Svalbard, Arctic Norway	Polar bear	0.7-4.7 ng/g LW	Gabrielsen *et al.* 2004	
Canadian Arctic	Polar bear	1.04-11.3 ng/g LW	Muir *et al.* 2006	
Bjørnøya, Arctic Norway	Glacous gulls	0-7.9 ng/g LW	Herzke *et al.* 2003	
Norway	White-tailed sea eagle	6-184 ng/g LW	Herzke *et al.* 2005	In eggs. Endangered Species
Sweden	Peregrine falcons	110-9200 ng/g LW	Lindberg *et al.* 2004	Endangered species
Australia	Melon-headed whale	4.8 ng/g LW	Law *et al.* 2003	
Canada	Beluga whale	108 ng/g LW	Law *et al.* 2003	Vulnerable species
Netherlands	Mussels	0.3-11 ng/g LW	Law *et al.* 2003	Marine+freshwater
Sweden	Frog	5.6 ng/g LW	De Wit *et al.* 2004	
Canada	Zooplankton	0.46 ng/g LW	Law *et al.* 2003	

2.3.2 Trends

Most trend analysis show an increase in concentrations of PBDEs in the environment and in humans from the beginning of the 1970s, with a peak around the mid-1990s and a stabilisation or subsequent levelling off in Europe (Covaci *et al.* 2002, Fängström *et al.* 2005, Thomsen *et al.* 2005 and Knudsen *et al.* 2005), but with a continuous increase in the Arctic (Vorkamp *et al.* 2005, AMAP 2002 and AMAP 2005). PentaBDEs are reported in the studies to follow the same trend as ΣPBDEs. This increase has also been seen in North America, in air, soil and sediment, and wildlife, but insufficient data exist to allow comment on trends in the human population.

In the Asia-Pacific region a study on northern fur seals on the Pacific coast of Japan shows an increase of PBDEs to about 150 times between 1972 and 1994, and then levels decreased to about 50% in 1998 (Kajiwara *et al.* 2004). The reduction in PBDEs values was assumed to be due to the voluntary phase out of C-PentaBDE in Japan in 1990. BDE-99 levels showed the same pattern as ΣPBDEs.

Analysis of archived herring gull eggs (sampled in 1981, 1983, 1987, 1989, 1990, 1992, 1993, 1996, 1998, 1999 and 2000) enabled Norstrom *et al.* (2002) to establish temporal trends in PBDE concentrations over the period 1981-2000. At Lake Michigan, Lake Huron and Lake Ontario sampling sites, concentrations of tetra- and pentabromodiphenyl ethers (that is, BDE-47, BDE-99 and BDE-100) increased by 71-112-fold over these two decades (from 4.7 to 400.5 µg/kg ww at Lake Ontario; from 8.3 to 927.3 µg/kg ww at Lake Michigan; from 7.6 to 541.5 µg/kg ww at Lake Huron). These increases were found to be exponential at all three locations ($r^2 = 0.903 - 0.964$, $p < 0.00001$).

Wakeford *et al.* (2002) undertook sampling of eggs of the great blue heron in 1983, 1987, 1991, 1996, 1998 and 2000 in southern British Columbia and found that total PBDE concentrations (sum of tetra-, penta- and hexabromo-congeners) increased from 1.31 to 287 µg/kg ww between 1983 and 1996, but then dropped slightly to 193 µg/kg ww in 2000. They also undertook sampling of the eggs of thick billed murre in the Canadian North in 1975, 1987, 1993 and 1998, and observed a trend of gradually increasing PBDE concentrations (sum of tetra-, penta- and hexabromo-congeners) in these eggs from 0.43-0.89 µg/kg ww in 1975, to 1.83-3.06 µg/kg ww in 1998.

PBDEs have been detected in a variety of marine mammals. Alaee *et al.* (1999) reported average PBDE (di-to hexaBDE) concentrations in the blubber of marine mammals from the Canadian Arctic as 25.8 µg/kg lipid in female ringed seals (*Phoca hispida*), 50.0 µg/kg lipid in male ringed seals, 81.2 µg/kg lipid in female beluga (*Delphinapterus leucus*) and 160 µg/kg lipid in male beluga. BDE-47, a tetrabromodiphenyl ether, was the predominant congener, followed by the pentabromo BDE-99. Ikonomou *et al.* (2000, 2000b) reported PBDE concentrations in biota samples from the west coast and Northwest Territories of Canada. The highest concentration of of total PBDE residues, 2269 µg/kg lipid, was found in the blubber of a harbour porpoise form the Vancouver area. With a concentration of about

1200 µg/kg, one congener, BDE-47, accounted for slightly more than half of the total PBDE in the sample. Ikonomou *et al.* (2002a) analyzed temporal trends in Arctic marine mammals by measuring PBDE levels in the blubber of Arctic male ringed seals over the period 1981-2000. The mean total concentrations increased exponentially, from 0.572 µg/kg lipid in 1981 to 4.622 µg/kg in 2000, a greater than eightfold increase. They determined that Penta- and HexaBDEs are increasing at approximately the same rate (doubling time 4.7 and 4.3 years, respectively), more rapidly than TetraBDEs, for which the doubling time was 8.6 years. Once again, BDE-47 was predominant, followed by BDE-99 and BDE-100.

A marked increase in tissue PBDE levels was also evident in blubber samples collected from San Francisco Bay harbour seals over the period 1989 to 1998 (She *et al.* 2002). Total PBDEs (the sum of BDEs 47, 99, 100, 153 and 154) rose from 88 µg/kg lipid to a maximum of 8325 µg/kg lipid over this short period. Stern and Ikonomou (2000) examined PBDE levels in the blubber of make SE Baffin Bay beluga whales over the period 1982-1997, and found that the levels of total PBDEs (tri-to hexa-congeners) increased significantly, Mean total PBDE concentrations were about 2 µg/kg lipid in 1982, and reached a maximum value of about 15 µg/kg lipid in 1997. BDE-47 was the dominant congener, with a mean concentration of approximately 10 µg/kg lipid in 1997. Total PBDE residues (concentrations for individual congeners not provided) in the blubber of St Lawrence estuary belugas sampled in 1997-1999 amounted to 466 (±230) µg/kg ww blubber in adult males, and 655 (±457) µg/kg ww blubber in adult females. These values were approximately twenty times higher than concentrations in beluga samples collected in 1988-1990 (Lebeuf *et al.* 2001).

The results from a modelling exercise utilizing the European variant (EVn) BETR multimedia environmental fate model were presented for the C-PentaBDE product by Prevedouros *et al.* (2004). To predict future atmospheric concentration trends, the model was used in its fully dynamic mode over the period 1970-2010. It predicted that atmospheric concentrations would have peaked around 1997, and then declined with an overall "disappearance" half-life of 4.8 years. The model steady state simulations gave generally good agreement with measured data for BDE- 47 and BDE-99. The empirical data for North America presented above, however, show continuing increases in concentrations, at least up the year 2000, and so while the model results match some European data with fair agreement, they are not in accord with data from North America.

Three dated sediment cores from locations in Western Europe were analyzed for 14 BDE congeners (Zegers *et al.*, 2003). Cores from the Drammenfjord (Norway), the western Wadden Sea (The Netherlands) and Lake Woserin (Germany) showed a time dependent pattern in the distribution of BDEs since the start of production of PBDE formulations. Two of the three commercial formulations could be distinguished. The penta-mix formulation is clearly present from the beginning of the 1970s. This is in agreement with data for the industrial production of this formulation. In the cores from the Netherlands and Germany, concentrations of BDE congeners associated with the C-PentaBDE were levelling off in the most recent layers (1995 & 1997), whereas those in the Drammenfjord were still increasing in 1999. The absence of all BDE congeners in the older (deeper) layers of all three cores, as well as in several 100 to 150 million year old layers of clay from Kimmeridge, UK, indicated that these BDE congeners are not produced naturally.

Human exposure to polychlorobiphenyls and PBDEs in Japan in 1980 and 1995 showed that levels of the latter had increased substantially over the twenty-year period, although there was great variation between regions. The main congeners detected in serum were BDE-47 and BDE-99. Most total PBDE levels had more than doubled, and in one area increased twenty-fold, with 1995 values falling in the range 0.6 – 41.4 ng/g lipid Koizumi *et al.* 2006).

2.3.3. Bioavailability

Environmental studies on bioavailability have detected uptake of PentaBDE in soil organisms (Matscheko *et al.* 2002), sediment dwelling organisms (Magnusson *et al.* 2003) and aquatic organisms (Lithner *et al.* 2003, Voorspoels *et al.* 2003, Marsch *et al.* 2004, Kierkegaard *et al.* 2004, and Sinkkonen *et al.* 2004), making PentaBDE's way into the food webs evident. Subsequent bioaccumulation and biomagnification of the compound has been detected and described in Section 2.2.2.

Soil exposed to PBDEs in various ways was analyzed for BDE-47, BDE-66, BDE-99, BDE-100, BDE-153, BDE-154 and BDE-183 (Matscheko *et al.*, 2002). Earthworms collected at all soil sampling sites were analyzed as well. The BDE congener profile in all soil samples was dominated by BDE-47 and BDE-99. Accumulation of the compounds in earthworms from the sites yielded a direct relationship between the concentrations in the soil and concentrations in the worms. The biota-soil accumulation factors (BSAFs) of BDE congeners BDE-47, BDE-99 and BDE-100 were around 5 (organic matter/lipids). Thus, earthworms living in contaminated soils will accumulate tissue BDE concentrations and, as these animals represent the base of the terrestrial food chain for many organisms, this form a pathway for the accumulation of BDEs in organisms at higher trophic levels.

The western Scheldt estuary is subject to a variety of suspected PBDE sources, such as a brominated flame retardant manufacturing plant, Antwerp harbour, and the textile industry located further upstream. PBDE concentrations in samples of biota, including crab, shrimp, starfish, benthic fish (such as dab, goby, plaice and sole) and gadoid fish (such as bib and whiting) from the estuary were compared to those in samples from the Belgian North Sea beyond the mouth of the estuary (Voorspoels *et al.*, 2003). Eight BDE congeners (BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183 and BDE-209) were determined. Concentrations observed in the estuarine samples were up to 30 times higher than in those from the Belgian North Sea, with an increasing gradient towards Antwerp. Concentrations in the North Sea ranged from 0.02 to 1.5 µg/kg wet weight in benthic invertebrates and goby, from 0.06 to 0.94 µg/kg wet weight in fish muscle, and from 0.84 to 128 µg/kg wet weight in fish liver. The corresponding ranges in samples from the estuary were from 0.2 to 30, 0.08 to 6.9, and from 15 to 984 µg/kg wet weight, respectively. The ratio BDE-99/BDE-100 was found to be highly location- and species-dependent, possibly relating to differences in metabolism. In shrimp, the value of this ratio (4:1) was very similar to that observed in the Bromkal formulation and in estuarine sediment, and was similar in shrimp from both the North Sea and the estuary, implying both that these congeners are readily bioavailable and that shrimp lack the ability to metabolize either congener. On a lipid weight basis, concentrations of BDE-47 ranged from 3 to 108 µg/kg lipid weight in samples from the North Sea, and from 8 to 1,550 µg/kg lipid weight in estuarine samples. BDE-47 was the most abundant congener in all samples, comprising 43 to 75% of ΣBDE.

Thomas *et al.* (2004) conducted an input-output balance study of BDEs on three captive, juvenile grey seals. The animals were fed a diet of herring for six months, and the study was performed during the last three months of this period. BDE analysis was undertaken using GC-ECNIMS. Consistently high absorption (89 - 99%) was observed for all PBDE congeners studied (BDE-28, BDE-47, BDE-49, BDE-99, BDE-100, BDE-153, BDE-154 and BDE-209).

2.3.4 Human exposure

Studies, assessments and reviews referred to in this section have shown that the main routes for human exposure are food, and exposure to dust in indoor air at home and workplaces due to levels in products like furniture and electronic devices. Fish and agriculture products are the main food sources of PentaBDE for humans, and mother's milk for the nursing child. Fatty fish from contaminated areas are a major source (Sjödin *et al.* 2003). PentaBDE has been detected in various foods (VKM 2005, Burniston *et al.* 2003 and Bocio *et al.* 2003) as well as in indoor dust (Shoeib *et al.* 2004 and Wilford *et al.* 2005). Levels in foods in the US have been reported by Schecter *et al.* (2004), Schecter *et al* 2006, and Huwe *et al.* (2005). There are several hazard assessments in EU and US, looking into the exposure of humans

(VCCEP 2003, COT 2004, VKM 2005). They conclude that the available hazard or exposure information is inadequate to fully characterize the risks.

About 5% of the individuals in general populations have been found to be subjected to elevated exposure (Thomsen *et al.* 2005 b). This, together with estimates of the half life of C-PentaBDE congeners in humans, raises concern for long-term effects on human health. The half-lives for these congeners in humans have been estimated to be 1,040 days (BDE-99) and 573 days (BDE-100) (Geyer *et al.* 2004).

Domestic house dust is likely to be a significant source where furniture, carpet or appliances contain C-PentaBDE. This has been discussed in Section 2.1.1. It is not clear which sources are the greatest, and there could be wide variations depending on lifestyle and diet.

Several studies have detected levels of PentaBDE in sewage sludge (Matscheko *et al.* 2002, Fabrellas *et al.* 2004, Motche and Tanner 2004 and Sjödin *et al.* 2003, Hale 2002). Sewage sludge is considered to be one of the main sinks for PBDEs. The application of sewage sludge to agricultural land is one of the reasons for detected levels of PentaBDE in food products. This can explain the detected levels in vegetables and root crops in experimental studies. Levels in fish and root crops can be the source of exposure to domestic animals like chickens and pigs, and the source of PBDEs in meat products for human nourishment.

A Canadian global study showed that PentaBDE is widespread in human milk in populations all over the world (Ryan 2004). There are data on levels in human blood serum and milk from USA, Canada, Mexico, Japan, the EU region, the Arctic region and Scandinavia. A meta-analysis by Hites (2004), using data published up to mid-2003, showed that serum and milk levels in the US were much higher than those in Europe - ~35 ng/g *vs* ~ 2 ng/g lipid – and were doubling on average every 4-6 years. BDE-47 and BDE-99 were the major congeners detected. Considerably higher levels are found in humans from North America in general. About 5% of general populations have been found to be subjected to elevated exposure. Thus, together with estimates of the half-life of PentaBDE congeners in humans, raiss concern for long-term effects on human health (Thomsen *et al.* 2005b).

Levels increasing from the 1980s to the 2000s have been observed in mother's milk from Sweden as well as in blood from Germany and Norway (Sjödin *et al.* 2003). A more recent study in Sweden (Fängström *et al.* 2005) assessed the temporal trends of polybrominated diphenyl ethers (PBDEs), in mothers' milk in the Stockholm area. The pooled samples were covering the time period 1980 to 2004, with emphasis on samples from the last ten years. Concentrations of BDE-47, BDE-99 and BDE-100 reached a peak in the mid-1990s and are now clearly showing decreasing levels. The concentrations are however still much higher than in 1980.

The objective of a recent Norwegian study was to complete and extend a previous study on time trends of PBDEs in Norwegian pooled serum samples (Thomsen *et al.* 2005a) and put together an overview of the PBDE body burden in the general population from 1977 to 2004. The temporal trend of the sum of seven PBDEs (BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154 and BDE-183) in the pooled serum from the present study are in close agreement with the levels found in a previous study by the same authors. In general, for similar time periods the levels in breast milk seem to be somewhat lower than in the serum, but the same overall trend is observed. This confirms that the PBDE body burdens in these regions have risen rapidly from 1977 to about 1997, but now seem to have stabilized or even to have decreased. This is in accordance with the trends observed in Swedish breast milk, as an indicator of the European situation, but may not be true of levels in North America. The PBDE level was previously found to be about twice as high in a serum pool from infants up to four years of age compared to serum pools from elderly persons. This finding was confirmed in the Norwegian study. However, in 2002, children between the ages of 5 and 14 years showed higher levels of PBDEs than the average adult.

Contemporary PBDE concentrations in Europe and Asia are remarkably similar, with low median values on a lipid basis for all countries and relatively small variations. The situation in North America is completely different with median values for individual studies in the range of 20-50 ng/g LW (Ryan 2004). However, in parallel with the regional differences that were reported above for biota, the levels in breast adipose tissue taken from women living in San Francisco Bay area in 2000 were almost two orders of magnitude higher than what has been reported in human milk from Sweden (Sjödin *et al.* 2003). A more recent study of levels in human adipose tissue in New York was published by Johnson-Restrepo *et al.* (2005). The study of 40 males and 12 females of a range of ages and ethnicities showed wide variations in lipid PBDE concentrations, with mean values substantially higher than the medians. Median concentrations were: BDE-47, 29.3 ng/g lipid; BDE-99, 10.3 ng/g lipid; BDE-100, 12.0 ng/g lipid.

In a preliminary screening of PBDEs in plasma and milk samples from Mexican women, the levels were well above European levels of PBDEs reported so far (López *et al.* 2004). The mean level of PBDEs (with BDE-209 excluded) in Mexican women living in urban areas was approx. 20 ng/g LW in plasma. The levels in women living in rural areas in Mexico were however comparable with women living in rural areas in Sweden. (BDE-209 levels were only detected in women living in the Mexican city).

Ryan (2004) detected a big individual variation in levels in the general population in a study from Canada. The values span more than three orders of magnitude, with a few values showing a much greater level. Levels detected in the Canadian Arctic in Ryan's study (2004) were increasing. Values in human milk from the Faroe Islands showed the same trend (Fängström *et al.* 2004).

Two studies in Australia indicated that levels of PBDEs in Australian breast milk and blood serum are higher than those in Europe but lower than those found in North America (Harden *et al.* 2004 and 2005).

*Table 2.6 Data on mean levels of PentaBDE (**BDE-99**) (ng/g LW) in humans from different parts of the world.*

Data	Country/region	Levels	References	Year	Comments
blood	The Netherlands	0.8	Weiss *et al.* 2004	unknown	
blood	Norway	1.0	Thomsen *et al.* 2004	1999	
blood	Mexico	2.0	López *et al.* 2004	2003	Urban population
blood	Australia	2.3	Harden *et al.* 2004	2003	
milk	Germany	0.2	Harden *et al.* 2004	2000	
milk	Sweden	0.3	Fängström *et al.* 2005	2003	Urban population
milk	Mexico	0.6	López *et al.* 2004	2003	Rural population
milk	Sweden	0.5	López *et al.* 2004	2003	Rural population
milk	United Kingdom	0.9	Harden *et al.* 2004	?	median
milk	Faroe Islands	1.0	Fängström *et al.* 2004	1999	Rural population
milk	Australia	1.9	Harden et al. 2005	2002/2003	
milk	Canada	4	Ryan *et al.* 2002	2002	Rural population
milk	USA	28	Päpke *et al.* 2001	2000	Urban population

Although they are less relevant that environmental data, results from occupational studies bear out the facility with which the PBDEs are taken up by human bodies. In Sweden, occupational exposure to PBDE has been identified among electronics recycling personnel (Sjødin *et al.*, 1999) and in technicians responsible for repair and maintenance of computers (Jacobsson *et al.*, 2002) as well as in nearby soil and sediment (Wang *et al.* 2005). Also workers in industry manufacturing C-PentaBDE, or polyurethane foam and electronic equipment containing it can be exposed to PentaBDE. There is an extensive literature on such exposures.

2.3.5 Debromination

There is growing interest in the fate of PBDEs in the environment. In experiments reported by Stapleton *et al.* (2004), carp were fed food spiked with individual BDE congeners for 62 days, and tissue and excreta were examined. At least 9.5±0.8% of BDE-99 in the gut was reductively debrominated to BDE-47 (one less bromine) and assimilated in carp tissues. Similarly, 17% of the heptabromo congener BDE-183 was reductively debrominated to hexabromo congeners. The authors noted that body burdens of PBDEs may thus reflect direct uptake from exposure as well as debromination of more highly brominated congeners. Highly selective reductive microbial debrominations were observed in experiments reported by He *et al.* (2006). Hepta- and Octa-BDEs were produced in cultures of *Sulfurospirillum multivorans* to which DecaBDE had been added, but OctaBDE was not attacked in a similar system. Cultures of an alternative organism, *Dehalococcoides sp.*, failed to attack the DecaBDE but an OctaDBE mixture was extensively changed, yielding a mixture of Hepta- through Di-BDEs which included the PentaBDE, BDE-99. The authors draw attention to the potential for conversion of higher congeners in the environment to more toxic congeners with fewer bromine substituents. Further studies particularly environmental monitoring studies focussing on congeners for which the primary source is likely to be debromination reactions, are required to clarify the role of debromination in determining the final mix of PBDE congeners in the environment.

Hydroxylated BDEs (OH-BDEs) have been detected and identified as metabolites in several species after exposure to specific BDE congeners but have also been found to occur as natural products in marine sponges and ascidians (Marsch *et al.* 2004). Methoxylated BDEs (MeO-BDEs) have also been reported as natural products present in marine sponges and green algae. It would seem that the origin of these substances can be natural, anthropogenic or both. Nine OH-BDEs and six MeO-BDEs were identified in blood of Baltic Sea salmon (*Salmo salar*) using newly synthesized standards (Marsch *et al.*, 2004). All of the identified OH- and MeO-BDEs were substituted with four or five bromine atoms and five of them also had one chlorine substituent. Fourteen have the methoxy or hydroxy group substituted in the position *ortho*-to the diphenyl ether bond. The structures of several of the compounds support natural rather than anthropogenic origins. However, at least one of the OH-BDEs (4'-OH-BDE-49) may be a hydroxylated metabolite of BDE-47. Estrogenic activity of some hydroxylated PBDEs has been reported by Meerts *et al.* (2001).

Other studies of metabolism of PBDEs are summarized in Section 2.2.2.1.

2.4 Hazard assessment for endpoints of concern

Evidence to date suggests that the major congeners of the C-PentaBDE formulation, BDE-47 and BDE-99, are likely to be more toxic and bioaccumulative than other PBDE congeners. Although the toxicology of PBDEs is not completely understood, some studies on PentaBDE have demonstrated reproductive toxicity, neurodevelopmental toxicity and effects on thyroid hormones. The neurotoxic effects of PBDEs are similar to those observed for PCBs and so children exposed to PBDEs are likely to be prone to subtle but measurable developmental problems. It is presumed that PBDEs are endocrine disrupters, but research results in this area are scant (Siddiqi *et al.* 2003).

While further studies follow internationally-accepted guidelines might be needed to make a full risk assessment of the situations of children, there are sufficient data for development of the present risk profile.

It is acknowledged that these conclusions rest to some extent on examination of reviews, rather than reanalysis of primary data, but in general the studies under review have followed internationally accepted experimental protocols. Nonetheless, there is no significant disagreement between some reported results and later analyses, such as that of the US Voluntary Children's Chemical Evaluation Program (VCCEP) (2005).

2.4.1 Ecotoxicity

Recent studies show that exposure to BDE-47 can cause growth inhibition in colonies of the plankton algae (*Skeletonema costatum*) and a depression on reproductive output of the zooplankton *Daphnia magna* (Källqvist *et al.* 2006).

A recent paper by Timme-Laragy *et al.* (2006) showed adverse effects on fish development at low concentrations. However, the endpoints that were affected in this report (behavioural learning) are not usually accepted risk assessment endpoints. Other endpoints that would be acceptable, such as growth or survival, were not affected.

Canada was able to perform a risk quotient analysis for each congener, integrating known or potential exposures with known or potential adverse effects. In its simplest form, the risk quotient may be described by the equation:

$$\text{Risk quotient} = \frac{\text{exposure reference value}}{\text{toxicity reference value}}$$

and it is customary to use conservative values in order to highlight the worst case.

Exposures were estimated local to emission sources including areas receiving urban drainage (wildlife consumers) and downstream of a polymer processing facility (benthic organisms). Adjustment factots of 100-1000-fold were applied to critical toxicity values to reflect extrapolation from laboratory to fielod conditions, intraspecies and interspecies variations in sensitivity, and because compounds are bioaccumulative and persistent.

A risk quotient value >1 signifies the likelihood or potential for adverse effects to occur, while those <1 imply no danger to organisms. The Canadian results shown in Table 3.1 are based partly on Canadian empirical data and partly on surrogate data from Swedish and US sources.

Table 3.1 Risk quotient values for PentaBDE (Environment Canada 2006, Canadian Wildlife Table 8).

Commercial Product	**Pelagic organisms**	**Benthic organisms**	**Soil organisms**	**Wildlife consumers**
C-PentaBDE	$4x10^{-3}$	45.2	0.13-0.26	149

These values reflect the bioaccumulation of PentaBDE which causes organisms higher in the food chain to be exposed to greater risk.

2.4.2 Effects in mammals

In a review article on toxic effects of brominated flame retardants, Darnerud (2003) drew on a range of primary literature to conclude that 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 C-PentaBDE products cause effects at the lower dosages. The critical effects of PentaBDE are those on neurobehavioral 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) (Darnerud 2003). Note that some data reported in Table 2.7 show levels below these. More recent information, especially for North America, is available in Birnbaum and Staskal (2004).

Blubber biopsy and blood samples were collected from weaned grey seal (*Halichoerus grypus*) pups and juveniles during 1998 and 1999 (Hall *et al.*, 2003). Fifty four post-weaned pups and fifty five first year juveniles (of which thirteen were recaptured post- weaned pups) were studied. The median concentrations of ΣBDE (14 congeners) were 0.17 and 0.46 µg/kg lipid weight in the blubber of the pups and the juveniles, respectively. The study indicated that thyroid hormone levels in the blood of grey seals during their first year of life were significantly, and positively, related to ΣBDE concentrations in blubber, after accounting for the effects of possible confounding variables. Such an association is not, in itself, sufficient evidence for a causal relationship, but is in accordance with the hypothesis that these compounds can act as endocrine disrupters in grey seal pups.

Darnerud (2003) concluded in his review that for PentaBDEs, the critical effects among the available studies seem to be developmental neurotoxicity and, although 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, a number of PBDEs were capable of inducing cell death of cerebellar granule cells in culture (Reistad *et al.*, 2002, Reistad and Mariussen 2005). The LOAEL value for PentaBDE could be set to 0.6–0.8 mg/kg body wt., based on the most sensitive effect observed, neurobehavioral effects during early development (Darnerud 2003, although it is not the task of the POPRC to set a regulatory level, for construction of which resort would need to be made a wider range of data.

In a hazard assessment by the Committee on Food Safety in Norway (VKM 2005) the following toxic effects of exposure to BDE-99 or the C-PentaBDE formulation was reported: neurotoxicity, effects on neurobehavioral development, effects on the thyroid hormone system and hispatological alterations in the tyroid and liver.

*Table 2.7 Overview of No Observed Effect level (NOEL) and Lowest Observed Effect Level (LOEL) after oral administration of **BDE-99** congener or C-PentaBDE formulations. Bold values are the lowest LOEL or NOEL detected.**

PentaBDE	Duration	Dose	NOEL mg/kg/ day	LOEL mg/kg/day	Endpoint	Species	Reference
BDE-99	s.d	0.8 or 12.0 mg/kg	n.d.	0.8	Neurotoxicity Behaviour, motor activity level and learning	mouse	Eriksson *et al.* 2001
BDE-99	s.d	0.6, 6, or 30 mg/kg	n.d.	0.6	Developmental- and neurotoxicity Behaviour - hypoactive	mouse	Branchi *et al.* 2002
BDE-99	s.d	0.4, 0.8, 4.0, 8.0, or 16 mg/kg	**0.4**	**0.8**	Developmental- and neurotoxicity Behaviour	mouse	Viberg *et al.* 2004 Sand *et al.* 2004
BDE-99	s.d.	0,06 and 0,3 mg/kg to pregnant female	**n.d.**	**0,06**	Developmental- and neurotoxicity Behaviour (increased activity)	rat, F1 gen.	Kuriyama *et al.* 2005
BDE-99	s.d.	0,06 and 0,3 mg/kg to pregnant female	**0,06**	**0,3**	Reduced testis size and number of sperms	rat, F1 gen.	Kuriyama *et al.* 2005

Penta mix DE-71	30 d	0.01, 0.05, 0.1, 0.5, or 1.0 mg/kg/day	1	n.d.	Growth, food intake, hematology, histopatology Clinical chemistry	rat	Great lakes Chemical Corporation 1985
Penta mix DE-71	30 d	0, 3, 30, or 60 mg/kg/day	3	30	Liver weight, puberty, reproduction, liver enzymes, T_4-reduction	Male rat	Stoker *et al.* 2004
Penta mix DE-71	30 d	0, 3, 30, or 60 mg/kg/day	n.d.	3	T_4-reduction	Female rat	Stoker *et al.* 2004
Penta mix DE-71	35 d	0, 1, 10 or 30 mg/kg/day	1	10	T_4-reduction Liver enzymes	pregnant rat	Zhou *et al.* 2002, Zhou *et al.* 2001
Penta mix DE-71	90 d	0-0.44 mg/kg/day	n.d.	0.44	Liver enzymes	rat	Carlson 1980
Penta mix DE-71	90 d	0, 2,10, or 100 mg/kg/day	0-2	2-10	Hepatocyto-megali Tyreoidea hyperplasi	rat	Great lakes Chemical Corporation 1984

n.d. = not defined, s.d. = single dose

* Most of the studies are in line with the OECD test guidelines and for those are not, the quality of the study is assessed to be adequate.

The PBDE mixture known as DE-71 (71% bromine by mass, and containing BDE-47, BDE-99, BDE-100, BDE-153, BDE-154) delays the puberty and suppresses the growth of androgen-dependent tissues in male Wistar rat following a peri-pubertal exposure. These effects suggest that DE-71 may be either inducing steroid hormone metabolism or acting as an androgen receptor (AR) antagonist (Stoker *et al.* 2005).

Talsness *et al.* (2005) evaluated the effects of environmentally relevant concentrations (low doses) of BDE-99 on the female reproductive system in rats. Ultra structural changes compatible with altered mitochondrial morphology were observed in the ovaries of the F1 offspring. No statistically significant changes in ovarian follicle counts were observed. External and skeletal anomalies were detected in offspring (F2) from two different dams (F1) with early developmental exposure to 300 µg BDE-99/lkg BW. Exposure to BDE-99 resulted in female reproductive tract changes in the F1 generation which were apparent at adulthood.

In utero exposure to a single low dose of BDE-99 disrupts neurobehavioral development and causes permanent effects on the rat male reproductive system apparent in adulthood (Kuriyama *et al.* 2005). Also in this study, the effects of developmental exposure to BDE-99 on juvenile basal motor activity levels and adult male reproductive health were assessed. The exposure to low-dose BDE-99 during development caused hyperactivity in the offspring at both time points (postnatal days 36 and 71) and permanently impaired spermatogenesis by the means of reduced sperm and spermatid counts. The doses used in this study of 60 and 300 µg/kg BW are relevant to human exposure levels, being approximately 6 and 29 times, respectively, higher than the highest level reported in human breast adipose tissue. This is the lowest dose of PBDE reported to date to have an *in vivo* toxic effect in rodents and supports the premise that low-dose studies should be encouraged for hazard identification of persistent environmental pollutants. The study by Viberg *et al.* (2004) shows that neonatal exposure to BDE-99 can induce developmental neurotoxic effects, such as changes in spontaneous behaviour (hyperactivity), effects that are dose-response related and worsen with age. The changes are seen in C57/B1 mice of both sexes. Spontaneous behaviour (locomotion, rearing, and total activity) was observed in two-, five- and eight-month-old mice.

2.4.3 Toxicity to humans

Several hazard assessments have been produced in EU and in US. The conclusions in the hazard assessments elaborated are qualified by the lack of sufficient knowledge of the toxicology of PentaBDE to enable assessment of the risk to humans (COT 2004, VKM 2005 and VCCEP 2003). The toxicological importance for humans of detected effects in laboratory animals is not clear. There is still not enough knowledge of the mechanisms, half-life and metabolism of PentaBDE in experimental animals and humans (VKM 2005).

The conclusion in the hazard assessment by the Committee on Food Safety in Norway was that the exposure through food and mother's milk is considerably lower than the observed NOEL in laboratory mammals (VKM 2005). It is believed that long-time exposure to lower doses of PentaBDE can cause health effects, since PentaBDE accumulates in the human body. Since the half-life of PentaBDE in humans is not known it is not possible today to conclude on long-time exposure effects. This is true even for the US situation, where levels may be 10-20 times those observed in Europe, but pharmacokinetics, toxicology, exposure and other critical data are lacking.

Vulnerable groups could however be pregnant women, embryos and infants, because of effects on the thyroid hormone balance, and the embryo's development of the central nervous system. During pregnancy, maintenance of the thyroid hormone balance is a physiological challenge. Embryos and infants are particularly vulnerable for reductions in thyroid hormone levels (VKM 2005). Infants are exposed to PentaBDE through the diets of their mothers' milk, since PentaBDE is lipophilic and accumulates in the milk (VKM 2005).

3. Synthesis of information

3.1 Summary

PentaBDE meets all of the Annex D screening criteria, and details are included (for the sake of completeness) in Table 3.2, below.

In the absence of production controls, the levels detected in humans, other species and the environment have been observed to rise steeply and this increase is observed in remote locations as well as closer to sites of production and use. In the US, where C-PentaBDE was in high use until recently and where it remains in such materials as polyurethane foam incorporated into consumer products, there has been a build-up in human tissue.

PentaBDE in soil or sediment is readily incorporated into the food chain and bioaccumulates in the fatty tissues of top predators, including humans.

There are toxicological studies of concern that demonstrate neurodevelopmental impacts in animals at low tissue levels that are of relevance to levels observed in populations. Such body burdens remain under close review.

An assessment of the impact of PBDEs on the environment was recently concluded by Environment Canada (2006), taking into account critical studies and lines of evidence that support the conclusion that these commercial substances entering the environment have or may have an immediate or long-term harmful effect on the environment or its biodiversity.

4. Concluding statement

Pentabromodiphenyl ether (C-PentaBDE) is a synthetic mixture of anthropogenic origin with no known natural occurrence. It can be concluded therefore that the presence of components of PFOS in the environment is the result of anthropogenic activities. Long range transport must be responsible for its presence in areas such as the Arctic region, remote from sites of production and release. PentaBDE degrades slowly in the environmernt and can bioaccumulate and biomagnify in mammals and piscivorous birds.

The phase out of C-PentaBDE production and use has led to a reduction in current use but many materials in use, such as polyurethane foams and plastics in electronic equipment, contain PentaBDE which is slowly released to the environment. This release will be accelerated at end-of-life of such materials, especially during recovery and recycling operations.

Although levels of PentaBDE in human blood and milk, and in other environmental species, are falling in Europe, they continue to increase in North America and the Arctic region.

Based on the information in this risk profile, C-PentaBDE, due to the characteristics of its components, is likely, as a result of long-range environmental transport and demonstrated toxicity in a range of non-human species, to cause significant adverse effects on human health and the environment, such that global action is warranted.

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