RISK ASSESSMENT OF COMBINED EXPOSURES TO MULTIPLE CHEMICALS: A WHO/IPCS FRAMEWORK

EXAMPLE CASE-STUDY A: POLYBROMINATED DIPHENYL ETHERS (PBDES)

Contents

Note to readers

Contributors to this case-study include Mary Albert, Kathy Hughes and M.E. (Bette) Meek of the Existing Substances Division, Safe Environments Programme, Health Canada, Ottawa, Ontario, Canada. The case-study was prepared for the purpose of illustrating and testing the draft World Health Organization/International Programme on Chemical Safety (WHO/IPCS) framework on the risk assessment of combined exposures to multiple chemicals. It is presented here to facilitate the process of public comment.

An example of a framework analysis for a screening assessment conducted under the Canadian Environmental Protection Act is presented here. The assessment group is polybrominated diphenyl ethers, or PBDEs. The tiers of assessment for this assessment group are illustrated conceptually in Figure 1.

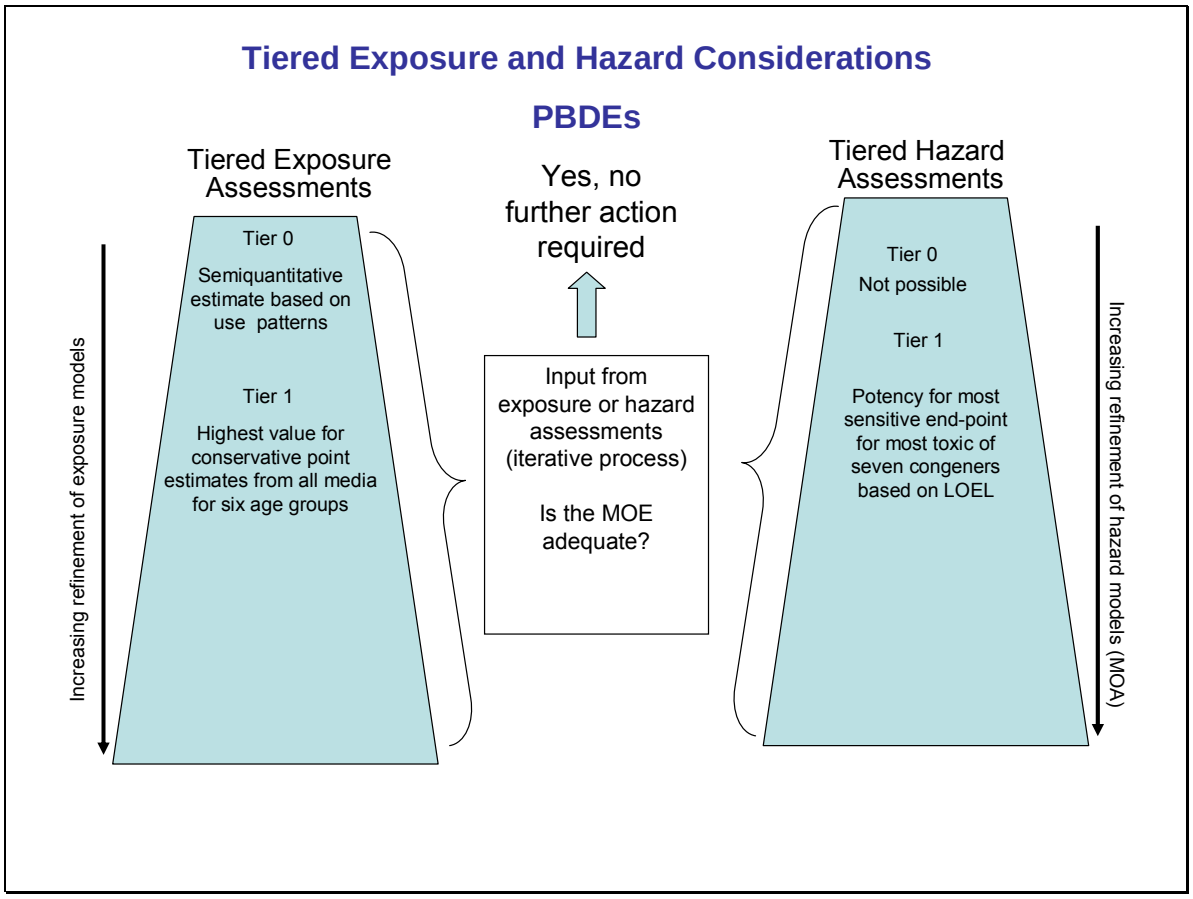

Figure 1: Conceptual illustration of tiers of analysis for PBDEs.

1. CONSIDERING THE NEED FOR A FRAMEWORK ANALYSIS

Relevant data are considered here as a basis to determine whether or not a framework analysis is appropriate and the potential nature of the assessment group.

- *What is the nature of exposure? Are the key components known? Are there data available on the hazard of the mixture itself?*

The focus of this assessment is consideration of the risk of exposure of the population in the general environment, including through consumer products, as a basis to consider whether subsequent risk management is required. The majority of identified data relevant to the evaluation of human health risk relate to the commercial mixtures, with much less information being available for individual congeners.

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. The three main commercial mixtures containing the seven isomers that were the subject of the assessment are commercial pentabromodiphenyl ether, or ComPeBDE (usually containing a mixture of PBDEs with 4–6 bromines), commercial octabromodiphenyl ether, or ComOcBDE (usually containing a mixture of PBDEs with 6–9 bromines), and commercial decabromodiphenyl ether, or ComDeBDE (usually containing PBDEs with 9–10 bromines).

- *Is exposure unlikely or very low, taking into account the context?*

No. There is potential for exposure of the general population through direct contact with products in which these PBDEs are contained. The general population is also potentially exposed to PBDEs in the environment through the use and disposal of these products.

- *Is there a likelihood of co-exposure within a relevant timeframe?*

Yes. There is overlap in congeners within the commercial mixtures and reason to believe that their kinetics will be similar, based on similarity in physicochemical properties.

- *What is the rationale for considering compounds in an assessment group?*

The assessment group contains seven isomers with identical base structure, overlap in congeners within the commercial mixtures, similarities in uses and common target organs. Trends in physicochemical properties and toxicity vary consistently with increasing degree of bromination.

2. PURPOSE AND FOCUS OF THE ASSESSMENT

This case-study addresses a screening-level risk assessment for PBDEs conducted under the Canadian Environmental Protection Act. The principal objectives of screening assessments are to efficiently identify those substances that can be set aside as non-priorities for further work or for which risk should be more fully characterized in priority substance assessments. There is also provision to recommend risk management on the basis of both screening and priority substance assessments.

Several PBDEs were identified as meeting criteria specified within regulations under the relevant legislation for persistence and/or bioaccumulation. They were also considered to be "inherently toxic" to non-human organisms. On this basis, they were nominated for inclusion in a pilot phase for preparation of a screening assessment.

PBDEs are a class of substances containing an identical base structure that differ in the number of attached bromine atoms (n = 1–10). Selection of the seven PBDE congener groups considered in this assessment was based on their potential use in Canada (i.e. their designation as existing substances included on the Domestic Substances List) (Table 1). The three main commercial mixtures containing these seven isomers are commercial pentabromodiphenyl ether, or ComPeBDE (usually containing a mixture of PBDEs with 4–6 bromines), commercial octabromodiphenyl ether, or ComOcBDE (usually containing a mixture of PBDEs with 6–9 bromines), and commercial decabromodiphenyl ether, or ComDeBDE (usually containing PBDEs with 9–10 bromines).

Table 1: List of PBDEs considered in the assessment (Health Canada, 2006).

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

3. THE FRAMEWORK ANALYSIS

Having determined that a framework analysis is appropriate and (at least) the initial composition of an assessment group, available data are considered in a tiered (hierarchical) and integrative (considering both exposure and hazard) fashion, relying in early stages on crude and conservative estimates as a basis to determine whether additional assessment and/or data generation are required. In each of the tiers, estimates of exposure and measures of potency are developed and compared and uncertainties considered. The margin between estimated exposure and hazard is considered in the context of associated uncertainties as a basis to consider whether or not a higher-tier assessment is required. The nature of considerations that constituted the basis for determining that a higher-tier assessment is required (i.e. adequacy of the margin of exposure in the context of uncertainty associated with both estimated exposure and hazard) is explicitly stated.

3.1 Tier 0

3.1.1 Exposure assessment

A semiquantitative measure of exposure was available for these substances developed on the basis of the relative ranking of PBDEs during the categorization of all substances on the Domestic Substances List under the Canadian Environmental Protection Act. In this exercise, potential for exposure was determined based on their volume of production, the numbers of producing and/or using companies and the sum of "expert ranked uses". Expert ranking for the latter was based on the extent to which the uses were considered to contribute to potential exposure of the general population, derived from several workshops involving relevant experts.

On this basis, four of the congeners (tetra, penta, hexa and hepta) were considered to present "lowest potential for exposure of the general population in Canada"; three of the congeners (octa, nona and deca) were considered to present "intermediate potential for exposure of the general population". Semiquantitative measures of exposure were developed through comparison of relative rankings, physicochemical properties and use patterns with substances for which deterministic estimates of exposure were available.

3.1.2 Hazard assessment

In view of the absence of reference or tolerable intakes or concentrations for the relevant congeners, a hazard index (i.e. the sum of exposures divided by the reference value for each of the individual components of an assessment group) could not be developed.

3.1.3 Risk characterization/analysis of uncertainties

As these summed semiquantitative estimates of exposure exceeded a conservative measure of hazard (i.e. the lowest-observed-effect level [LOEL] for the most toxic congener), additional assessment was considered necessary (see section 3.2.2 below).

3.2 Tier 1

3.2.1 Exposure assessment

Available data upon which to base estimates of population exposure to PBDEs are quite disparate, ranging from concentrations in specific media for individual congeners or congener groups to concentrations of total PBDEs, without further identification of specific congeners. In view of the limitations of the data to meaningfully estimate exposure to individual congeners or congener groups and the limited objectives of a screening assessment, conservative upper-bounding estimates of total intake of PBDEs were derived based on maximum levels in air, water, dust, food and human breast milk and standard intake values for six age groups within the Canadian population.

Based on reported concentrations of PBDEs in ambient and indoor air, water, various foodstuffs, human breast milk and dust, along with standard reference values for intake, an upper-bounding estimate of daily intake of total PBDEs (i.e. the tetra to deca congeners considered here) ranged from 0.2 to 2.6 µg/kg body weight (bw) per day for six different age groups of the general population, including breastfed infants, in Canada (Health Canada, 2006). 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-breastfed age group). The age group with potentially the greatest exposure was 0- to 6-month-old breastfed infants, with breast milk accounting for 92% of the exposure (see Table 3 in the appendix at the end of case-study A).

These upper-bounding estimates of exposure were considered conservative, in that they were based on summed estimates for all congeners for which data were available and highest measured concentrations for many media. Quantitative implications of this degree of conservatism were taken into account in determining the adequacy of the margin of exposure (see section 3.2.3).

Upper-bounding estimates of intake in food for subpopulations consuming more traditional or country foods were not substantially greater (i.e. less than 2-fold). 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 were also negligible in comparison with intake from food (Health Canada, 2006).

3.2.2 Hazard assessment

The majority of identified data on the toxicity of PBDEs relate to the commercial mixtures, with much less information being available for individual congeners. Although a full range of toxicity studies was not available for all congeners or commercial mixtures, target systems

and organs for the PBDEs are similar, including the liver, the thyroid and early behavioural development. 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 for each of the congener groups considered in this assessment (where possible), are presented in Table 2 (supporting data are presented in Table 4 in the appendix to this case-study). Critical effects of PBDEs were those that occur on the liver and on 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.

Table 2: Overview of critical health effects and effect levels for PBDE congener groups and commercial products (Health Canada, 2006).

Congener	*LOEL (mg/kg-bw per day)*	*End-point*	*References*
TeBDE	11	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)
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	2.2	Developmental: behavioural (mouse)	Viberg et al. (2001a, 2001b, 2003); Viberg (2002)

The selected critical effect level was 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. Selection of this critical effect level was supported by additional information on similar effects being observed in mice exposed to the penta congener by maternal administration and in neonatal mice administered single, relatively low doses of the tetra, hexa and deca congeners by the same investigators. A somewhat lower LOEL of 0.44 mg/kg-bw per day for ComPeBDE, based on alterations in hepatic enzyme activities, was not considered critical based on the lack of observation of histopathological changes in the liver at this or higher doses (Health Canada, 2006).

3.2.3 Risk characterization/analysis of uncertainties

As a basis for development of conservative margins for the purposes of screening and in light of the similarity of health effects associated with the various PBDEs considered here, the selected critical effect level was compared with an upper-bounding estimate of exposure to total PBDEs (i.e. the tetra to deca congeners considered here) for the potentially most highly exposed subgroup.

Comparison of the critical effect level (i.e. 0.8 mg/kg-bw for neurodevelopmental effects in mice following neonatal exposure) with the upper-bounding deterministic estimate of exposure for the intake of total PBDEs (2.6 µg/kg-bw per day in breastfed infants) resulted in a margin of exposure of approximately 300.

Margins based on available biomonitoring data were approximately 10-fold less. These were estimated through back-calculation of intakes by first-order kinetic modelling of limited data on levels in blood of the general population and comparison of estimated body burden for the critical study in animals with that for breastfed infants. However, confidence in these estimates was considered to be less, 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 physicochemical properties.

The degree of conservatism in this margin is relevant to its interpretation. One critical aspect is the large interindividual variability in levels of PBDEs in breast milk within the general population. It should be noted that mean and median values for levels in breast milk were as much as 400- and 200-fold less, respectively, than the maximum values on which the estimates of exposure were based. In addition, the critical effect level with which the estimate of exposure was compared was that for the most sensitive effect for the most toxic congener. In comparison, effect levels in chronic studies for the same congener were approximately 100 times greater than that used to calculate the margin of exposure.

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. 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). Prediction of trends in body burdens is precluded by the limited information on the toxicokinetics of PBDEs in humans and experimental 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 the derived 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, as well as the biological adversity or severity of the effects deemed critical was found to require additional in-depth evaluation of the relevant data. Development of additional, more meaningful information on population exposure to PBDEs was also considered desirable.

However, in view of the smaller margin between the most conservative estimated critical values for exposure and effects on the environment in comparison with that for human health and resulting recommended action to protect the environment, in-depth evaluation of PBDEs from a human health perspective was considered a low priority at this time. This conclusion is consistent with experience in other countries that risk management actions to protect the environment have resulted in a reduction of exposure of humans. It also contributes to increasing efficiency in the assessment and management of prioritized chemical substances.

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Appendix to case-study A on PBDEs: Supporting data

Table 3: 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[a]			*0.5–4 years*[d]	*5–11 years*[e]	*12–19 years*[f]	*20–59 years*[g]	*60+ years*[h]
	Formula fed[b]	*Breastfed*[c]	*Not formula fed*					
Ambient air[i]	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[j]	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[k]	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[l]			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[m]	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}

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 litres/day (not formula fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

[b] 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). This study was the only data point for the medium.

[c] 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 & Patry, 2001a, 2001b; Ryan et al., 2002a, 2002b). Breastfed children 0–6 months of age are assumed to have an intake rate of 0.75 kg of breast milk per day (Health Canada, 1998). The percent fat of human breast milk has been estimated at 4% (USEPA, 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 & 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).

[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 litres of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 litres of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 litres of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

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

[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 litres of water per day and to ingest 30 mg of soil per day. Consumption of food

groups reported in Health Canada (1998).

[i] 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, Canada, in the year 1994–1995 (Bidleman et al., 2001). Canadians are assumed to spend 3 h outdoors each day (Health Canada, 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).

[j] 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 h indoors each day (Health Canada, 1998). Data considered in the selection of critical data also included Bergman et al. (1999) and Pettersson et al. (2001).

[k] 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). Data considered in the selection of critical data also included Environment Agency Japan (1983, 1989, 1991).

[l] 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). 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). 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 detection limits 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 isomer), 0.04 ng NoBDE/g (unspecified isomer) 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), Loganathan 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 & Platz (2001), Johnson & 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).

[m] 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, USA (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), DeBoer et al. (2000), Christensen & Platz (2001), DeBoer & 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).

Table 4: Summary of health effects information for PBDE congener groups and commercial mixtures.[a]

End-point	*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; Chemische Fabrik Kalk GmbH, 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 (USEPA, 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]

End-point	*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 & Darnerud, 1998 / 2002; Darnerud and Thuvander, 1998) [Additional studies: / Thuvander & 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 & Thuvander, 1998 / Thuvander & 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]

End-point	*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 mg/kg diet): 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 & Machotka, 1979]
Carcinogenicity/ 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)

End-point	*Congener group*							*Commercial mixture*	
	TeBDE	***PeBDE***	***HxBDE***	***HeBDE***	***OcBDE***	***NoBDE***	***ComPeBDE***	***ComOcBDE***	***ComDeBDE/DeBDE***
									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]
Genotoxicity and related end-points: in vivo									**Negative:** rat bone marrow (cytogenetic aberrations), rat liver (DNA damage measured by alkaline elution) (Norris et al., 1975c; Kitchin et al., 1992 / 1993 / Kitchin & Brown, 1994)

End-point	*Congener group*						*Commercial mixture*		
	TeBDE	***PeBDE***	***HxBDE***	***HeBDE***	***OcBDE***	***NoBDE***	***ComPeBDE***	***ComOcBDE***	***ComDeBDE/DeBDE***
Genotoxicity and related end-points: 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 & 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)

End-point	*Congener group*						*Commercial mixture*		
	TeBDE	***PeBDE***	***HxBDE***	***HeBDE***	***OcBDE***	***NoBDE***	***ComPeBDE***	***ComOcBDE***	***ComDeBDE/DeBDE***
Neurodevelop-mental 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 / 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 postnatal day 10, observation period 6 months) (Viberg et al., 2002a)				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) [Additional studies: Gilbert & Crofton, 2002; Taylor et al., 2002; MacPhail et al., 2003]		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 / 2001b / 2003 / Viberg, 2002)

End-point	*Congener group*						*Commercial mixture*		
	TeBDE	***PeBDE***	***HxBDE***	***HeBDE***	***OcBDE***	***NoBDE***	***ComPeBDE***	***ComOcBDE***	***ComDeBDE/DeBDE***
Developmental/ reproductive toxicity (see also Neurodevelop-mental 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) [Additional studies: Argus Research Laboratories Inc., 1985b / BFRIP, 1990 / Hoberman et al., 1998; Zhou et al., 2000 / 2002; Taylor et al., 2002; 2003; Laws et al., 2003]	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: USEPA, 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; 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 oedema 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 / USEPA, 1989) [Additional studies: Norris et al., 1975c / Schwetz et al., 1975]

DNA, deoxyribonucleic acid; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOEL, lowest-observed-effect level; LOEC, lowest-observed-effect concentration; NOEL, no-observed-effect level.

[a] Notes:
- NOELs were reported only when LOELs were unavailable.
- ComDeBDE and DeBDE were not separated owing 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.