Health Canada Santé Canada

State of the Science Report
for a Screening Health Assessment

Polybrominated Diphenyl Ethers (PBDEs)

[Tetra-, Penta-, Hexa-, Hepta-, Octa-, Nona- and Deca- Congeners]

[CAS Nos. 40088-47-9, 32534-81-9, 36483-60-0, 68928-80-3, 32536-52-0, 63936-56-1, 1163-19-5]

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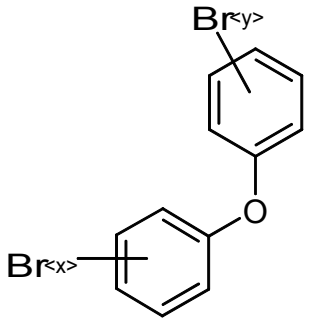

Figure 1: Base structure of PBDEs considered in this assessment, where x + y = 4–10

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of Health and the Environment to conduct screening assessments for substances that have been categorized to determine whether they pose a risk to human health or the environment. On the basis of a screening assessment, the Ministers can propose to take no further action in respect of the substance, to add the substance to the Priority Substances List for a more in-depth assessment or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act.

Screening assessments of risks to human health address responsibilities of the Minister of Health under Paragraph 64(c) of CEPA 1999 to determine whether or not a substance is "entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health." Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/exsd.

Several polybrominated diphenyl ethers (PBDEs) have been identified as meeting the Section 73 criteria for persistence and/or bioaccumulation and inherent toxicity to non-human organisms and nominated for inclusion in a pilot phase for preparation of screening assessments under CEPA 1999.

This State of the Science Report for a screening health assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing Substances Division of Health Canada, and their content was reviewed at several meetings of senior Divisional staff. The documents were subsequently externally reviewed for adequacy of data coverage and defensibility of the conclusions. The assessments on health and environmental aspects were approved by the joint Environment Canada/Health Canada CEPA Management Committee. The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca. Information on the screening environmental assessment is available at http://www.ec.gc.ca/substances/ese.

Information identified as of July 2003 was considered for inclusion in this screening health assessment.[1] The critical information and considerations upon which the assessment is based are summarized below.

Identity, Uses and Sources of Exposure

PBDEs are a class of substances that contain an identical base structure (see Figure 1), but differ in the number of attached bromine atoms (n = 1–10). Of the 10 congener groups (comprising 209 individual congeners in total), seven are on the Domestic Substances List (i.e., n = 4–10) and are considered in this assessment (Table 1).

Table 1: List of PBDEs considered in the assessment

Congener group	Acronym	CAS No.	No. of individual congeners
Tetrabromodiphenyl ether	TeBDE	40088-47-9	42
Pentabromodiphenyl ether	PeBDE	32534-81-9	46
Hexabromodiphenyl ether	HxBDE	36483-60-0	42
Heptabromodiphenyl ether	HeBDE	68928-80-3	24
Octabromodiphenyl ether	OcBDE	32536-52-0	12
Nonabromodiphenyl ether	NoBDE	63936-56-1	3
Decabromodiphenyl ether	DeBDE	1163-19-5	1

PBDEs do not occur naturally in the environment; they are generally produced synthetically as mixtures, referred to as commercial pentabromodiphenyl ether (ComPeBDE, which is predominantly a mixture of TeBDE, PeBDE and HxBDE), commercial

[1] The potential impact of preliminary results of a monitoring study conducted by Health Canada (2003) was also considered.

octabromodiphenyl ether (ComOcBDE, which contains mainly HeBDE, OcBDE and HxBDE, but may also contain small amounts of PeBDE, NoBDE and DeBDE) and commercial decabromodiphenyl ether (ComDeBDE, of which current formulations are almost entirely DeBDE, with a small amount of NoBDE) (IPCS, 1994). The identical base structure and combination of congener groups within the different commercial mixtures support consideration of a category approach to assessment of these compounds. In addition, to the extent that the data permit comparison, consideration of these compounds as a group is supported by trends in physical/chemical properties with increasing degree of bromination.

Results of a Section 71 survey under CEPA 1999 (Environment Canada, 2001) indicate that uses of PBDEs in Canada are similar to those in other countries, primarily as additive flame retardants in a wide variety of consumer products, such as internal electric/electronic components of and casings for household appliances/electronics (e.g., hair dryers, televisions, computers), furniture upholstery and cushioning, and wire and cable insulation (IPCS, 1994). ComDeBDE is primarily used in the high-impact polystyrene component of electronic equipment housings and is also the only commercial PBDE product used to flame retard upholstery textiles. ComOcBDE is predominantly used in acrylonitrile butadiene styrene to flame retard business equipment housings. ComPeBDE is used almost exclusively in flexible polyurethane foam, which is used as cushioning in upholstered furniture (Wenning, 2002).

Hazard Characterization and Exposure Assessment

The majority of identified data relevant to the evaluation of risk to human health relate to the commercial mixtures, with much less information being available for individual congeners. Based on preliminary assessment of the available toxicological data, the critical effects and effect levels for the ComPeBDE, ComOcBDE and ComDeBDE commercial mixtures, as well as each of the congener groups considered in this assessment (where possible), are presented in Table 2, with a more extensive summary of the health effects associated with each presented in Table 3. It appears that the critical effects of PBDEs occur on the liver and neurobehavioural development. Owing to the limited nature of the database for some substances, confidence in the assessment for each PBDE congener group and commercial mixture varies.

In consideration of the above information, the critical effect level considered most appropriate for assessment of risk to human health in a screening context is the conservative value of 0.8 mg/kg-bw (for PeBDE), based on neurobehavioural effects consisting of changes in locomotion, rearing and total activity in a dose- and time-related manner observed in neonatal mice administered a single oral dose by gavage on postnatal day 10 and observed for a subsequent 5-month period (Eriksson et al., 1998, 2001). Effects on neurobehavioural development have also been observed in neonatal mice exposed to higher doses of PeBDE on different postnatal days (Eriksson et al., 1999, 2002; Viberg et al., 2000 [abstract], 2002b), as well as in pups exposed to PeBDE via maternal administration (although there was no relationship between dose and magnitude of effect) (Branchi et al., 2002, 2003). However, no effect on motor activity was observed in rats exposed to up to 100 mg ComPeBDE/kg-bw per

day from gestation day 6 to postnatal day 21 (Taylor et al., 2002 [abstract], 2003 [abstract]; MacPhail et al., 2003 [abstract]), although effects similar to those observed at 0.8 mg PeBDE/kg-bw were observed in neonatal mice administered single, relatively low doses of TeBDE, HxBDE and DeBDE by the same group of investigators (Eriksson et al., 1998, 2001; Viberg et al., 2001a [abstract], 2001b [abstract], 2002a [abstract], 2003; Viberg, 2002 [personal communication]). Since these congener groups are also present in the commercial mixtures ComPeBDE, ComOcBDE or ComDeBDE, it is appropriate to consider this Lowest-Observed-Effect Level (LOEL) for PeBDE as critical in a screening assessment of the health hazard of this group of PBDEs as a whole. [N.B.: Although a lower LOEL of 0.44 mg/kg-bw per day was observed for ComPeBDE, this LOEL was based on alterations in hepatic enzyme activities, and no histopathological changes in the liver were observed at this or higher doses (Carlson, 1980b).] In addition, critical LOELs for other effects (changes in liver weight or histopathology) observed in longer-term studies in rodents administered ComPeBDE or ComOcBDE are within an order of magnitude of this conservative LOEL. This conservative critical effect level is also considered protective for the small increase in the incidence of liver tumours observed in mice and the increase in neoplastic nodules observed in rats chronically administered much higher doses of DeBDE, in view of the lack of weight of evidence for the genotoxicity of PBDEs.

Available data upon which to base estimates of population exposure to PBDEs are quite disparate, in that some authors reported concentrations in media for individual congeners or congener groups, whereas others reported levels of total PBDEs, without further identification of specific congeners measured. Thus, it is difficult to derive meaningful estimates of exposure to individual congeners or congener groups. For the purpose of this screening assessment, in light of the similarity of health effects associated with the various PBDEs considered here, critical effect levels were compared with an upper-bounding estimate of exposure to total PBDEs (i.e., the tetra- to deca- congeners considered here), as a basis for development of conservative margins for the purposes of screening.

Based on reported concentrations of PBDEs in ambient and indoor air,[2] water, various foodstuffs, human breast milk and dust, along with standard reference values for six different age groups, including breast-fed infants, an upper-bounding estimate of daily intake of total PBDEs (i.e., the tetra- to deca- congeners considered here) ranges from 0.2 to 2.6 µg/kg-bw per day for various age groups of the general population in Canada. Food (including breast milk) represents the principal source of exposure for the majority of the age groups (although dust was the principal source of exposure for the 0- to 6-month-old non-breast-fed age group) (see Table 4). The age group with potentially the greatest exposure was 0- to 6-month-old breast-fed infants, with breast milk accounting for 92% of the exposure. Consistent with the limited intent of screening assessments to develop upper-bounding estimates of exposure, this estimate was based

[2] In a recent study by Health Canada (2003), for which only preliminary results are available, the maximum concentration of PBDEs (TeBDE to HeBDE) in samples of residential indoor air from 72 homes in Ottawa was 3.6 ng/m^3. However, this value does not impact upon the upper-bounding estimates of daily intake of total PBDEs because of the relatively small contribution of air to overall exposure.

on the maximum concentration of PBDEs measured in breast milk (589 ng/g lipid). It should be noted, though, that the mean and median values in the study were approximately 40- and 200-fold less, respectively, than this value (i.e., 15 and 2.9 ng/g lipid, respectively) (Ryan and Patry, 2001a, 2001b; Ryan et al., 2002a, 2002b). The authors noted that there was much interindividual variation in levels of PBDEs in breast milk, with some very high values for individual samples. Based on limited data, levels of PBDEs in human breast milk in Canada appear to be increasing with time (e.g., there was a 9-fold increase in mean concentration between 1992 and 2001) (Ryan et al., 2002a).

These upper-bounding estimates of exposure are considered conservative, in that they are based on summed estimates for all congeners for which data are available. Data for each of the congeners were based on the highest measured concentrations for many media. Upper-bounding estimates of intake in food for subpopulations consuming more traditional or country foods, based on limited information on maximum concentrations of PBDEs and consumption patterns of such foods, are not substantially greater (i.e., less than 2-fold). Emissions of PBDEs from consumer products that have been treated with flame retardant formulations containing these substances (e.g., televisions or computer casings) could contribute to overall exposure. However, intakes via inhalation from such sources estimated on the basis of information on average use patterns and concentrations in emissions are negligible (i.e., up to 5×10^{-4} µg/kg-bw per day) in comparison with intake from food. Similarly, estimates of intake from dermal contact with dust or oral contact with household products treated with flame retardants containing the penta- and octa- congeners (ENVIRON International Corporation, 2003a, 2003b) are also negligible in comparison with intake from food.

In view of the nature of the effects determined to be critical (i.e., neurodevelopmental effects in mice following neonatal exposure), consideration of the upper-bounding estimate of intake in breast-fed infants as the critical measure of exposure in this screening assessment is considered appropriate. Alternative approaches to developing upper-bounding estimates of exposure were also considered (e.g., back-calculation of intakes based on first-order kinetic modelling of limited data on levels in the blood of the general population, and comparison of estimated body burden for the critical study in experimental animals with that estimated for breast-fed infants). However, confidence in the resulting estimates, which result in margins of exposure approximately 10-fold less than that presented below, is extremely low, owing to the considerable limitations of the relevant data on biological half-lives of PBDEs in humans and their seeming inconsistency with what would be expected based on relevant physical/chemical properties (i.e., the high log octanol/water partition coefficients of PBDEs).

Conclusion for Human Health

Comparison of the critical effect level (i.e., 0.8 mg/kg-bw) with the upper-bounding deterministic estimate of exposure (i.e., the metric of exposure in which confidence is greatest) for the intake of total PBDEs for the potentially most highly exposed age group (2.6 µg/kg-bw per day in breast-fed infants) results in a margin of exposure of approximately 300. As discussed

above, the selected critical effect level and deterministic estimates of exposure are considered quite conservative, consistent with the preliminary nature of screening health assessments.

The conservative nature of the margin of exposure does not, however, take into account the potential continuing increase in body burden of PBDEs (based on data for breast milk), should similar use patterns continue. Prediction of trends in body burdens is precluded by the limited information on the toxicokinetics of PBDEs in humans and animals and transfer from human breast milk to infants as well as the uncertainty in half-lives for removal processes for PBDEs in environmental media. Determination of the adequacy of this margin to address elements of uncertainty associated with limitations of the database for health effects and population exposure (in which confidence overall is considered to be moderate), intraspecies and interspecies variations in sensitivity, extrapolation from acute exposure to chronic exposure for the critical effect, as well as the biological adversity or severity of the effects deemed critical requires additional in-depth evaluation of the relevant data. It also requires development of additional, more meaningful information on population exposure to PBDEs.

However, since PBDEs meet the criteria under Paragraph 64(a) of CEPA 1999 on the basis of environmental considerations (http://www.ec.gc.ca/substances/ese/), more in-depth evaluation of PBDEs from a human health perspective is considered a low priority, unless information becomes available to indicate that measures recommended to control exposure of environmental organisms to PBDEs will not be protective for human health. This priority is based on the smaller margin between the most conservative estimated critical values for exposure and effects on the environment (http://www.ec.gc.ca/substances/ese/) in comparison with that for human health (approximately 7[3] versus 300) and experience in other countries that risk management actions to protect the environment have resulted in a reduction of exposure of humans.

[3] Based on comparison of the values that formed the basis for the risk quotient analysis for wildlife (i.e., a LOEL of 2 mg/kg-bw per day for ComPeBDE for effects on the liver in rats [Great Lakes Chemical Corporation, 1984] and the dose ingested by mink consuming fish containing 1.25 mg total PBDEs/kg wet weight [Johnson and Olson, 2001]).

Table 2: Overview of critical health effects and effect levels for PBDE congener groups and commercial products

	LOEL (mg/kg-bw per day)	**Endpoint**	**Reference**
TeBDE	10.5	Developmental behavioural (mouse)	Eriksson et al., 2001
PeBDE	0.8	Developmental behavioural (mouse)	Eriksson et al., 1998, 2001
HxBDE	0.9	Developmental behavioural (mouse)	Viberg et al., 2002a (abstract)
HeBDE	–	–	
OcBDE	–	–	
NoBDE	–	–	
ComPeBDE	2	Liver histopathology: subchronic dietary study (rat)	Great Lakes Chemical Corporation, undated a
ComOcBDE	5	Liver weight: subchronic dietary study (rat)	Great Lakes Chemical Corporation, 1987
ComDeBDE/ DeBDE	2.22	Developmental behavioural (mouse)	Viberg et al., 2001a (abstract), 2001b (abstract), 2003; Viberg, 2002 (personal communication)

Table 3: Summary of health effects information for PBDE congener groups and commercial mixtures[1]

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Acute toxicity: oral				Lowest **oral LD_{50}** (rabbit) = >2000 mg/kg-bw (Kopp, 1990)			Lowest **oral LD_{50}** (rat) = 5000 mg/kg-bw (Pharmakon Research International Inc., 1984) [Additional studies: Great Lakes Chemical Corporation, undated a / 1982 / 1988 / Dow Chemical Company, 1977 / Ameribrom Inc., 1990; Fowles et al., 1994]	Lowest **oral LD_{50}** (rat) = >5000 mg/kg-bw (Kopp, 1990) [Additional studies: Great Lakes Chemical Corporation, 1982 / 1987 / 1988 / 1990; Kalk, 1982]	Lowest **oral LD_{50}** (rat) = >2000 mg/kg-bw [77.4% DeBDE, 21.8% NoBDE, 0.8% OcBDE] (Norris et al., 1973 / 1974 / 1975a / 1975c) [Additional studies: Great Lakes Chemical Corporation, undated b / 1982 / 1984; Kitchin et al., 1992 / 1993 / Kitchin and Brown, 1994]
Acute toxicity: inhalation							Lowest **inhalation LC_{50}** (rat) = >200 000 mg/m^3 (Great Lakes Chemical Corporation, undated a) [Additional studies: / Dow Chemical Company, 1977 / Great Lakes Chemical Corporation, 1982 / 1988 / Kopp, 1990; Haskell Laboratory, 1987]	Lowest **inhalation LC_{50}** (rat) = >50 000 mg/m^3 (U.S. EPA, 1986) [Additional studies: Great Lakes Chemical Corporation, 1987 / 1988]	Lowest **inhalation LC_{50}** (rat) = >48 200 mg/m^3 (Great Lakes Chemical Corporation, undated b) [Additional studies: / Great Lakes Chemical Corporation, 1982; 1984]
Acute toxicity: dermal							Lowest **dermal LD_{50}** (rabbit) = >2000 mg/kg-bw (Great Lakes Chemical Corporation, undated a) [Additional studies: / Dow Chemical Company, 1977 / Great Lakes Chemical Corporation, 1982 / 1988]	Lowest **dermal LD_{50}** (rat) = >2000 mg/kg-bw (Great Lakes Chemical Corporation, 1987) [Additional studies: / Great Lakes Chemical Corporation, 1982 / 1990]	Lowest **dermal LD_{50}** (rabbit) = >2000 mg/kg-bw (Great Lakes Chemical Corporation, undated b) [Additional studies: / Great Lakes Chemical Corporation, 1982; 1984]

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Short-term repeated-dose toxicity	Lowest **oral (gavage) LOEL** (rat and mouse) = 18 mg/kg-bw per day: decreased thyroxine levels (2,2',4,4'-TeBDE, 98% purity, 14 days) (Hallgren and Darnerud, 1998 / 2002; Darnerud and Thuvander, 1998) [Additional studies: / Thuvander and Darnerud, 1999 / Hallgren et al., 2001]						Lowest **oral (diet) LOEL** (rat) = 5 mg/kg-bw per day: increased absolute and relative liver weights (28 days) (Great Lakes Chemical Corporation, undated a) [Additional studies: / Dow Chemical Company, 1977 / Great Lakes Chemical Corporation, 1982 / 1988; Carlson, 1980a; Von Meyerinck et al., 1990; Fowles et al., 1994; Darnerud and Thuvander, 1998 / Thuvander and Darnerud, 1999 / Hallgren et al., 2001; Zhou et al., 2001]	Lowest **oral (diet) LOEL** (rat) = 5 mg/kg-bw per day: increased absolute and relative liver weights (28 days) (Great Lakes Chemical Corporation, 1987) [Additional studies: / Great Lakes Chemical Corporation, 1988; Dow Chemical Company, 1982 / Ethyl Corporation, 1990; Carlson, 1980a; Zhou et al., 2001] Lowest **inhalation LOEC** (rat) = 12 mg/m^3: dose-related hepatic lesions (14 days) (Great Lakes Chemical Corporation, 1987) [Additional study: / Great Lakes Chemical Corporation, 1988]	Lowest **oral (diet) LOEL** (rat) = 80 mg/kg-bw per day: enlarged livers, generative cytoplasmic changes in the kidney and thyroid hyperplasia (77.4% DeBDE, 21.8% NoBDE, 0.8% OcBDE, 30 days) (Sparschu et al., 1971 / Norris et al., 1973 / 1974 / 1975a / Kociba et al., 1975a) [Additional studies: Great Lakes Chemical Corporation, undated b / 1982 / 1984; Carlson, 1980a; NTP, 1986; Zhou et al., 2001]

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Subchronic toxicity							Lowest **oral (diet) LOEL** (rat) = 2 mg/kg-bw per day: liver cell degeneration and necrosis (composition not stated, 90 days) (Great Lakes Chemical Corporation, undated a) [Additional studies: / Dow Chemical Company, 1977 / Great Lakes Chemical Corporation, 1982 / 1988 / Wil Research Laboratories Inc., 1984; Carlson, 1980b]	Lowest **oral (diet) LOEL** (rat) = 5 mg/kg-bw per day (100 ppm): increased absolute and relative liver weights (composition not stated, 13 weeks) (Great Lakes Chemical Corporation, 1987) [Additional studies: / International Research and Development Corporation, 1977 / Great Lakes Chemical Corporation, 1988; Carlson, 1980b] Lowest **inhalation LOEC** (rat) = 15 mg/m^3: centrilobular hepatocellular hypertrophy (13 weeks) (Great Lakes Chemical Corporation, 2001)	No effects observed in mice at highest dose of 8060 mg/kg-bw per day (99% DeBDE, 13 weeks) (NTP, 1986) [Additional studies: NTP, 1986 (rats); Hazleton Laboratories, 1979a; 1979b; Rutter and Machotka, 1979]

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Carcino-genicity/ chronic toxicity									Increased incidence of **neoplastic nodules in the liver in rats** at ≥1120 mg/kg-bw per day (diet); no increase in incidence of hepatic carcinomas (103 weeks) A marginal increase (statistically significant only at the low dose) in the incidence of **hepatocellular adenomas and carcinomas combined in mice** at ≥3200 mg/kg-bw per day (diet, 103 weeks) (NTP, 1986 / Huff et al., 1989)
									Lowest **oral (diet) non-neoplastic LOEL** (rat) = 2240 mg/kg-bw per day: thrombosis, degeneration of the liver, fibrosis of the spleen and lymphoid hyperplasia (NTP, 1986 / Huff et al., 1989) [Additional studies: Kociba et al., 1975a / 1975b / Norris et al., 1975a / 1975b / Dow Chemical Company, 1994]

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Genotoxicity and related endpoints: *in vivo*									**Negative:** rat bone marrow (cytogenetic aberrations), rat hepatic (DNA damage measured by alkaline elution) (Norris et al., 1975c; Kitchin et al., 1992 / 1993 / Kitchin and Brown, 1994)
Genotoxicity and related endpoints: *in vitro*	**Positive**: mammalian cells (intragenic recombination) (Helleday et al., 1999)						**Negative:** *Salmonella typhimurium*, *Saccharomyces cerevisiae* (mutagenicity) (Great Lakes Chemical Corporation, undated a) [Additional studies: Dow Chemical Company, 1977 / Great Lakes Chemical Corporation, 1982 / 1988 / Ethyl Corporation, 1985 / Ameribrom Inc., 1990; Chemische Fabrik Kalk GmbH, 1978; Dead Sea Bromide Works, 1984; Zeiger et al., 1987] **Positive:** *S. typhimurium* (ISC Chemicals Ltd., 1977) **Weak positive:** human peripheral blood lymphocytes (chromosomal aberrations) (no composition data provided) (Microbiological Associates Inc., 1996a / 1996b)	**Negative:** *S. typhimurium*, *S. cerevisiae* (mutagenicity), human fibroblast cells (DNA damage), Chinese hamster ovary cells (sister chromatid exchange), human peripheral blood lymphocytes (chromosomal aberrations) (Great Lakes Chemical Corporation, 1982 / 1987 / 1988; Microbiological Associates Inc., 1996c / 1996d; Great Lakes Chemical Corporation, 1999)	**Negative:** *S. typhimurium*, *S. cerevisiae (*mutagenicity), *Escherichia coli* WP2 *uvrA* (mutagenicity), Syrian hamster embryo (cell transformation), mouse lymphoma (mutagenicity), Chinese hamster ovary cells (sister chromatid exchange and chromosomal aberrations) (Shoichet and Ehrlich, 1977; Great Lakes Chemical Corporation, undated b / 1984 / 1988; 1982; NTP, 1986; McGregor et al., 1988 / Myrh et al., 1990 / Henry et al., 1998; LeBoeuf et al., 1996; MA Bioservices Inc., 1998) **Indeterminant:** BALB-C-3T3 cells (transformation) (Matthews et al., 1993)

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Neurodevel-opmental toxicity	Lowest **oral (gavage) LOEL** (mouse) = 10.5 mg/kg-bw: change in activity patterns and habituation capability (2,2',4,4'-TeBDE >98%, one dose on postnatal day 10, observation period 5 months) (Eriksson et al., 2001)	Lowest **oral (gavage) LOEL** (mouse) = 0.8 mg/kg-bw: change in activity patterns and habituation (2,2',4,4',5-PeBDE >98%, one dose on postnatal day 10, observation period 5 months) (Eriksson et al., 1998, 2001) [Additional studies: Viberg et al., 2000 (abstract) / 2002b / Eriksson et al., 1999 / 2002; Branchi et al., 2002, 2003]	Lowest **oral LOEL** (mouse) = 0.9 mg/kg-bw: impaired spontaneous motor behaviour, learning and memory (2,2',4,4',5,5'-HxBDE, no purity data, one dose on post-natal day 10, observation period 6 months) (Viberg et al., 2002a [abstract])				Lowest **oral (gavage) LOEL** (rat) = <100 mg/kg-bw per day (not further specified): decreased cue-based performance in fear conditioning test (no composition data, gestation day 6 to postnatal day 21, observation period not stated); no change in motor activity observed up to 100 mg/kg-bw per day (Taylor et al., 2003 [abstract]) [Additional studies: Gilbert and Crofton, 2002 (abstract); Taylor et al., 2002 (abstract); MacPhail et al., 2003 (abstract)]		Lowest **oral (gavage) LOEL** (mouse) = 2.22 mg/kg-bw: changes in spontaneous behaviour (one dose on postnatal day 3, observation period 6 months) (Viberg et al., 2001a [abstract] / 2001b [abstract] / 2003 / Viberg, 2002 [personal communication])

Endpoint	Congener group						Commercial mixture		
	TeBDE	**PeBDE**	**HxBDE**	**HeBDE**	**OcBDE**	**NoBDE**	**ComPeBDE**	**ComOcBDE**	**ComDeBDE/DeBDE**
Develop-mental/ reproductive toxicity (see also Neurodevel-opmental toxicity)							Lowest **oral (gavage) LOEL** (rat) = 3 mg/kg-bw per day: decreased thyroxine (product DE-71, no composition data, postnatal days 23–53) (Stoker et al., 2003 [abstract]) [Additional studies: Argus Research Laboratories Inc., 1985b / BFRIP, 1990 / Hoberman et al., 1998 (abstract); Zhou et al., 2000 (abstract) / 2002; Taylor et al., 2002 (abstract); 2003 (abstract); Laws et al., 2003 (abstract)]	Lowest **oral (gavage) LOEL** (rabbit) = 15 mg/kg-bw per day: increased liver weight (0.2% PeBDE, 8.6% HxBDE, 45% HeBDE, 33.5% OcBDE, 11.2% NoBDE, 1.4% DeBDE; gestation days 7–19) (Breslin et al., 1989) [Additional studies: U.S. EPA, 1986 (determined same as Argus Research Laboratories Inc., 1985a, which states purity to be 6.9% HxBDE, 46.8% HeBDE, 35.9% OcBDE, 10.4% NoBDE) / Hoberman et al., 1998 (abstract); Great Lakes Chemical Corporation, 1987 / 1988] Lowest **inhalation LOEC** (rat) = 200 mg/m^3: lack of corpora lutea (no composition data, 13-week study) (Great Lakes Chemical Corporation, 2001)	Highest **oral (gavage) NOEL** (rat) = 1000 mg/kg-bw per day: increased early resorptions were observed at this dose, but the values were within historical control values (composition: 97% DeBDE, 2.66% NoBDE; gestation days 0–19) (Hardy et al., 2002) Lowest **oral (gavage) LOEL** (rat) = 1000 mg/kg-bw per day: increased litters with subcutaneous edema and delayed bone ossification 10 and 100 mg/kg-bw per day: increased resorptions (not significant at higher dose level) (composition: 77.4% DeBDE, 21.8% NoBDE, 0.8% OcBDE; gestation days 6–15) (Norris et al., 1973 / 1974 / 1975a / Hanley, 1985 / U.S. EPA, 1989) [Additional studies: Norris et al., 1975c / Schwetz et al., 1975]

[1] Notes:

- No-Observed-Effect Levels (NOELs) were reported only when no LOELs were available.
- ComDeBDE and DeBDE were not separated due to the lack of reporting of purity and the high purity of the current commercial product.
- Lower effect levels identified that did not indicate a dose–response relationship, statistical significance and/or toxicological relevance were not included in the summary table.
- / used between studies suspected to be the same study.
- ; used between studies suspected to be different studies.

Table 4: Upper-bounding estimate of PBDE daily intake for the general population

Route of exposure	**Estimated intake (µg/kg-bw per day) of PBDEs by various age groups**							
	0–6 months[1]			**0.5–4 years[4]**	**5–11 years[5]**	**12–19 years[6]**	**20–59 years[7]**	**60+ years[8]**
	formula fed[2]	**breast fed[3]**	**not formula fed**					
Ambient air[9]	7.7×10^{-5}	7.7×10^{-5}	7.7×10^{-5}	1.7×10^{-4}	1.3×10^{-4}	7.3×10^{-5}	6.3×10^{-5}	5.5×10^{-5}
Indoor air[10]	4.4×10^{-4}	4.4×10^{-4}	4.4×10^{-4}	9.3×10^{-4}	7.3×10^{-4}	4.1×10^{-4}	3.6×10^{-4}	3.1×10^{-4}
Drinking water[11]	1.4×10^{-3}	2.4	5.2×10^{-7}	5.9×10^{-7}	4.6×10^{-7}	2.6×10^{-7}	2.8×10^{-7}	2.9×10^{-7}
Food[12]			2.0×10^{-2}	5.8×10^{-1}	4.8×10^{-1}	2.7×10^{-1}	2.6×10^{-1}	1.7×10^{-1}
Soil/dust[13]	2.3×10^{-1}	2.3×10^{-1}	2.3×10^{-1}	3.6×10^{-1}	1.2×10^{-1}	2.8×10^{-2}	2.4×10^{-2}	2.3×10^{-2}
Total intake	2.3×10^{-1}	2.6	2.5×10^{-1}	9.5×10^{-1}	6.0×10^{-1}	3.0×10^{-1}	2.8×10^{-1}	1.9×10^{-1}

1 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in EHD (1998).

2 Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day. TeBDE to HeBDE congeners were identified in a composite sample of baby formula at a value of 14 ng/kg (Ryan, undated [unpublished data]). This study was the only data point for the medium.

3 The sum of the maximum concentrations of TeBDE to HeBDE identified in 72 samples of human breast milk collected in 1992 in Canada was 589 ng/g fat (Ryan and Patry, 2001a, 2001b; Ryan et al., 2002a, 2002b). Breast-fed children 0–6 months of age are assumed to have an intake rate of 0.75 kg of breast milk per day (EHD, 1998). The percent fat of human breast milk has been estimated at 4% (U.S. EPA, 1997). No data on levels of OcBDE, NoBDE or DeBDE in human milk were identified. Data considered in the selection of critical data also included Darnerud et al. (1998, 2002), Meironyte et al. (1998), Ryan and Patry (2000), Strandman et al. (2000), Atuma et al. (2001), Papke et al. (2001), Hori et al. (2002), Meironyte Guvenius et al. (2002) and Ohta et al. (2002).

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in EHD (1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in EHD (1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in EHD (1998).

[7] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in EHD (1998).

[8] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in EHD (1998).

[9] The maximum sum of the PBDEs (not all congeners were specified, but the majority of the value was from TeBDE to HxBDE congener groups) was 2.2 ng/m^3, measured in 14 ambient air samples from the Yukon in the year 1994–1995 (Bidleman et al., 2001). Canadians are assumed to spend 3 hours outdoors each day (EHD, 1998). Data considered in the selection of critical data also included Bergman et al. (1999), Dodder et al. (2000), Alaee et al. (2001), Sjodin et al. (2001), Strandberg et al. (2001), Gouin et al. (2002) and Harner et al. (2002).

[10] No data on levels of PBDEs in residential indoor air were identified. Three samples of indoor air from "domestic" sources in the United Kingdom were analysed, and the sum of one congener of TeBDE, two congeners of PeBDE and two congeners of HxBDE was reported at a maximum value of 1.6 ng/m^3 (Wijesekera et al., 2002). Six samples of indoor air from a laboratory in Norway were analysed, and one HeBDE congener was not detected (detection limit = 0.006 ng/m^3) (Thomsen et al., 2001). Two samples of air from a teaching hall in Sweden were analysed, and DeBDE was reported at a maximum concentration of 0.17 ng/m^3 (Sjodin et al., 2001). No data were available for OcBDE or NoBDE. These values were added together and used to calculate the upper-bounding estimate of exposure. Canadians are assumed to spend 21 hours indoors each day (EHD, 1998). Data considered in the selection of critical data also included Bergman et al. (1999) and Pettersson et al. (2001).

[11] No data on levels of PBDEs in drinking water were identified. As a surrogate, the maximum value of PBDEs as a group (13 pg/L) detected in surface water from Lake Ontario was used (Luckey et al., 2001 [abstract]). Data considered in the selection of critical data also included Environment Agency Japan (1983, 1989, 1991).

[12] The concentrations of the sum of PBDEs were reported in 49 specific food items; the highest food item values were assumed to represent the concentration in each of the eight food groups (dairy, fats, vegetables, cereal products, meat and poultry, eggs, mixed dishes and fish) that include these food items. A concentration of zero was assumed for the remaining four food groups (fruits; foods primarily sugar; nuts and seeds; and soft drinks, alcohol, coffee, tea). Values for the TeBDE to HeBDE congeners were reported in a Canadian study of 40 food composite samples. The maximum values used in the upper-bounding estimate of exposure were for fat (113 ng/kg), cheese (62 ng/kg), meat (1183 ng/kg), egg (332 ng/kg), mixed dishes (207 ng/kg), cereal products (70 ng/kg) and vegetables (104 ng/kg) (Ryan, undated [unpublished data]). Twenty-one samples of salmon from Lake Michigan collected in 1996 identified a maximum of 148.6 ng/g wet weight for TeBDE to HxBDE (Manchester-Neesvig et al., 2001). HeBDE was detected in marine fish (0.030 ng/g whole weight) sampled in the Yukon (Ryan, undated [unpublished data]). No data on levels of OcBDE in food were identified. One study in the United Kingdom used the commercial OcBDE product DE-79 for identification and found levels of up to 12 µg/kg wet weight in fish muscle (Allchin et al., 1999). Neither DeBDE nor NoBDE was detected in farmed or wild salmon from British Columbia, with a detection limit of 0.65 pg/g and 1.04 pg/g wet weight, respectively (Easton et al., 2002). Samples of chicken fat from the southern United States contained a maximum of 0.01 ng OcBDE/g (unspecified congener), 0.04 ng NoBDE/g (unspecified congener) and 2.91 ng DeBDE/g (Huwe et al., 2002). The maximum values or detection limits were added together and used to estimate the upper-bounding estimate of exposure. Data considered in the selection of critical data also included Kruger (1988), DeBoer (1990), Jansson et al. (1993), Sellstrom et al. (1993, 1998), Longanathan et al. (1995), Haglund et al. (1997), Alaee et al. (1999, 2002), Asplund et al. (1999a, 1999b), Ikonomou et al. (1999, 2002), Olsson et al. (1999), Dodder et al. (2000, 2002), Hale et al. (2000, 2001), Christensen and Platz (2001), Johnson and Olson (2001), Jones et al. (2001), Moisey et al. (2001), Zegers et al. (2001), Boon et al. (2002), Christensen et al. (2002), Jacobs et al. (2002), Luross et al. (2002), Norstrom et al. (2002), Ohta et al. (2002), Rice et al. (2002), Wakeford et al. (2002), Wijesekera et al. (2002) and Rayne et al. (2003).

[13] No data on levels of TeBDE to HeBDE in soil not influenced by point sources were identified. As a surrogate, the sum of the maxima of one congener of TeBDE (BDE47) and two congeners of PeBDE (BDE99, BDE100) was reported as 35 760 ng/g in household dust from Massachusetts (Rudel et al., 2003). The sum of the

maximum values of a further congener of TeBDE (BDE49), PeBDE (BDE85), HxBDE (BDE153, BDE154), HeBDE (BDE183) and DeBDE was reported as 20 443 ng/g in household dust from Germany (Knoth et al., 2002). No data on levels of OcBDE in soil or dust were available. OcBDE was detected in sediment from Japan at a maximum level of 22 µg/kg dry weight (Environment Agency Japan, 1989, 1991). These values were added together and used as a surrogate for soil in the upper-bounding estimate of exposure. Data considered in the selection of critical data also included Sellstrom et al. (1998), Allchin et al. (1999), Christensen and Platz (2001), DeBoer et al. (2000), DeBoer and Allchin (2001), Hale et al. (2001, 2002), Leonards et al. (2001), Pettersson et al. (2001), Dodder et al. (2002), Matscheko et al. (2002) and Rayne et al. (2003).

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