2.3.7 Humans

EC (2003) presents some information on the levels of components of c-OctaBDE measured in human samples including human milk, blood, and adipose tissue. Large variations among individuals were generally observed, but significant differences between the control population and occupationally exposed groups were also reported.

In a recent study (Toms et al., 2007) the concentrations of PBDEs (18 congeners from BDE17 to BDE-183) found in Australian human milk were lower than those reported from North America but higher than those reported from Europe and Asia

Thomsen et al., 2007, investigated the levels of PBDEs in 21 pooled serum samples archived from the general Norwegian population (from 1977 to 2003). In serum from men (age 40–50 years) the sum of seven PBDE congeners (28, 47, 99, 100, 153, 154 and 183) increased from 1977 (0.5 ng/g lipids) to 1998 (4.8 ng/g lipids). From 1999 to 2003 the concentration of PBDEs seems to have stabilised.

Fernandez et al., 2007, have reported a study of the detection of PBDEs in the adipose tissue of women from Spain. Mean ∑PBDE (BDE 28, 75, 71, 47, 66, 77, 100, 119, 99, 85, 154, 153, 138, and 183) levels were 3.85 and 0.36 ng/g of lipid, respectively. Among PBDEs, congeners 153, 47, 183, 99, and 100 were the most frequent and abundant and together constituted 96% of the total amount of PBDEs in adipose tissue. Concentrations of PBDEs in this population were similar to those reported in other parts of Spain and in Swedish and Belgium populations but lower than those found in other Western countries.

PBDEs were measured in samples of human blood serum taken from 23 donors in Wellington, New Zealand. Concentrations expressed as the sum of congeners 47, 99, 100, 153, 154, and 183 (∑PBDE) were – at an average of 7.17 ng ∑PBDE g (lipid)$^{-1}$ – within the range reported for human tissues in Europe, but lower than in Australia and North America (Harrad et al., 2007).

Based on the measured PBDE levels detected in various meat, fish and dairy food products, an average daily dietary intake estimate of PBDEs was calculated in a study carried out in Belgium. PBDE intake calculations were estimated between 23 and 48 ng/day of total PBDEs. Fish is the major contributor to the total daily PBDE-intake (around 40%) due to the high PBDE levels in this type of food, although it is only a minor constituent of the Belgian diet. Meat products account for around 30% of the total dietary intake of PBDEs. Dairy products and eggs contribute to a lesser degree (less than 30%, Voorspoels et al., 2007).

Schuhmacher et al., 2007 have carried out an study to compare levels of PBDEs due to dietary intake and population living near a hazardous waste incinerator (HWI), in Spain. This study suggests that dietary intake is more relevant for human exposure to PBDEs than living near the HWI. Dietary intake of PBDEs for standard adult women were 72 and 63 ng/day for PBDEs, for residents in urban and industrials areas, respectively. Mean PBDE concentrations were 2.2 and 2.5 ng/g fat for women living in urban and industrial zones, respectively. Similar results have also been reported in a study carried out in Korea (Lee et al., 2007)

Exposure to components of c-OctaBDE in remote areas is confirmed and based on the available information should be attributed to a combination of releases and transport of c-OctaBDE, c-PentaBDE (for HexaBDE) and c-DecaBDE (for NonaBDE), and to the debromination of DecaBDE in the environment including biota. There is no sufficient information for assessing these processes in quantified terms. The exposure route is mainly via food. In addition to the feeding strategy, several additional confounding factors are associated to the species to specific differences observed in the isomer distribution pattern of PBDE in wildlife. These factors include, among others, species-specific differences in assimilation, metabolism and depuration of different isomers, even with the same level of bromination.

Measured levels of Hexa and Hepta components of c-OctaBDE in biota from remote areas seem to be the best available information for estimating exposure as result of LRET for these chemicals. Knudsen et al (2005) have recently review temporal trends of PBDE in eggs from three bird species, three locations and three sampling times (from 1983 to 2003) from Northern Norway. Spatial differences were only observed for HexaBDE 153, and increases in the measured concentration from 1983 to 2003 were observed for the HexaBDE 153 and 154 and the HeptaBDE 183. Mean values were around 1 µg/kg ww for each isomer and maximum values above 10 µg/kg ww were observed for BDE 154 and 183. Inter-species differences could be associated to feeding behavior and migration. In general the concentrations were lower than those reported for similar species in industrialized areas and those observed in terrestrial predatory birds. The presence of Hexa and HeptaBDE in fish from remote alpine lakes in Switzerland (Schmid et al., 2007) reported to be related to atmospheric deposition confirms the potential for atmospheric long-range transport. Hexa to NonaBDE have been found in salmon in the Atlantic Ocean west of Iceland (Burreau et al. 2006).

Despite its large molecular size, the evidence demonstrates the capability of c-OctaBDE components to cross the cellular membranes and to accumulate in biota. Although the information is limited, the assimilation and metabolisms of each isomer may vary significantly among species, but also in relation to the administered dose. As a consequence, it is essential to understand the toxicokinetics of these chemicals at environmentally relevant concentrations. These differences would justify the disparities observed in the assessment of biomagnification potential for different trophic chains.

Like for other chemicals with similar properties, aging processes are expected to reduce the bioavailability, and the experiments conducted on sediment dwelling organisms comparing the bioaccumulation in spiked sediments and from contaminated biosolids offer and indirect support for this hypothesis.

2.4 Hazard assessment for endpoints of concern

2.4.1. Experimental studies

2.4.1.1. Aquatic Organisms

The EU Risk Assessment report (EC, 2003), presents a set of studies on the commercial mixture and concludes that for water it seems sensible to assume that no adverse effects on aquatic organisms are likely to occur at concentrations up to the substance's water solubility. However it must be noted, first, that aquatic organisms are also exposed from food and/or sediment; and second, that setting this strong conclusion on chemicals such as PBDEs requires multigenerational or at least full life-cycle assays on the three taxonomic groups covering a large list of sublethal effects, information which is unavailable at this time.

2.4.1.2. Benthic Organisms

There are two available 28 day spiked sediment studies on *Lumbriculus variegatus* using the c-OctaBDE product (Great Lakes Chemical Corporation 2001a, b). These studies found no statistically significant effects relevant to survival, reproduction or growth at the highest tested concentration (1272 mg/kg dw and 1340 mg/kg dw measured for sediments with 2.4% and 5.9% OC, respectively). Kinetic data from Ciparis and Hale (2005) confirms the expected exposure and bioaccumulation under these conditions.

2.4.1.3. Soil Organisms

Survival and growth of earthworms, *Eisenia fetida,* were not affected by a 56 day exposure to a commercial OctaBDE formulation in an artificial soil at concentrations up to 1470 mg/kg dw (measured concentration in sediments with 4.7% OC) (Great Lakes Chemical Corporation 2001c).

The toxicity of c-OctaBDE to corn (*Zea mays*), onion (*Allium cepa*), ryegrass (*Lolium perenne*), cucumber (*Cucumis sativa*), soybean (*Glycine max*), and tomato (*Lycopersicon esculentum*) was evaluated in a 21-day emergence and growth study using an artificial sandy loam soil (Great Lakes Chemical Corporation 2001d). No statistically significant effects were observed for any plant species between the controls and the treatments for emergence, survival or growth at any of the tested concentrations (up to 1190 mg/kg dw, measured concentration).

2.4.1.4. Mammals and Birds

The lowest reported NOAEL for traditional endpoints is a NOAEL of 2 mg/kg/d based on slight fetotoxicity at 5 mg/kg/d (considered relevant in the EU report) or 5 mg/kg bw/d based on increased liver weights and decreased body weight gain among the maternal treatment group and delayed fetal skeletal ossification at 15 mg/kg bw/d (for those reviewers that do not consider relevant the slight fetotoxicity effects) described by Breslin et al. (1989) in a developmental toxicity study with Saytex 111 on New Zealand White rabbits exposed orally via gavage over days 7 to 19 of gestation.

Effects on other endpoints have been described at lower concentrations, including:

- A significant increase in EPN detoxification and *p*-nitroanEROD and isole demethylation in male Sprague-Dawley rats at an oral dose of 0.60 mg/kg bw/day OBDE formulation for 14-days.
- dose-dependent depletion of serum total thyroxine T4 and induced pentoxyresorufin *O*-deethylase (PROD) activities in rats receiving 10 or more mg/kg bw/day of commercial OctaBDE (Zhou et al. 2001)
- Delayed neurotoxic effects. Neonatal mice exposed to a single dose of 0.45 mg BDE153/kg bw on postnatal day 10 showed when tested at 2, 4 and 6 months of age altered motor behavior. Spatial learning ability and memory function in the adult mice were also affected (Viberg et al.,2001)
- Eriksson et al. (2002) confirmed neurotoxic effects (aberrant behavioral responses) on developing male mice exposed to 0.45 to 9.0 mg/kg bw of BDE153 on day 10 of development. The effects were comparable to those

observed for PCB153 leading the authors to speculate that interactive neurotoxic action may be possible between the two compounds.

- These neurotoxic effects have also been observed after a single oral dose of NonaBDE 206 or OctaBDE 203 administered on postnatal day 3 or 10 to, or PBDE 183; with disturbances in spontaneous behavior, leading to disrupted habituation and a hyperactive condition in adults at the age of 2 months. (Viberg et al., 2006).
- Immunomodulation effects in captive nestling American kestrels (*Falco sparverius*) have been reported by Fernie et al. (2005). Eggs within each clutch, divided by laying sequence, were injected with safflower oil or PentaBDE congeners-47, -99, -100, and -153 dissolved in safflower oil (18.7 µg PBDEs/egg). For 29 days, nestlings consumed the same PBDE mixture (15.6+/-0.3 ng/g body weight per day), reaching PBDE body burden concentrations that were 120x higher in the treatment birds (86.1+/-29.1 ng/g ww) than controls (0.73+/-0.5 ng/g ww). PBDE-exposed birds had a greater PHA response (T-cell-mediated immunity), which was negatively associated with increasing BDE-47 concentrations, but a reduced antibody-mediated response that was positively associated with increasing BDE-183 concentrations. There were also structural changes in the spleen (fewer germinal centers), bursa (reduced apoptosis) and thymus (increased macrophages), and negative associations between the spleen somatic index and PBDEs, and the bursa somatic index and BDE-47. Immunomodulation from PBDE exposure may be exacerbated in wild birds experiencing greater environmental stresses.
- Fernie et al., 2006 also reported for the same species and test conditions that exposure did not affect hatching or fledging success. PBDE-exposed nestlings were larger (weight, bones, feathers) as they gained weight more quickly and ate more food, the latter in association with their PBDE body burdens. BDE-100 was most influential on nestling growth, being positively associated with size, weight gain, and food consumption. Increasing concentrations of BDE-183 and -153 were related to longer bones and BDE-99 to longer feathers. The larger size of the PBDE-exposed birds may be detrimental to their bone structure and have excessive energetic costs.
- In vitro studies indicates that BDE (including the HexaBDE 153) affected protein kinase C (PKC) and calcium homeostasis in cerebellar granule neuronal cultures in a similar way to those of a structurally-related polychlorinated biphenyl (PCB) (Kodavanti et al., 2005).

Although these studies do not allow a quantitative assessment, they indicate the need for addressing long-term and delayed effects, as well as specific mechanisms of action, in the evaluation of potential health and ecosystem adverse effects.

2.4.2. Monitoring data on effects

There are several scientific papers comparing population effects observed in the field with measured concentrations of POP like chemicals, including Hexa to NonaBDE in individuals from different species.

Unfortunately, wild populations are co-exposed to a mixture of PBDEs as well as to other related brominated and chlorinated persistent pollutants, and with the current level of knowledge epidemiological investigations can just present associations but no cause-effect relationships between the exposure/accumulation of the components of the commercial OctaBDE mixtures and potential adverse effects observed in wildlife.

A similar situation is observed regarding human health data, and no studies offering conclusive evidence on the hazards of Hexa to NonaBDE for humans at environmentally relevant exposure levels have been found.

3. Synthesis of the information

A quantitative evaluation of the specific risks of c-OctaBDE is not possible due to the presence of its components in commercial Penta- and Deca mixtures, and the lack of information; this include the absence of information for supporting quantitative assessments of the role on debromination and the lack of a solid body of toxicological and ecotoxicological information for the mixture and its components; covering the long-term low level exposure conditions and the sublethal endpoints considered relevant for assessing the risk of a POP candidate. Australia and Canada have reported quantitative risk assessments for health and for the environment based on risk quotients and margins of safety suggesting a potential risk. The evaluations do not cover expected conditions in remote areas but are useful in the overall assessment (Environment Canada, 2006; NICNAS, 2007).

In this risk profile, Hexa to NonaBDE have been considered the relevant components in c-OctaBDE. It should be noted that other BDE are also found in commercial mixtures, including those present in c-PentaBDE and c-DecaBDE..

The persistence of these PBDE in the environment is well documented. The only relevant degradation pathways identified until now are photolysis, anaerobic degradation and metabolism in biota, acting through debromination and producing other BDE which may have higher toxicity and bioaccumulation potential.

The bioaccumulation potential depends on the level of bromination. HexaBDE shows a significant potential for bioconcentration and biomagnification; HeptaBDE biomagnifies through the food web but at a lower extend than that expected from the Kow. Octa and NonaBDE have been found in biota but no food-web biomagnification has been observed. Metabolisms and/or reduced bioavailability explain the divergences between observations and Kow predictions. The contribution of metabolism through debromination into other BDEs is supported by and increasingly amount of scientific evidence.

Biota monitoring data in remote areas cover Hexa and HeptaBDE and offer the best demonstration on the potential for long range transport of c-OctaBDE components. Theoretically this presence could also be explained by the transport of DecaBDE and its subsequent debromination. However, it is not realistic to assume that DecaBDE debromination may explain the process without additional transport from other congeners. The role of atmospheric transport is confirmed for Hexa and HeptaBDE based on its detection in alpine lakes.

Unfortunately, the available information on the toxicity and ecotoxicity of Hexa to NonaBDE is very limited and does not offer enough information for presenting sound toxicological and ecotoxicological profiles for each isomer, mixtures of isomers and commercial mixtures.

No relevant effects have been observed in aquatic, sediment and soil laboratory studies; but the measured endpoints and the exposure conditions, employed in these assays are clearly insufficient for a proper assessment of chemicals such as Hexa to NonaBDE. Ecotoxicity tests on these types of chemicals should cover if possible several generations or at least a full life cycle, and the measured endpoints must include sublethal effects associated to the accumulation and re-mobilization of the PBDEs during critical periods of development and reproduction, as well as the ecologically relevant consequences of metabolic changes. In addition, all environmentally relevant exposure routes must be addressed. The available tests do not fulfill these conditions,.

The available information on mammals and birds offer relevant information. The lowest reported NOAEL for traditional endpoints is 2-5 mg/kg bw/d based on slight fetotoxicity or increased liver weights and decreased body weight gain among the maternal treatment group and delayed fetal skeletal ossification. These effects are relevant for the health and the ecological assessment and therefore useful for assessing risks for humans and wildlife. Nevertheless, the additional available information also creates concerns on the capability of these traditional endpoints for assessing the toxicological profile of Hexa to NonaBDE in mammals and other vertebrates.

The immuno-toxicological effects and particularly the delayed neurotoxic effects observed after a single dose require specific attention. Although a quantitative evaluation of these effects in terms of its potential risk for human health and ecosystem is not possible based on the current level of information, the reported observations must be analyzed with care. Certainly, the doses at which the effect have been observed are well above exposure levels in remote areas estimated from current monitoring data for a single congener. However, the effects have been observed for different congeners, and realistic environmental exposure occurs for a mixture of PBDEs. There is not enough information for considering if these effects may be additive or even more than additive in synergistic exposures. The margins between effects observed in the lab and estimated oral exposure levels in the field (based on monitoring data) are not so high when the different isomers/homologues are summed. McDonald (2005) estimated a critical body burden for HexaBDE 153 of 2000 µg/kg lipid based on the NOEL of 0.45 mg/kg reported by Viberg et al 2003 and gives a margin of safety of 7 between this level and the 95 percentile of total PBDE levels in US human populations. It should be noted that HexaBDE 153 concentrations close to these value have been found in several species and geographic sites (see Canada info 2 for a review) and total PBDE concentrations frequently exceed largely this threshold.

The degradation of PBDEs in the environment and biota is a key issue as higher congeners are converted to lower, and possibly more toxic, congeners. This possibility has been demonstrated for debromination of DecaBDE and several c-OctaBDE components (see references above) but the extent to which different PBDEs can be degraded under various conditions, the role of metabolism in addressing the bioaccumulation potential, and the identity of any lower congeners that may be produced, is an active research field. New results will need to be assessed by the POPRC as they appear in refereed literature.

There is an increasing evidence suggesting similar toxicological profiles and therefore, equivalent hazards and concerns, between PBDEs and PCBs, although the mode of action seems to be better categorized by AhR-independent mechanisms, as PBDEs do bind but not activate the AhR-AhR nuclear translocator protein-XRE complex (Peters et al., 2006) and appear capable of up-regulating CYP2B and CYP3A in rats at doses similar to that for non-dioxin-like

PCB153 (Sanders et al., 2005). As the persistence, bioaccumulation potential and long range transport of the c-OctaBDE components are well documented, the confirmation of an equivalent level of hazard for these two groups should be sufficient for confirming a long-range transport associated risk

4. Concluding statement

The evaluation of the human and environmental risk of commercial OctaBDE associated to its potential for long range transport must consider that the commercial product is a mixture of components with different properties and profiles, which may also be released to the environment due to its presence as components of other PBDE commercial products and also produced in the environment by debromination of commercial DecaBDE.

Although the production of c-OctaBDE has ceased in developed countries and there is no information suggesting that the chemical is produced elsewhere, it must be noticed that the product is still present and released from articles in use and during their disposal. Model estimations and measured levels in sewage sludge suggest that current emissions are still significant.

The persistence of the Hexa to NonaBDE is well documented. The main route of degradation is debromination forming other BDEs, also of concern. The potential for certain components in c-OctaBDE to bioaccumulate and also for biomagnification in some trophic chains is also sufficiently documented and confirmed by the good agreement between field observations in monitoring programmes and toxicokinetic studies. Monitoring data in remote areas confirm the potential for long-range transport and at least for some congeners the relevance of atmospheric distribution in this process.

The highest difficulty appears for the estimation of the potential hazard of the commercial mixture and its components. There are traditional ecotoxicological and toxicological studies where no effects have been observed even at unrealistically high concentrations. However, an in-depth assessment of these studies considering in particular the properties and toxicokinetic of PBDE indicates that the test design, exposure conditions and measured endpoints are not appropriate for a sound assessment of these types of chemicals. Thus, the lack of effects reported in those tests should be considered with care. In addition, specific studies have reported particular hazards such as delayed neurotoxicity and immunotoxicity which may be particularly relevant in the assessment of both human health and ecosystem risks.

Based on the existing evidence, it is concluded that the Hexa and HeptaBDE components of the commercial octabromodiphenyl ether are likely, as a result of LRET, to lead to significant adverse human health and/or environmental effects, such that global action is warranted.

The increasing evidence related to debromination of Octa and Nona BDE into BDEs with POPs properties and considering that under Article 8, paragraph 7(a) of the Convention states that the lack of full scientific certainty shall not prevent a proposal from proceeding, it is concluded that the Octa and NonaBDE components of the commercial octabromodiphenyl ether are likely, as a result of LRET, to lead to significant adverse human health and/or environmental effects, such that global action is warranted.

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