinogen and can also be regarded as a substance capable of disrupting the endocrine system.

As hexabromobiphenyl can travel in the atmosphere far from its sources, neither a single country nor group of countries alone can abate the pollution caused by this substance. Regional action has already been considered necessary and hexabromobiphenyl is totally banned under the Convention on Long-range Transboundary Air Pollution Protocol on Persistent Organic Pollutants. Although the production and use of hexabromobiphenyl seems to be ceased in most countries, its reintroduction remains possible. This could lead to increased releases and levels in the environment.

Based on the available data, hexabromobiphenyl is likely, as result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted.

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ANNEX A

Table A.1 Concentrations of hexabromobiphenyl (PBB 153) in Arctic predators.

Year of sampling	Location	Species	Tissue	Concentration µg/kg lipid
1999-2002	East Greenland	Polar bear (*Ursus maritimus*) [1]	Blubber	33-44
1998	Faroe Islands	Fulmar (*Fulmarus glacialis*) [1]	Fat	16-26
2001	Faroe Islands	Pilot whale (*Globicephala melas*) [1]	Blubber	8.7-17
< 1987	Arctic Ocean	Guillemot (*Uria aalge*) [2]	Muscle	50 [6]
2002	East Greenland	Ringed seal (*Phoca hispida*) [1]	Blubber	0.34-0.42
1998-2002	West Greenland	Ringed seal (*Phoca hispida*) [1]	Blubber	n.d.
< 1987	Svalbard	Ringed seal (*Phoca hispida*) [2]	Blubber	4 [6]
1981	Svalbard	Ringed seal (*Phoca hispida*) [3]	Blubber	0.42
< 1988	Svalbard	Seal sp. [4]	? (mean)	0.8
1998	East Greenland	Minke whale (*Balaenoptera acutorostrata*) [1]	Blubber	0.56-1.2
1999-2001	Barents Sea	Arctic char (*Salvelinus alpinus*) [5]	Muscle	n.d.-52
1986	Lapland	Whitefish (*Coregonus sp.*) [2]	Muscle	0.29
2002	East Greenland	Shorthorn sculpin (*Myoxocephalus scorpius*) [1]	Liver	n.d.
2002	West Greenland	Shorthorn sculpin (*Myoxocephalus scorpius*) [1]	Liver	n.d.

n.d. = Not detected. Limits of detection are not well described in the references.

1: Vorkamp *et al.*, 2004,
2: Jansson *et al.*, 1987,
3: Jansson *et al.*, 1993,
4: Krüger, 1988 (Quoted from EHC 152),
5: Evenset *et al.* 2005.
6: FireMaster(R) BP-6

Table A.2 **Concentrations of hexabromobiphenyl (PBB 153) in biota, collected in subarctic and temperate regions outside the vicinity of Michigan.**

Year of sampling	Location	Species	Tissue	Concentration µg/kg lipid
Aquatic species				
1979-85	Baltic Sea	Grey seal (*Halichoerus grypus*) [2]	Blubber	26
< 1987	Baltic Sea	Harbour seal (*Phoca vitulina*) [7]	Blubber	20
< 1987	~North Sea	Harbour seal (*Phoca vitulina*) [7]	Blubber	3
< 1987	Baltic Sea	Guillemot (*Uria aalge*) [7]	Muscle	160
1987-88	US mid Atlantic	Bottlenose dolphin (*Tursiops truncatus*) [8]	?	14-20
< 1999	North Sea	Whitebeaked dolphin (*Lage-norhynchus albirostris*) [10]	?	13 (wwt)
1987	S. Sweden	Arctic char (*Salvelinus alpinus*) [2]	Muscle	0.42
1986	Bothnian Bay	Herring (*Clupea harengus*) [2]	Muscle	0.092
1987	Baltic Proper	Herring (*Clupea harengus*) [2]	Muscle	0.16
1987	Skagerak	Herring (*Clupea harengus*) [2]	Muscle	0.27
< 1988	Germany	River fish (average) [1]	?	0.60
< 1988	Baltic Sea	Fish [1]	?	2.39
< 1988	North Sea	Fish [1]	?	1.31
1997	USA, Great Lakes	Lake trout (*Salvelinus nanay-cush*) (range of means) [6]	Whole fish	0.19-2.08
Predatory birds				
< 1987	Baltic Sea	White tailed sea eagle (*Hali-aeetus albicilla*) [7]	Muscle	280
1977	USA, 29 states	Bald eagle (*Haliaeetus leuco-cephalus*) [9]	Carcass	< 0.03 – 0.07 (wwt?)
1977	USA, 29 states	Bald eagle (*Haliaeetus leuco-cephalus*) [9]	Brain	< 0.03 – 0.05 (wwt?)
1982-86	S. Sweden	Osprey (*Pandion haliaeetus*), corpses [2]	Muscle	22
2003-2004	Belgium	7 species of predatory birds, corpses (range of medians) [3]	Muscle	2-35
2003-2004	Belgium	7 species of predatory birds, corpses (range of medians) [3]	Liver	2-43
1998-2000	Belgium	Little owl (*Athene noctua*) [5]	Unhatched eggs	1-6
1991-2002	Norway	6 species of predatory birds (range of medians) [4]	Unhatched eggs	0.2-9.4 µg/kg wwt
Terrestrial herbivores				
1986	S. Sweden	Rabbit (*Oryctlagus cuniculus*) [2]	Muscle	n.d.
1985-86	S. Sweden	Moose (*Alces alces*) [2]	Muscle	n.d.
1986	N. Sweden	Reindeer (*Rangifer tarandus*) [2]	Suet (fat)	0.037

n.d. = Not detected. Limits of detection are not well described in the references.

1: EHC 152 (IPCS, 1994), 2: Jansson *et al.* 1993, 3: Jaspers *et al.*, 2006, 4: Herzke *et al.*, 2005, 5: Jaspers *et al.*, 2006, 6: Luross *et al.*, 2002, 7: Jansson *et al.* 1987, 8: Kuehl *et al.* 1991 (quoted from US ATDSR, 2004), 9:Kaiser *et al.*, 1980 (quoted from US ATSDR, 2004), 10: de Boer *et al.*, 1999 (quoted from US ATSDR, 2004).

Table A.3. Summary of key toxicological studies on hexabromobiphenyl.

Species (test material)	Study type	Effect	LOAEL/ NOAEL	Ref.
Rat Fischer 344/N (FF-1)	Short-term/acute toxicity, 14-day repeat dose, 5 single daily doses per week	Body weight loss, emaciation, hepatotoxicity, renal & adrenal changes, atrophy of thymus; necrosis of splenic lymphoblasts)	1000 mg/kg/day (LOAEL)	Gupta and Moore 1979 (as quoted in US ATSDR, 2004).
Rat	Short-term/acute toxicity10 day repeat dose gavage study	decreased thyroid serum T4 hormones	3 mg/kg bw/day (LOAEL) 1 mg/kg bw/day (NOAEL)	Allen-Rowlands *et al.* 1981(as quoted in US ATSDR, 2004).
Rat, Sprague Dawley (BP-6)	30-day dietary feeding study	increased number and decreased size of thyroid follicles	0.05 mg/kg/day (LOAEL)	Akoso *et al.* 1982 (as quoted in US ATSDR, 2004).
Mouse B6C3F1 (FF-1)	Short-term/acute toxicity, 14-day repeat dose, 5 single daily doses per week	Hepatocyte enlargement and single-cell necrosis	0.3 mg/kg bw/day (NOAEL)	Gupta *et al.* 1981 (as quoted in US ATSDR, 2004).
Guinea Pig (PBB not specified)	30-day dietary feeding study	vacuolation and fatty changes in liver	0.04 mg/kg bw/day	Sleight and Sanger 1976, (as quoted in US ATSDR,2004).
Balb/c) Mouse (BP-6)	Short-term/acute toxicit, 10 day oral dietary study	suppressed antibody-mediated response to SRBC, thymic atrophy)	130 mg/kg bw/day (LOAEL)	Fraker and Aust 1978, (as quoted in US ATSDR, 2004).
Rat Fischer 344/N (FF-1)	6 month gavage study, 5 single daily doses per week	decreased lymphoproliferative responses and decreased delayed hypersensitivity responses)	3 mg/kg bw/day (LOAEL)	Luster *et al.* 1980 (as quoted in US ATSDR, 2004).
Rhesus Monkey (FF-1)	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)	Allen *et al.* 1978; Lambrecht *et al.* 1978 (as quoted in US ATSDR, 2004).
Rat, Sprague Dawley (BP-6)	7 month dietary feeding study	decreased thyroid serum T3 and T4 hormones	0.45 mg/kg bw/day (LOAEL)	Byrne *et al.* 1987, (as quoted in US ATSDR, 2004).

Note: FF-1 and BP-6 in column 1 refer to FireMaster(R) FF-1 and FireMaster(R) BP-6, the PBBs used in the toxicity study described.

Table A.3 (continued) Summary of key toxicological studies on hexabromobiphenyl.

Species (test material)	Study type	Effect	LOAEL/ NOAEL	Ref.
Rat Fischer 344/N (FF-1)	25 wk gavage study, 5 single daily doses per week	gastric ulcers, decreased serum thyroid T4 hormone) hepatic, haematological disorders, thymic atrophy, progressive nephropathy	0.3 mg/kg bw/day (LOAEL) 0.1 mg/kg bw/day (NOAEL)	NTP 1983, (as quoted in US ATSDR, 2004).
Rat Sprague-Dawley Holtzman (FF-1)	4 week gavage study, 5 single daily doses per week	decreased motor activity	6 mg/kg bw/day (LOAEL) 3 mg/kg bw/day (LOAEL	Geller *et al.* 1979, (as quoted in US ATSDR, 2004).
Rat, Sprague Dawley (BP-6)	6 month gavage study, 5 single daily doses per week	delayed acquisition of locomotion and reduced open field activity in offspring).	2 mg/kg bw/day (LOAEL) 0.2 mg/kg bw/day (NOAEL)	Henck *et al.* 1994, (as quoted in US ATSDR, 2004).
Monkey, Rhesus (FF-1)		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)	Lambrecht *et al.* 1978; Allen *et al.* 1978; 1979, (as quoted in US ATSDR, 2004).
Rat, Wistar (BP-6)	15-day reproductive toxicity study, dosing between gestational day 0-14	no implantations in 2/5 rats	28.6 mg/kg bw/day (LOAEL) 14.3 mg/kg bw/day (NOAEL)	Beaudoin 1979, (as quoted in US ATSDR, 2004).
Rat, Sprague Dawley	Gavage study in pregnant rats, dosing between gestional day 7-15	Reproductive: Delayed vaginal opening in pups	0.04 mg/kg bw/day (NOAEL)	Harris *et al.* (1978) (as quoted in BKH Final Report 2000)
Rat, Sprague Dawley (BP-6)	40 day dietary feeding study	Reproductive deficits in learning behavior in offspring, 6 months after prenatal and lactational exposure)	0.2 mg/kg bw/day (LOAEL)	Henck and Rech 1986, (as quoted in US ATSDR, 2004).

Note: FF-1 and BP-6 in column 1 refer to FireMaster(R) FF-1 and FireMaster(R) BP-6, the PBBs used in the toxicity study described.

Table A.3 (continued) Summary of key toxicological studies on hexabromobiphenyl.

Species (test material)	Study type	Effect	LOAEL/ NOAEL	Ref.
Rat, Fischer 344/N (FF-1)	6 month gavage study, 5 single daily doses per week dosages of 0, 0.1, 0.3, 1, 3, or 10 mg/kg/day	hepatocellular adenoma and carcinoma, cholangiocarcinoma (females only	3 mg/kg bw/day (LOAEL)	NTP 1983, (as quoted in US ATSDR, 2004).
Mice B6C3F1 (FF-1)	6 month gavage study, 5 single daily doses per week dosages of 0, 0.1, 0.3, 1, 3, or 10 mg/kg/day	hepatocellular adenoma and carcinoma	10 mg/kg bw/day (LOAEL)	NTP 1983, (as quoted in US ATSDR, 2004
Mice B6C3F1 (FF-1)	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)	NTP 1992, (as quoted in US ATSDR, 2004).
Humans	Females accidentally exposed in the Michigan incident	relationship between serum PBBs and risk of breast cancer	relationship between serum PBBs of > 2 pbb and risk of breast cancer when compared with the reference group (<2 ppb),	Henderson *et al.* 1995, (as quoted in US ATSDR, 2004).
Humans	Michigan farm residents accidentally exposed in the Michigan incident	Significant reduction of in vitro immunological function		Bekesi *et at.* 1979, 1985 (as quoted in US ATSDR, 2004) Bekesi *et al*, 1987
Humans	Females accidentally exposed in the Michigan incident	Possible disturbance in ovarian function as indicated by menstrual cycle length and bleed length		Davis *et al.*, 2005
Humans	Offspring of females accidentally exposed in the Michigan incident	breastfed girls exposed to high levels of PBB in utero had an earlier age at menarche	Effects at > or =7 ppb in breast milk	Blanck *et al.*, 2000, (as quoted in US ATSDR, 2004)

Note: FF-1 and BP-6 in column 1 refer to FireMaster(R) FF-1 and FireMaster(R) BP-6, the PBBs used in the toxicity study described.

ANNEX B
HEXABROMOBIPHENYL ISOMERS

IUPAC Number[8]	Name	CAS Registry number[9].
	Hexabromobiphenyl	36355-01-8
128	2,2',3,3',4,4' hexabromobiphenyl	82865-89-2
129	2,2'3,3',4,5 hexabromobiphenyl	
130	2,2',3,3',4,5' hexabromobiphenyl	82865-90-5
131	2,2',3,3',4,6 hexabromobiphenyl	
132	2,2',3,3',4,6' hexabromobiphenyl	119264-50-5
133	2,2',3,3',5,5' hexabromobiphenyl	55066-76-7
134	2,2',3,3',5,6 hexabromobiphenyl	
135	2,2',3,3',5,6' hexabromobiphenyl	119264-51-6
136	2,2',3,3',6,6' hexabromobiphenyl	
137	2,2',3,4,4',5 hexabromobiphenyl	81381-52-4
138	2,2',3,4,4',5' hexabromobiphenyl	67888-98-6
139	2,2',3,4,4',6 hexabromobiphenyl	
140	2,2',3,4,4',6' hexabromobiphenyl	
141	2,2',3,4,5,5' hexabromobiphenyl	120991-47-1
142	2,2',3,4,5,6 hexabromobiphenyl	
143	2,2',3,4,5,6' hexabromobiphenyl	
144	2,2',3,4,5',6 hexabromobiphenyl	119264-52-7
145	2,2',3,4,6,6' hexabromobiphenyl	
146	2,2',3,4',5,5' hexabromobiphenyl	
147	2,2',3,4',5,6 hexabromobiphenyl	
148	2,2',3,4',5,6' hexabromobiphenyl	
149	2,2',3,4',5',6 hexabromobiphenyl	69278-59-7
150	2,2',3,4',5,6' hexabromobiphenyl	93261-83-7
151	2,2',3,5,5',6 hexabromobiphenyl	119264-53-8
152	2,2',3,5,6,6' hexabromobiphenyl	
153	2,2',4,4',5,5' hexabromobiphenyl	59080-40-9
154	2,2',4,4',5,6' hexabromobiphenyl	36402-15-0
155	2,2',4,4',6,6' hexabromobiphenyl	59261-08-4
156	2,3,3',4,4',5 hexabromobiphenyl	77607-09-1
157	2,3,3',4,4',5' hexabromobiphenyl	84303-47-9
158	2,3,3',4,4',6 hexabromobiphenyl	
159	2,3,3',4,5,5' hexabromobiphenyl	120991-48-2
160	2,3,3',4,5,6 hexabromobiphenyl	
161	2,3,3',4,5',6 hexabromobiphenyl	
162	2,3,3',4',5,5' hexabromobiphenyl	
163	2,3,3',4',5,6 hexabromobiphenyl	
164	2,3,3',4',5',6 hexabromobiphenyl	82865-91-5
165	2,3,3',5,5',6 hexabromobiphenyl	
166	2,3,4,4',5,6 hexabromobiphenyl	
167	2,3',4,4',5,5' hexabromobiphenyl	67888-99-7
168	2,3',4,4',5',6 hexabromobiphenyl	84303-48-0
169	3,3',4,4',5,5' hexabromobiphenyl	60044-26-0

(US ATSDR (2004)[10])

[8] Ballschmiter and Zell 1980

[9] From EHC 152 (IPCS, 1994).

[10] Note: the US ATSDR List does not include the two CAS numbers included in EHC 192 1997