Human Health State of the Science Report on Decabromodiphenyl Ether (decaBDE)

Health Canada

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Synopsis

Decabromodiphenyl ether (decaBDE) belongs to a group of structurally related chemicals known as the polybrominated diphenyl ethers (PBDEs). DecaBDE does not occur naturally in the environment and is not manufactured in Canada. However, decaBDE may be imported into Canada as a commercial mixture, or in consumer products, particularly electronic and electrical goods and textiles. The primary use of decaBDE in Canada is as a flame retardant in thermoplastics and polymer resins.

In 2006, two reports on PBDEs were published: *Ecological Screening Assessment Report on Polybrominated Diphenyl Ethers* and *State of the Science Report for a Screening Health Assessment: Polybrominated Diphenyl Ethers (PBDEs)*. The conclusion of the ecological screening assessment report was that decaBDE, along with other assessed PBDEs (both reports considered PBDEs containing between 4 and 10 bromine atoms), met the criteria set out in paragraph 64*(a)* of the *Canadian Environmental Protection Act, 1999* (CEPA 1999). On the basis of a recommendation by the Ministers of the Environment and Health published in the Canada Gazette, PBDEs, including decaBDE, were added to Schedule 1 of CEPA 1999.

In August 2010, Environment Canada published an ecological state of the science (SOS) report that examined new environmental data pertaining to the bioaccumulation and transformation of decaBDE. In the present report, Health Canada has examined new human health information that has become available on decaBDE since the original health assessment of PBDEs was published in 2006.

The health effects of decaBDE have been well studied. In laboratory animals, decaBDE affects early fetal/neonatal development, the liver, the thyroid and potentially the endocrine system. The available studies suggest that decaBDE does not have significant genotoxic potential, and there is limited evidence for carcinogenicity in experimental animals.

The predominant sources of exposure are breast milk for breast-fed infants, mouthing of hard plastic toys for children ages 0.5 to 4 years of age and indoor dust and food for all other age groups. Comparison of the critical effect levels in mammalian studies with the upper-bounding estimates of intake of decaBDE for the potentially most highly exposed age groups (breastfed infants and children aged 0.5–4 years) results in margins of exposure that are considered to be adequate to address uncertainties in the health effects and exposure databases. Comparison of the critical effect level for acute exposure with the upper-bounding exposure estimate for children (aged 0.5–4 years) mouthing hard plastic toys containing decaBDE also results in a margin of exposure considered to be adequate to address uncertainties in the health effects and exposure databases. Additionally, recent unpublished biomonitoring data measuring levels of decaBDE in human serum in the general population of Canada suggest that the upper-bounding estimates of daily intake are conservative. This further supports the adequacy of the margins of exposure derived in this report.

Ongoing ecological risk management initiatives in Canada are expected to result in a reduction of human exposure to decaBDE and other PBDE congeners.

State of the Science Report

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Decabromodiphenyl Ether (decaBDE)

CAS[1] No. 1163-19-5

Figure 1: Decabromodiphenyl ether

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999), the Minister of Health may gather information and conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether 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.

Decabromodiphenyl ether (decaBDE) and other polybrominated diphenyl ethers (PBDEs) (i.e., those with four to nine bromine atoms) were nominated for inclusion in a pilot phase for preparation of screening assessments under CEPA 1999. As a result, an *Ecological Screening Assessment Report on Polybrominated Diphenyl Ethers* (Environment Canada 2006) and a *State of the Science Report for a Screening Health Assessment: Polybrominated Diphenyl Ethers (PBDEs)* (Health Canada 2006) were both published in 2006 and the Ministers published their final conclusions and recommendation for adding the PBDEs to Schedule 1 of CEPA 1999 in July 2006 (Canada 2006).

Environment Canada published an ecological state of the science (SOS) report for decaBDE in August 2010 (Environment Canada 2010). This SOS report includes new information on the bioaccumulation and transformation of decaBDE not considered in the original ecological

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screening assessment report on PBDEs. Based on the updated literature, the SOS report examines whether decaBDE meets the criteria for bioaccumulation as defined in the *Persistence and Bioaccumulation Regulations* under CEPA 1999 (Canada 2000) or whether the substance may transform in the environment to bioaccumulative products. It does not make a conclusion on the toxicity of decaBDE, as the substance was previously found to meet the criteria for toxicity under paragraph 64(a) of CEPA 1999. Links to all of the above-mentioned reports are available at www.ec.gc.ca/toxiques-toxics/Default.asp?lang=En&n=98E80CC6-1&xml=5046470B-2D3C-48B4-9E46-735B7820A444.

Health Canada initiated a review of the state of the science with a focus on decaBDE in order to evaluate information not considered in the original report for a screening health assessment of PBDEs.

This evaluation is considered a state of the science (SOS) review. While it does not critique all studies cited, it considers the reliability of individual studies when forming a weight of evidence for the evaluation of risk to human health. This SOS report on decaBDE was prepared by evaluators within the Existing Substances Risk Assessment Program of Health Canada and incorporates input from other programs within Health Canada. This SOS report has also undergone external written peer review and consultation. Comments on the technical portions were received from scientific experts selected and directed by Meridian Environmental Inc. and from staff of Australia's National Industrial Chemicals Notification and Assessment Scheme for adequacy of data coverage and defensibility of the conclusions. Although external comments were taken into consideration, the final content of the SOS report remains the responsibility of Health Canada.

Information identified as of September 2011 was considered for inclusion in this SOS report. Additionally, one Canadian study published after this date and identified during public comments was added. The critical information and considerations upon which the assessment is based are summarized below.

Identity, Sources and Uses

Decabromodiphenyl ether (decaBDE) belongs to a group of structurally related chemicals known as the polybrominated diphenyl ethers (PBDEs) and is numbered according to the International Union of Pure and Applied Chemistry as the BDE-209 congener, with a corresponding structure of 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether (Birnbaum and Cohen Huba 2006; La Guardia et al. 2006) (Figure 1). DecaBDE is listed on the Government of Canada's Domestic Substances List. For additional background information on decaBDE, the reader should refer to the ecological SOS report on decaBDE published by Environment Canada in August 2010 (Environment Canada 2010).

DecaBDE does not occur naturally in the environment. Results of a section 71 survey under CEPA 1999 (Canada 2001) indicated that decaBDE is not manufactured in Canada. However, decaBDE may be imported into Canada either in the form of its commercial mixture, DecaBDE, or in consumer products, particularly electronic and electrical goods and textiles. The current commercial product typically contains 97–98% decaBDE along with 0.3–3.0% other PBDEs, mainly nonabromodiphenyl ether (nonaBDE). Older commercial DecaBDE products typically contained 77.4% decaBDE, 21.8% nonaDBE and 0.8% octabromodiphenyl ether (octaBDE) (IPCS 1994). This assessment considers both decaBDE and its commercial mixture, DecaBDE.

Results of a section 71 survey under CEPA 1999 (Canada 2001) indicated that, similar to other countries, the primary uses of decaBDE in Canada are as a flame retardant in thermoplastics and polymer resins with widespread application in a variety of consumer electronic and electrical goods, such as televisions, computers, household appliances, hairdryers, cables and wires. DecaBDE is also widely used in the construction and automobile industries and is found in textiles used for furniture upholstery, carpets, curtains, etc. (Alaee et al. 2003; BSEF 2009; Ghanem and Baker 2009).

Exposure Assessment

Environmental Media and Food

There are currently limited data on the levels of decaBDE in environmental media and food, especially Canadian-specific data. Available data upon which to base estimates of general population exposure to decaBDE are quite disparate, in that some authors reported concentrations of decaBDE (measured as the BDE-209 congener) in media, whereas others reported levels of total PBDEs without further identification of specific concentrations of BDE-209. For the purposes of this assessment, only studies that specifically report BDE-209 concentrations are considered in order to derive meaningful estimates of exposure of the general population to decaBDE.

Based on reported concentrations of decaBDE in ambient and indoor air, dust, water, various foodstuffs and human breast milk, along with standard reference values for six different age groups, including breastfed infants, upper-bounding estimates of total daily intake of decaBDE were determined to range from 0.0079 to 0.187 μg/kg-bw per day for the various age groups of the general population in Canada (Table 1). The predominant sources of exposure are breast milk for breast-fed infants and indoor dust and food for all other age groups, except children ages 0.5 to 4 years (see consumer products section). (Note: As discussed in the next section, recent unpublished biomonitoring data measuring levels of decaBDE in human serum in the general population of Canada suggest that the upper-bounding estimates of daily intake are conservative.)

As decaBDE is not manufactured in Canada, the greatest industrial contribution of decaBDE to ambient air is expected to occur during its use in the manufacture of consumer products. Facilities engaged in the recycling of computer and electronic goods are also expected to contribute to increased ambient air concentrations of decaBDE in those localized areas; overall, however, exposure of the general Canadian population to decaBDE from ambient air is considered to be low. As noted above, indoor dust and food are the predominant sources of exposure of the general Canadian population to decaBDE (Table 1). DecaBDE can be released from consumer products and become incorporated into indoor dust or adsorbed onto airborne particles, which may then be inhaled and/or ingested (Hale et al. 2002; Takigami et al. 2008). Data on the levels of decaBDE in food are limited, but recent studies have shown low concentrations of decaBDE in a number of food groups, including meat, dairy products, fish, shellfish, eggs and oils (Gomara et al. 2006; Schecter et al. 2006a; Guo et al. 2007, 2008; Akutsu et al. 2008; Knutsen et al. 2008; van Leeuwen and de Boer 2008; Covaci et al. 2009; Fernandes et al. 2009; Dirtu and Covaci 2010; J. Wang et al. 2010; Shanmuganathan et al. 2011; Ucar et al. 2011). Compared with the lower brominated PBDEs, such as pentabromodiphenyl ether (pentaBDE), however, the contribution of food to the overall exposure of the general population in Canada to decaBDE is relatively low and is similar to the contribution from the ingestion of indoor dust (Table 1). Data on the levels of decaBDE in human breast milk are available (Inoue et al. 2006; Chao et al. 2007; Gomara et al. 2007; Johnson-Restrepo et al. 2007; She et al. 2007; Wu et al. 2007; Antignac et al.

2009; Jin et al. 2009; Koh et al. 2010; Thomsen et al. 2010; Park et al. 2011; Siddique et al. 2012). Recent North American studies have shown that regional differences are evident in the concentrations of BDE-209 reported in human breast milk. Siddique et al. (2012) reported a mean and 95th percentile of 15 and 46 ng/g lipid, respectively, of BDE-209 in breast milk. A total of 87 samples were collected from mothers in Sherbrooke, Quebec (collected in 2003-2004) and Kingston, Ontario (collected in 2008-2009). Johnson-Restrepo et al. (2007) did not detect BDE-209 in 38 samples of breast milk collected in 2004 in Massachusetts (limit of detection = 0.005 ng/g lipid; as cited in Päpke et al. 2004), whereas Wu et al. (2007) reported a maximum BDE-209 concentration of 10.9 ng/g lipid measured in breast milk obtained between April 2004 and January 2005 from women residing in the Boston, Massachusetts, area. She et al. (2007) reported a maximum BDE-209 concentration of 4.26 ng/g lipid in 40 samples of human breast milk collected in 2003 in the northwestern United States and Vancouver, British Columbia. Schecter et al. (2006b) reported a maximum concentration of 2.5 ng/g lipid in the breast milk from 11 mothers in Texas. Park et al. (2011) reported a maximum BDE-209 concentration of 55.3 ng/g lipid obtained between 2003 and 2005 from women residing in California. The principal sources of exposure to decaBDE for the 0- to 0.5-year age group included breast milk in the breastfed group but indoor dust in the non-breastfed groups (see Table 1 and discussion under "Risk Characterization").

Biomonitoring

Preliminary data from two Canadian biomonitoring studies, the Organohalogens in Pooled Serum Specimens from the Canadian Health Measures Survey (CHMS) and the Chemicals, Health and Pregnancy (CHirP) study, indicate that the concentration of decaBDE reported in Canadian serum shows a lower range of concentrations reported in serum of adults and children than those reported in the USA (Lunder et al. 2010; US EPA 2010; Rawn et al. 2011; Webster et al. 2011). In the CHM Survey, decaBDE was analysed in 59 pooled serum samples from 4583 Canadians (aged 6–79 years). Concentrations ranged from below the limit of detection to 9.6 ng/g lipid, with a population-weighted geometric mean concentration of 1.1 ng/g lipid (Rawn et al. 2011). The concentration of decaBDE was highest in 6- to 11-year-olds, with a geometric mean concentration of 3.8 ng/g lipid (Rawn et al. 2011). In the CHirP study, decaBDE in maternal serum was collected at 15 weeks' gestation from a volunteer sample of pregnant women in the Vancouver, British Columbia, area (Webster et al. 2011). BDE-209 was detected in 18.5% of analysed maternal samples with a geometric mean concentration of 2.63 ng/g lipid (Webster et al. 2011). Comparatively, in a recent study in the United States, decaBDE levels in the serum of 20 pairs of mothers and their children from 11 different US states were reported (Lunder et al. 2010). The range of decaBDE concentrations in the mothers' serum was from below the limit of quantification to 3.2 ng/g lipid, with a mean of 1.7 ng/g lipid. The reported range in US children aged 1.5–4 years was from below the limit of quantification to 19 ng/g lipid, with a mean of 3.5 ng/g lipid (Lunder et al. 2010). Additional biomonitoring studies of PBDEs, including BDE-209, in the United States have recently been reviewed, with concentrations in serum ranging from less than 1.0 to 233 ng/g lipid (US EPA 2010).

Other recent studies worldwide have reported concentrations of BDE-209 in adult blood (Sjodin et al. 2008; Roosens et al. 2009; Zhu et al. 2009; Frederiksen et al. 2010; Johnson et al. 2010; Uemura et al. 2010; Kalantzi et al. 2011; Liu et al. 2011; Vizcaino et al. 2011), children's blood (Pérez-Maldonado et al. 2009; Lunder et al. 2010), umbilical cord blood (Jin et al. 2009; Frederiksen et al. 2010; Wu et al. 2010; Vizcaino et al. 2011), human placental tissue (Frederiksen et al. 2009) and human semen (Liu et al. 2011). Alcock et al. (2011) reviewed the available published human serum data and noted that the frequency of positive detection within a

given sampling pool was variable and often very low; these authors suggested that a combination of uneven exposure routes and analytical difficulties with the compound itself may be confounding factors in the database. However, in the event of a large sampling pool, as is the case for the recent Canadian biomonitoring data shown above, no analytical difficulties in quantifying decaBDE were noted.

One study was identified that attempted to correlate human serum concentrations of decaBDE with breast milk measures. Schecter et al. (2006b) measured concentrations in serum and milk from 11 mothers in Austin, Texas, and found high variability in the ratios of decaBDE concentrations in blood and milk, suggesting that blood levels in this small sample could not be extrapolated to milk.

Consumer Products

Children's toys manufactured in China, specifically hard plastic toys, were also recently identified as a potential source of exposure of young children to decaBDE (Chen et al. 2009).

The potential exposure to decaBDE from mouthing of hard plastic toys was modelled using ConsExpo version 4.1 (ConsExpo 2006) (Table 2). A maximum BDE-209 concentration of 4 232 μg/g in hard plastic toys and a migration rate of 0.00296 $\mu g/cm^2$ per minute (Chen et al. 2009) were used to model the oral intake of BDE-209 by Canadian children in the 0.5- to 4-year age group. The upper-bounding estimate of exposure from the mouthing of hard plastic toys was 1.2×10^{-4} mg/kg body weight (kg-bw) per day (Table 2). This is twice the exposure estimate from soil (dust) for this age group (Table 1). Mouthing of hard plastic toys is estimated to be the highest source of exposure for children ages 0.5 to 4 years of age.

Uncertainties in the Exposure Assessment

The confidence in the upper-bounding estimates of exposure are moderate. Confidence in the biomonitoring data is high, as the data reflect exposure from all media and are not subject to the same limitations described below for multimedia samples. Biomonitoring data do not permit exposure source or route attribution.

The reported concentrations of BDE-209 in multiple media are uncertain for a number of reasons, including different sampling methods and unique microenvironments created by the introduction of new electronic goods and/or fabrics treated with decaBDE. Allen et al.(2008a) have proposed that such factors could potentially lead to spatial or regional variations in BDE-209 concentrations. Similarly, the photolytic degradation of BDE-209 in house dust (Harrad et al. 2008b; Stapleton and Dodder 2008) is thought to contribute to variations in indoor exposures. Recently, Alcock et al. (2011) concluded, based on their analysis of published studies, that measurement of decaBDE can be challenging, even for relatively simple matrices, such as sediment and dust. They noted that the choice of the analytical method used was less important than the laboratory's experience in measuring decaBDE and the awareness of those critical parameters in an assay protocol that may affect accurate determinations of decaBDE. Overall, although there are uncertainties in the the upper-bounding estimates of exposure to decaBDE, the availability of biomonitoring data for decaBDE in the serum of the general Canadian population (Rawn et al. 2011; Webster et al. 2011) strengthen the exposure database. Therefore, the limitations with the data on BDE-209 concentrations in multiple media are balanced by the availability of biomonitoring data.

Lastly, it has been suggested that BDE-202, BDE-179 and BDE-184 could be markers for debrominated forms of decaBDE, and consideration of these in characterizing general population exposure could increase the precision of exposure estimates for decaBDE (Stapleton and Dodder 2008). The margins of exposure derived were considered adequate to address such potential uncertainties.

Health Effects Assessment

This section focuses on new studies on the human health effects of decaBDE identified since the publication of the health assessment of PBDEs (Health Canada 2006), in particular those related to development, neurotoxicity and potential endocrine and immunotoxic effects. A summary of the new health effects studies associated with decaBDE is presented in Table 3. Studies determining the effect of decaBDE on other endpoints, such as genotoxicity, carcinogenicity and reproductive toxicity, were documented in the original Health Canada (2006) report.

As shown in Table 3, decaBDE's primary targets in laboratory animals appear to be early fetal/neonatal development, the liver, the thyroid and potentially the endocrine system. Acute oral treatment of neonatal rats and mice resulted in neurobehavioural changes in activity at adulthood, whereas oral treatment of rat and mouse dams at higher doses during pregnancy and lactation induced potential effects on the immune system of the offspring. Several studies in rodents found effects on the liver, notably increases in weight and certain enzyme activities, and also histopathological changes. A 28-day oral study in rats, enhanced to determine endocrine effects, found a dose-dependent decrease in epididymis weight and an increase in seminal vesicle weight, and the authors suggested that there was potentially an effect on steroidogenesis (Van der Ven et al. 2008a).

Effects on the Nervous System

The lowest decaBDE dose causing non-cancer effects in an acute dosing study was 2.22 mg/kg-bw. When decaBDE was administered as a single oral dose to 3-day-old mice in a specialized neurobehavioural toxicity study, assessment at 2 and 4 months of age indicated neurobehavioural changes, including decreased spontaneous activity (locomotion, rearing and total activity; hypoactivity) during the first 20 minutes after the mice were placed in a new environment. Additionally, a comparison of activity during this first 20-minute period with activity during the period 40–60 minutes after the mice were introduced to the novel environment, demonstrated a reduced ability to habituate (i.e., the treated mice were hyperactive, compared with controls, during the latter period). These findings generally showed a dose–response relationship at 2.22 mg/kg-bw and above. A comparison between the abilities of animals treated with a single dose to habituate at 2 and 4 months indicated a poorer performance at 4 months following a single dose (2.22 mg/kg-bw and greater), suggesting a decreasing capacity to habituate with time. A lower dose utilized in the study, 1.34 mg/kg-bw, had no effects (Johansson et al. 2008). Similarly, in mouse studies that followed a similar protocol, behavioural effects were reported at 2.22 mg/kg-bw and above. In these mice, a single oral dose on postnatal day (PND) 3 and assessment at 2–6 months of age showed treatment-related changes in spontaneous behaviour, decreased activity (hypoactivity) and poorer habituation (Viberg et al. 2001a,b, 2003; Viberg 2002; all previously reported in Health Canada 2006). Although the studies by Viberg (2002) and Viberg et al. (2001a,b, 2003) included a lower dose of 1.34 mg/kg-bw, it was administered on PND 10, not PND 3 (with assessment at 2–6 months of age, but no effects were observed). Independently, Rice et al. (2007) reported that neurobehavioural changes (alterations in reflexes, struggling behaviour, grip strength and locomotor activity) were noted in young mice (aged 14–70 days)

following previous gavage administration of 6 mg/kg-bw per day on PNDs 2–15. Similar effects (changes in locomotion, rearing, activity and habituation) were observed at 2 months of age in young rats that had been dosed on PND 3 with a single gavage dose of 6.7 mg/kg-bw (Viberg et al. 2007). In an independent follow-up study, Rice et al. (2009) reported neurobehavioural changes in 16-month-old mice (less efficient response to fixed-ratio schedule of food reinforcement, fixed-interval schedule and light–dark visual discrimination) compared with 70-day-old mice following daily administration by gavage of a dose of 20 mg/kg-bw on PNDs 2–15. There were no treatment-related differences between the two age groups at 6 mg/kg-bw day. These data suggest that aging appears to unmask behavioural effects not evident at a younger age, i.e. early decaBDE exposure appeared to impair learning behaviour in older but not younger mice. Although the exact dosing protocols utilized by Rice et al. (2007, 2009) differed from those utilized by the Viberg and Johansson studies (cited above), in both cases, a consistent finding was that developmental behavioural effects following decaBDE exposure appeared to worsen with age (consistent with a decreasing capacity to habituate with time). Based on these considerations, the dose level of 2.22 mg/kg-bw can be considered to represent the lowest-observed-adverse-effect level (LOAEL) for the acute delayed neurobehavioural toxicity of decaBDE.

Costa and Giordano (2011) reviewed the neurodevelopmental toxicity literature on decaBDE. In regards to 14 studies conducted in rats or mice (including those mentioned above), with protocols ranging from exposures during pregnancy to exposures during PNDs 2–41 (on either single or repeated days), the weight of the evidence based on their analysis of the majority of the studies indicated subtle developmental effects, particularly in pups subjected to locomotor activity or cognitive behaviour tests. In contrast, one of the studies conducted according to the Organisation for Economic Co-operation and Development (OECD) and the US Environmental Protection Agency (EPA) guidelines for developmental neurotoxicity failed to identify such effects in rat pups at doses higher than those used in the other studies. This study was available only in abstract form to Costa and Giordano (2011) when they wrote their review, but the full article has since been published by Biesemeier et al. (2011a) and is included here. In this study, Biesemeier et al. (2011a) dosed pregnant rats from gestation day 6 to lactation day 21 with DecaBDE (97.5% decaBDE plus 2.5% nonaBDE) at doses of 0–1000 mg/kg-bw per day, and neurobehavioural tests (startle response, learning and memory) were conducted on PNDs 20, 22, 60 and 62, whereas motor activity tests were conducted on PNDs 13, 17, 61, 120 and 180. The authors declared the no-observed-adverse-effect level (NOAEL) to be 1000 mg/kg-bw per day, but the numbers of pups found dead were higher in the 100 and 1000 mg/kg-bw per day groups than in the control group, and several other treatment-related effects were observed at 1000 mg/kg-bw per day (number of missing pups was increased, some of the motor activity parameters showed significant differences at 6 months in both sexes and a few of the brain morphometric analyses were significantly different at PND 21 in males and females and at PND 72 in males). Although the authors considered that these effects were within historical control values and an increased number of deaths at 100 and 1000 mg/kg-bw per day were not related to treatment, several different parameters were affected, historical control data were not provided in the supplementary data and, of particular note, significant differences in a number of motor activity parameters all occurred at the same time point (PND 180). Additionally, the authors did not provide a rationale for the increased number of missing pups at 1000 mg/kg-bw per day, and the brain morphometric effects in this study have been documented by other investigators.[2]

[2] Shibutani et al. (2011) also noted the significant differences in the brain morphometric analyses at 1000 mg/kg-bw per day and stated that Biesemeier et al.'s (2011a) supplementary data showed statistically significant decreases in brain hemisphere height in male pups on PND 72 even at the low dose of 1 mg/kg-bw per day.

Costa and Giordano (2011) reviewed mechanistic and in vitro studies related to neurodevelopmental toxicity associated with exposure to decaBDE. As shown in their review, additional studies conducted by Eriksson, Viberg, or Johansson et al., in their laboratory, showed that oral administration of decaBDE to mice on PND 3 resulted in increased synaptophysin and calcium/calmodulin-dependent protein kinase II protein levels in the brain hippocampus 7 days after exposure, whereas administration of octaBDE and nonaBDE on PND 10 resulted in the same effects 24 hours after administration. After 2 or 3 months of age, mice administered a single dose of heptabromodiphenyl ether (heptaBDE) on PND 3, octaBDE on PND 3 or 10 or nonaBDE on PND 10 showed the same alterations in spontaneous behaviour and habituation as those seen when decaBDE was administered on PND 3. The authors considered these findings as confirming their hypothesis that decaBDE exerts its developmental neurotoxicity via the accumulation of debrominated metabolites in the brain. However, further studies to determine whether any of these metabolites is responsible for the observed effects of BDE-209 [decaBDE], had not been conducted by these authors (or other researchers). While there were several publications by different authors on various effects of lower brominated PBDEs in vitro, there were few in vitro studies with decaBDE. Of those studies conducted on nerve tissue, similar cellular effects were observed with decaBDE as with other PBDEs (i.e., oxidative stress, decreased cell viability, apoptosis), but these effects were generally observed at higher concentrations (approximately 50 μM); the authors suggested that this was because decaBDE's bulky configuration prevents it from easily entering cells (Costa and Giordano 2011).

The apparent difference in developmental neurotoxicology results between studies conducted according to regulatory guidelines and those conducted in academic settings was further explored by Alcock et al. (2011). Although the studies by Eriksson, Viberg or Johansson et al. (in their laboratory) have consistently reproduced results indicating alterations in behaviour, habituation and memory that persisted in adult mice and rats when they were administered a single dose of decaBDE (and other PBDE congeners) during the "brain growth spurt" period (postnatal development spanning the first 3–4 weeks of life in rodents), no other laboratory has reported studies with similar or identical protocols. Other researchers (e.g., Hardy and Stedeford 2008; Hardy et al, 2009; Goodman 2009) have noted several limitations with these studies ranging from purity of the test compound, the experimental design, the methodology used to analyze and present the data and lack of information on the motion-measuring device. As shown above, Rice et al. (2007, 2009) also conducted developmental neurotoxicity studies of decaBDE in mice, but these followed US EPA guidelines, in which the litter was used as the statistical unit, and involved repeated dosing of different strains of mice over PNDs 2–15. Although the first study (Rice et al. 2007) did not replicate a consistent depression in motor activity over time, the follow-up study (Rice et al. 2009) showed neurobehavioural deficits in mice when they were tested at an older age (16 months), and in this case, the results were similar to those of Eriksson, Viberg, or Johansson et al., in that behavioural effects of developmental decaBDE exposure appeared to worsen with age. (Note: Alcock et al. [2011] cited the results of Rice et al. [2007] but not the data published in Rice et al. [2009].)

Other more recent in vivo studies that may have an impact on the developmental neurotoxicity evaluation of decaBDE are summarized below. These studies were not mentioned by Alcock et al. (2011) or Costa and Giordano (2011) or were cited as being "in press" by Costa and Giordano (2011).

In a developmental neurotoxicity study conducted by Fujimoto et al. (2011; reviewed in Costa and Giordano 2011), the authors determined a LOAEL of 0.7–2.4 mg/kg-bw per day (10 ppm in the diet) based on liver changes (increased liver weight and liver cell hypertrophy) and kidney

changes (increased cytoplasmic eosinophilia in renal proximal tubules) in rat pups; at the higher dose levels (7–23 and 66–224 mg/kg-bw per day, corresponding to 100 and 1000 ppm, respectively), decreases in the corpus callosum area and in 20,30-cyclic nucleotide 30-phosphodiesterase activity in the cingulated deep cortex in the pup brain were observed at postnatal week 11, indicating white matter hypoplasia in oligodendrocytes, whereas at 1000 ppm, levels of thyroid hormones were decreased, with hypertrophy of thyroid follicular cells.

Liang et al. (2010a) subjected adult mice to oral gavage of decaBDE for 15, 30 or 60 days at doses of 0–160 mg/kg-bw per day. Levels of malonyldialdehyde and superoxide dismutase in brain tissue were increased and decreased, respectively, at 40–160 mg/kg-bw per day, whereas acetylcholinesterase activity was decreased at 80 and 160 mg/kg-bw per day, but there were no significant changes at 0.1 mg/kg-bw per day. As the same effects were observed in mice subjected to a self-repair experiment (i.e., no self-repair), the authors concluded that these changes caused permanent effects on the nervous system and suggested that the neurotoxicity resulted through two possible mechanisms: via oxidative lipid peroxidation or affecting the production and release of neurotransmitters due to the decrease in acetylcholinesterase activity. Zhang et al. (2010) observed the same pattern of cellular response, increase of malonyldialdehyde level and decrease of superoxide dismutase level, along with a decrease in glutathione in brain tissue when mice were gavaged with a single dose of 500 mg/kg-bw, but at the single dose of 200 mg/kg-bw, only the superoxide dismutase level decreased significantly; these results suggest that high doses of decaBDE could induce oxidative stress in nervous tissue.

Pregnant rats were gavaged with decaBDE at a dose of 4.8 mg/kg-bw per day from gestation days 7 to lactation day 7 or only during lactation days 1–7. Results of this study indicated that decaBDE and/or its debrominated congeners are transferred to the offspring via *in utero* and lactational exposure, that tissue levels of PBDEs in the suckling rat pups were higher in the *in utero* plus lactational exposure group than in the lactation-only group, and that higher tissue concentrations of PBDEs appeared to occur during the early period of lactation (higher at PND 4 compared with PND 8). DecaBDE, nonaBDE and octaBDE were all identified in pup tissues (liver, kidney, brain, whole body), with nonaBDE being the most predominant "debrominated metabolite," and the pup brain showed the most significant difference in debrominated congener levels between treated and control pups (Zhang et al. 2011). In a study conducted by Cai et al. (2011; reviewed in Costa and Giordano 2011), the oral decaBDE dose of 4.8 mg/kg-bw per day (from gestation day 7 to PND 4) resulted in 10-fold lower levels of decaBDE in fetuses and pups compared with maternal levels, and nonaBDE and octaBDE levels were increased or showed slight changes in maternal blood and placenta over time, but were lower in fetuses and neonates, suggesting that the placenta acts as a barrier to decaBDE and its metabolites.

The studies by Fujimoto et al. (2011), Zhang et al. (2011) and Cai et al. (2011) were criticized by Biesemeier et al. (2011a,b,c) on several grounds, including failing to control for litter effects, failing to correlate findings in the pup brain with indices of developmental neurotoxicity determined by regulatory guidelines and failing to characterize the composition of the test article used, which thus prevented differentiation of impurities in the test article from true metabolites identified in pup tissues. In the case of the Fujimoto et al. (2011) study, the authors had the opportunity to respond to these criticisms (Shibutani et al. 2011) by indicating that they had recalculated their data using the litter as the experimental unit and that the results did not change their original conclusions. They also noted that morphometric changes should first be discussed in relation to cellular morphology and function of the brain area measured, which was missing in Beisemeier et al.'s (2011a) developmental neurotoxicity study, in which significant morphometic changes in the pup brain were observed. Finally, they noted that because thyrotoxic effects in

pups have been reported by other authors, thyroid parameters (weight, histopathology and thyroid hormone levels) should have been examined in Beisemeier et al.'s (2011a) study (see report of this study above).

Effects on the Endocrine and Immune Systems

An investigation into potential endocrine effects involved the administration of decaBDE to rats at 0 or 1.87–60 mg/kg-bw per day for 28 days by gavage in an emulsion vehicle that was designed to increase the bioavailability of decaBDE by approximately 3- to 4-fold compared with dietary administration. The authors did not characterize effect levels based on administered doses. Instead, a benchmark dose (BMD) approach was used to estimate the critical effect doses (CEDs) associated with 10% changes from controls for several parameters. This study did not assess neurobehavioural changes. A dose-dependent decrease in epididymis weight (CED = 4 mg/kg-bw per day) and a dose-dependent increase in seminal vesicle weight (CED = 1.5 mg/kg-bw per day) were observed, with no corresponding histopathological changes. The authors of the study suggested that the decreased epididymis weight and increased seminal vesicle weight could have reflected modulation of the sex steroid system. It is evident that these organs, which are functionally connected to each other, should show similar weight change responses if the responses were treatment related. These findings suggest that the observed changes, in opposite directions, were adaptive rather than adverse. At higher CEDs, the females showed increases in serum triiodothyronine (T_3) level and decreases in thymus and brain weights (CEDs = 58, 75 and 125 mg/kg-bw per day, respectively). Occasional slight centrilobular hypertrophy of the liver was observed in high-dose males only (no CED determined for this effect). The investigators also estimated $BMDL_{10}$s, the 95% lower confidence limits of the CEDs. There were no effects on appearance, behaviour, growth, or bone, sperm or immunology measures. The LOAEL in this study is considered to be 60 mg/kg-bw per day, based on slight centrilobular hypertrophy in the liver of males observed at this dose and evidence for decreasing thymus and brain weights in females (estimated CEDs of 75 and 125 mg/kg-bw per day, respectively) (Van der Ven et al. 2008a). The experimental methods and benchmark dose modeling of this study have been debated (Hardy et al 2008 and Van der Ven et al 2008b)

Some evidence of weak immunomodulatory effects has been reported in the offspring of female rats and mice fed diets supplying decaBDE from gestation day 10 until weaning. In one rat study, a maternal dose level of about 5 mg/kg-bw per day or above resulted in B-cell activation and a reduced number of natural killer (NK) cells in the offspring (Teshima et al. 2008). In another study, 2-week-old offspring from female rats fed decaBDE at 300 mg/kg-bw per day during pregnancy through to weaning of pups (no further details provided) showed differences in splenic structure and decreases in CD19 percentage and serum interferon-γ level compared with controls; the serum level of decaBDE was more than 10 times higher in the treated group offspring than in control offspring (502 vs. 46 ng/g lipid weight), whereas total metabolite concentrations were almost 3 times higher in the treated offspring (138 vs. 48 ng/g lipid weight); of the metabolite measures, heptaBDE had the greatest difference, with its levels being more than 4 times higher (93 vs. 22 ng/g lipid weight) than in control offspring (Zhou et al. 2010). In a mouse study, a significant increase in gene expression of cytokine RANTES (regulated upon activation, normal T-cell expressed, and presumably secreted) in the offspring was associated with a maternal dose level of 13 mg/kg-bw per day; there was some evidence of other effects, but these reached statistical significance only at a 10-fold higher dose level (130 mg/kg-bw per day) (Watanabe et

al. 2008).[3] In contrast, mouse pups dosed on PNDs 10–21 with a suprapharmacological dose of decaBDE (greater than the OECD limit dose), 3300 mg/kg-bw per day, showed a disorder of the primary immune response in bronchoalveolar lavage fluid (assessed on PND 28), which suggested that cytokine production was affected at this high dose (Watanabe et al. 2010).

Toxicokinetics

Several recently published studies have provided information to better characterize the absorption, distribution, metabolism and excretion of decaBDE in mammals (Hakk and Letcher 2003; Mörck et al. 2003; Sandholm et al. 2003; Huwe and Smith 2007a,b; Kierkegaard et al. 2007). The percentage of an administered dose absorbed across the gastrointestinal tract in rats ranged from approximately 7% to 26%, but one of the most extensive studies that provided key information showed that approximately 90% of the oral dose was excreted via the feces and 9% remained in the body as parent compound and metabolites (US EPA 2008; Environment Canada 2010). The metabolism of decaBDE in orally dosed mammals is summarized as follows:

- Reductive debromination to nona-, octa- and heptaBDEs is the likely first step in the metabolism of decaBDE in rats. However, in mice, the major metabolites identified in the liver, spleen and kidney were hepta-, hexa-, penta- and tetraBDEs (Liang et al. 2010b).
- The debrominated neutral metabolites then appear to undergo hydroxylation to form phenols or catechols, potentially via an arene oxide.
- The catechols may then be methylated, potentially by the action of catechol-*O*-methyltransferase, to form the observed guaicols.
- The guiacol metabolites could further oxidize to quinones, which are highly reactive and would bind to cellular macromolecules.
- The reactive intermediates would also be subject to rapid conjugation via Phase II metabolic processes, leading to water-soluble metabolites, which would be excreted via bile and feces, as was observed in conventional and cannulated rats.[4]

Studies by Huwe and Smith (2007a,b) appear to indicate that the neutral debrominated metabolites make up a very small fraction (~1%) of the total PBDE mass balance in rats exposed to decaBDE. This suggests that the hydroxylation and methylation pathways and resulting metabolites are highly significant in the metabolism of decaBDE (Environment Canada 2010).

The metabolites octaBDE and nonaBDE were found in the liver and kidney of male rats fed decaBDE at 100 mg/kg-bw per day for 3 months (F. Wang et al. 2010).[5] Also, although the molecular forms were not identified, decaBDE residues (bromine-81 isotope) were detected in liver, adrenal cortex and corpora lutea of ovaries in female rats dosed with decaBDE at 2 mg/kg-bw per day for 4 days (Seyer et al. 2010).

[3] Banasik et al. (2010) noted limitations in this study including not controlling for litter effects and not using appropriate immunological methods to definitely conclude impairment of the immune system (images presented were taken at low magnification, which precluded accurate assessment of cellular morphology).
[4] Although urinary excretion of water-soluble metabolites would also be expected, urinary excretion of radioactivity was very minimal in rats (US EPA 2008). However, the study by Liang et al. (2010b) showed that the majority of the debrominated metabolites in mouse kidney after 60 days of dosing with decaBDE were heptaBDE (40%), pentaBDE (26%), hexaBDE (19%) and tetraBDE (13%).
[5] Banasik et al. (2011) criticized several aspects of this study, including identification of metabolites via response factors without using known structures and authentic standards in the study. Wang et al. (2011) replied that semiquantification is a common and accepted approach to qualify compounds without standards and that they used the word "tentatively" in the description of the metabolites.

It is noted that this model for the metabolism of decaBDE is based mainly on studies in rats and that a model for human metabolism has not been established (US EPA 2008). In addition to the excretion routes identified in rodents, decaBDE may also be excreted to a limited extent in human breast milk. Park et al. (2011) reported the transfer of decaBDE to breast milk in the few samples with high decaBDE concentrations in California women, with heptaBDE or tetraBDE as the second major congener detected in the samples (see also description of Park et al. [2011] under "Exposure Assessment").

Lowest Effect Levels

The lowest adverse effect level (LOAEL) in this SOS report is considered to be 2.22 mg/kg-bw per day, based on the neurodevelopmental effect, a decreased capacity to habituate to new environments in mice dosed at PND 3 and assessed at 2 and 4 months of age (Johansson et al. 2008), and the weight of supporting evidence from more recent studies (Alcock et al. 2011; Costa and Giordano 2011; e.g. learning behaviour impaired in mice at older ages but not at early stages in response to neurobehavioural tests, as shown in Rice et al. 2007, 2009). The dose level of 2.22 mg/kg-bw per day was also previously selected as the effect level for decaBDE in Health Canada (2006), based on a limited preliminary developmental mouse data following single oral dosing on PND 3 and behavioural assessment at 2–6 months of age (Viberg et al., 2001a,b, 2003; Viberg, 2002 [cited in Health Canada 2006]).

Uncertainties in the Health Effects Assessment

Confidence in the oral health effects database for the health effects associated with decaBDE is considered to be moderate overall. The database is considered sufficient to characterize the likely most sensitive effects associated with general population exposure to decaBDE. However, there is limited information on effects via the inhalation and dermal routes of exposure.

Although the metabolism and toxicokinetics of decaBDE have been extensively studied in rodents, due to insufficient data on toxicokinetics in humans, a model for human metabolism has not been established. This may be important in relation to the reported neurotoxic effects of decaBDE.

Risk Characterization

The critical effect level for oral exposure considered most appropriate for risk characterization is the LOAEL of 2.22 mg/kg-bw (based on neurodevelopmental effects from exposure during the early days of life resulting in impaired learning behaviour in response to neurobehavioural tests in aging mice), based on several studies of different durations with appropriate endpoints. The dose level of 2.22 mg/kg bw/day was also chosen as the critical effect level for decaBDE in Health Canada (2006) based on similar development behavioural findings reported at this dose and above in other mouse studies that followed similar protocols.

As documented previously, these critical effect levels are also considered protective with regard to the increases in the incidence of benign liver tumours observed in rats chronically exposed at much higher (approximately 500-fold) oral doses of decaBDE, particularly in view of the fact that the available data for decaBDE (and PBDEs as a group) suggest that decaBDE does not have significant genotoxic potential (Health Canada 2004, 2006).

Further information supporting the choice of these LOAELs is presented below.

The US EPA used the LOAEL of 2.22 mg/kg-bw as the basis for setting a revised oral reference dose (RfD) for decaBDE (US EPA 2008), based on the same studies conducted by Eriksson, Viberg or Johansson et al. mentioned in the Health Effects section above. The final review of decaBDE by the US EPA (2008) addressed external peer review comments that has noted limitations in US EPA's endpoint selection. The US EPA noted that most reviewers agreed with using the studies conducted by Eriksson, Viberg or Johansson et al. as a basis for setting the RfD and that the neurodevelopmental findings from these studies were also supported by an expanding body of published studies from other authors demonstrating changes in motor and cognitive activities in rodents following administration of single or repeated doses of decaBDE and other PBDE congeners.

Since the 2008 US EPA final review of decaBDE, the data and the US EPA conclusions have been challenged and other critical effect levels have been proposed (Hardy et al. (2009), Goodman (2009), Williams and DeSesso (2010), TERA (2011)). However, recent published studies support the merit of the 2.22 mg/kg-bw level as a critical effect level for risk characterization. For example, in the follow-up study by Rice et al. (2009), results similar to those published by Eriksson, Viberg or Johansson et al. were observed, demonstrating that behavioural effects of developmental decaBDE exposure worsen with age (i.e. a decreased capacity to habituate to new environments or impaired learning behaviour in response to neurobehavioural tests). In a recent study by Fujimoto et al. (2011), the authors determined a LOAEL of 0.7–2.4 mg/kg-bw per day, based on liver and kidney changes in rat pups; at the higher dose levels (7–23 and 66–224 mg/kg-bw per day), evidence for brain white matter (oligodendrocytes) hypoplasia was observed. Similarly, Liang et al. (2010a) showed evidence of permanent nervous system effects in the brains of adult mice subjected to daily doses of decaBDE, whereas studies by Cai et al. (2011) and Zhang et al. (2011) provided evidence for transfer of decaBDE and/or its metabolites to pups both *in utero* and by breast milk feeding when dams were dosed with 5 mg/kg-bw per day, with increased concentrations observed in pups during the early lactation phase (i.e., when the primary source of nutrition is breast milk). Such studies provide corroborative evidence supporting treatment-related neurobehavioural effects observed in mice pups dosed on PND 3 with decaBDE (or heptaBDE or octaBDE, as well as octaBDE or nonaBDE dosed on PND 10). The ongoing debate in the scientific community on these studies is acknowledged (Biesemeier et al. 2011b,c; Shibutani et al. 2011).

Thus, the weight of evidence supporting the selection of 2.22 mg/kg-bw per day as a critical effect level is supported by reviews of other international jurisdictions (i.e., US EPA) and recently published data.

As shown in the "Exposure Assessment" section, published concentrations of decaBDE in breast milk from Canadian women (She et al. 2007; Siddique et al. 2012), were utilized in determining the upper-bounding estimate of daily intake from all sources of exposure for populations in Canada. These were very similar to the brest milk concentrations reported in the USA (Schecter et al. 2006b; Johnson-Restrepo et al. 2007; Wu et al. 2007; Park et al. 2011). Also, note that unpublished data from two Canadian biomonitoring studies (Rawn et al. 2011; Webster et al. 2011) indicate a lower range of concentrations reported in serum of Canadian adults and children than those reported in the USA (Lunder et al. 2010; US EPA 2010). Therefore, these preliminary Canadian biomonitoring data indicate that the upper-bounding estimates of daily decaBDE intake for Canadian populations are conservative.

Comparison of the critical effect level (2.22 mg/kg-bw per day) with the upper-bounding estimate of intake of decaBDE for the potentially most highly exposed age group (0.05–0.187 µg/kg-bw

per day in breastfed infants) results in a range of margins of exposure of approximately 11 900–44 400. Comparison of the critical effect level for acute exposure (2.22 mg/kg-bw) with the exposure estimate (1.2×10^{-4} mg/kg-bw) for children aged 0.5–4 years mouthing hard plastic toys results in a margin of exposure of 18 500. These margins of exposure are considered adequate to address uncertainties in the health effects and exposure databases.

Summary

In light of the limited data on the levels of decaBDE in environmental media and food, especially Canadian-specific data, and which include some information on the toxicokinetics of decaBDE in humans and experimental animals and the endpoint chosen for the critical effect (developmental neurobehaviour), the absence of significant potential for genotoxicity and limited carcinogenicity potential in experimental animals, it is considered that the estimated margins of exposure for decaBDE, as shown in the "Risk Characterization" section, are considered to be adequate to address uncertainties in the health effects and exposure databases. There is high confidence in these estimates of exposure, because the unpublished biomonitoring data of serum decaBDE levels in the general population of Canada, suggest that the upper-bounding estimates of daily intake in this report are conservative.

DecaBDE belongs to the group of PBDEs previously addressed by Health Canada (2006). In that review, Health Canada considered exposures to total PBDEs and derived a margin of exposure of approximately 300, based on comparison of the critical effect level (i.e., 0.8 mg/kg-bw per day) with the upper-bounding deterministic estimate of exposure for the intake of total PBDEs for the potentially most highly exposed age group (2.6 µg/kg-bw per day in breastfed infants). In comparison, the current review specifically for decaDBE demonstrates a significantly greater margin of exposure for breastfed infants, a susceptible subpopulation.

In 2006, PBDEs and its congeners, including decaBDE, were added to the List of Toxic Substances in Schedule 1 of CEPA 1999 on the basis of environmental considerations (Canada 2006). As a result of these environmental considerations, the Government of Canada (Canada 2008) implemented regulations that prohibit the manufacture, use, sale, offer for sale and import of tetraBDE, pentaBDE and hexaBDE congeners and mixtures, polymers and resins containing these substances. The manufacture of heptaBDE, octaBDE, nonaBDE and decaBDE congeners is also prohibited under these Regulations, and additional regulatory actions are under development. Continuing ecological risk management initiatives in Canada are expected to result in further reduction of human exposure to decaBDE and other PBDE congeners and corresponding increase in margins of exposure.

Table 1: Upper-bounding estimates of daily intake of decaBDE for the general population

Route of exposure	Estimated intake (µg/kg-bw per day) of decaBDE by various age groups							
	0–0.5 year[a]			0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
	Breast milk fed[b]	Formula fed[c]	Not formula fed					
Ambient air[i]	0.00 (3.7×10^{-6})[j]	0.00 (3.7×10^{-6})	0.00 (3.7×10^{-6})	0.00 (7.9×10^{-6})	0.00 (6.1×10^{-6})	0.00 (3.5×10^{-6})	0.00 (3.0×10^{-6})	0.00 (2.6×10^{-6})
Indoor air[k]	0.00 (3.9×10^{-6} – 4.4×10^{-4})	0.00 (3.9×10^{-6} – 4.4×10^{-4})	0.00 (3.9×10^{-6} – 4.4×10^{-4})	0.00 (8.4×10^{-6} – 9.6×10^{-4})	0.00 (6.5×10^{-6} – 7.4×10^{-4})	0.00 (3.7×10^{-6} – 4.2×10^{-4})	0.00 (3.2×10^{-6} – 3.6×10^{-4})	0.00 (2.8×10^{-6} – 3.2×10^{-4})
Drinking water[l]	—	—	—	—	—	—	—	—
Food and beverages[m]	0.016–0.187	0.00 (2.1×10^{-4})	0.038	0.024	0.014	0.0074	0.0047	0.00 (3.4×10^{-3})
Soil[n] (dust)	0.040	0.040	0.040	0.064	0.021	0.0050	0.0042	0.0042
Total intake	**0.05–0.187**	**0.041**	**0.079**	**0.089**	**0.036**	**0.013**	**0.0093**	**0.0079**

[a] 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 Health Canada (1998).

[b] A range of concentrations of BDE-209 reported in breast milk detected in studies involving Canadian women were considered. The lower maximum was calculated to be 0.17 µg/L whole milk [based on a reported 4.26 ng/g lipid x 4% (lipid content of breast milk) x 1.03 g/mL (density of breast milk)] identified in 40 samples of human breast milk collected in 2003 in the northwestern United States and Vancouver, British Columbia (She et al. 2007). The upper end of the range was 1.9 µg/L whole milk [based on the reported 95th percentile of 46 ng/g lipid x 4% (lipid content of breast milk) x 1.03 g/mL (density of breast milk)] measured in 87 samples of breast milk from women in Sherbrooke, QC (collected in 2003-2004) and Kingston, ON (collected in 2008-2009; Siddique et al. 2012). 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 fat percentage of human breast milk has been estimated at 4% (US EPA 1997). Studies considered in the selection of critical data also included Inoue et al. (2006), Schecter et al. (2006b), Chao et al. (2007), Gomara et al. (2007), Johnson-Restrepo et al. (2007), Wu et al. (2007), Antignac et al. (2009), Jin et al. (2009), Koh et al. (2010), Thomsen et al. (2010) and Park et al. (2011).

[c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day. BDE-209 was identified in samples of baby formula at values of 14.0 and 16.5 pg/g (Schecter et al. 2006a). For the purpose of determining an upper-bounding estimate of daily intake, the maximum value of 16.5 pg/g was used in this assessment. This study was the only data point for the medium.

[d] 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 Health Canada (1998).

[e] 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 Health Canada (1998).

[f] 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 Health Canada (1998).

[g] 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 Health Canada (1998).

[h] 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 Health Canada (1998).

[i] The maximum concentration of BDE-209 identified in ambient air was 105 pg/m^3, based on 35 samples obtained between January and June 2002, sampled at the James McLean Oliver Ecological Centre, 115 km northeast of Toronto, Ontario (Gouin et al. 2006). Studies considered in the selection of critical data also included Strandberg et al. (2001), Butt et al. (2004), Shoeib et al. (2004), Ter Schure et al. (2004), Wilford et al. (2004), Hoh and Hites (2005), Venier and Hites (2008), Chang et al. (2009), Su et al. (2009) and Schecter et al. (2010).

[j] Scientific notation is included in parentheses for values that were not true zeros or were rounded.

[k] A range of maximum concentrations of BDE-209 reported in indoor air were considered. The lower maximum concentration of 16 pg/m^3 was identified in homes in Texas (Schecter et al. 2010), and the upper maximum concentration of 1830 pg/m^3 was identified in homes in Germany (Vorkamp et al. 2011). Studies considered in the selection of critical data also included Fromme et al. (2009), Takigami et al. (2009) and Toms et al. (2009).

[l] No data on the levels of BDE-209 in drinking water were identified. Based on its very low water solubility and high log octanol–water partition coefficient, BDE-209 is expected to absorb predominantly to sediment and soils.

[m] The concentrations of BDE-209 were reported in 62 specific food items sampled in Dallas, Texas, between 2003 and 2004 (Schecter et al. 2006a). The highest food item values were assumed to represent the concentration in the five food groups (dairy, fats, meat and poultry, fish and eggs) for which data were available. The maximum concentrations used in the upper-bounding estimate of exposure were for fat (142 pg/g), cheese (481.4 pg/g), meat (166.6 pg/g) and egg (10.32 pg/g). Concentrations of BDE-209 were reported in lake trout from Lake Ontario (Canada) collected between 1979 and 2004 (Ismail et al. 2009). The maximum concentration used in the upper-bounding estimate of exposure for fish was 1300 pg/g. No data were available for the remaining food groups (fruits, vegetables, cereal products, mixed dishes, foods primarily sugar, nuts and seeds, and soft drinks and alcohol); thus, a concentration of zero was assumed. The maximum concentrations or detection limits were added together and used to calculate the upper-bounding estimates of exposure. Studies considered in the selection of critical data also included Gomara et al. (2006), Guo et al. (2007, 2008), Akutsu et al. (2008), Knutsen et al. (2008), van Leeuwen and de Boer (2008), Covaci et al. (2009), Fernandes et al. (2009), Dirtu and Covaci (2010), J. Wang et al. (2010) and Ucar et al. (2011).

[n] No data on the levels of BDE-209 in soil were identified in Canada. The ingestion of indoor dust is considered a significant source of indoor exposure to BDE-209, and the amount of indoor dust ingested each day is considered equivalent to the amount of soil ingested. (This issue is currently being investigated by Health Canada. At this point, no criteria or guidelines have been developed.) For the purpose of this assessment, an upper-bounding exposure estimate was derived based on the ingestion of indoor dust. The maximum concentration of BDE-209 identified in indoor dust was 10 000 ng/g based on 68 samples collected from homes in Ottawa, Ontario, between 2002 and 2003 (Wilford et al. 2005). Another Canadian study (Harrad et al. 2008a) reporting a maximum BDE-209 concentration of 1100 ng/g in indoor dust, based on seven samples collected in Toronto, Ontario, in September 2006, was also identified, but a concentration of 10 000 ng/g was selected to derive upper-bounding estimates of exposure in this assessment. Studies considered in the selection of critical data also included Schecter et al. (2005), Allen et al. (2008a,b), Batterman et al. (2009, 2010), Fromme et al. (2009), Takigami et al. (2009), D'Hollander et al. (2010), Dirtu and Covaci (2010), Harrad et al. (2010), Huang et al. (2010), Johnson et al. (2010), Kang et al. (2011) and Vorkamp et al. (2011).

Table 2: Estimates of oral exposure to decaBDE (BDE-209) from mouthing of hard plastic toys by children aged 0.5–4 years

Consumer product scenario	Algorithm and assumptions	Estimated exposure
Oral mouthing of hard plastic toys Based on algorithm from ConsExpo 4.1[a] Oral exposure to product; compound migrates from product to mouth	Maximum BDE-209 concentration of 4 232 000 ng/g[b] Migration rate of 2.96×10^{-9} g/cm^2 per minute[b] Body weight of 15.5 kg[c] Exposure frequency of 365/year[d] Weight fraction of compound of 0.42%[b] Product amount of 100 g[d] Contact area of 10 cm^2 [d] Exposure time of 60 min[e]	1.2×10^{-4} mg/kg-bw per day

[a] ConsExpo (2006).
[b] Chen et al. (2009).
[c] Health Canada (1998).
[d] Bremmer and van Veen (2002).
[e] Norris and Smith (2002).

Table 3. Summary of new health effects information for decaBDE

Endpoint	Lowest effect level/results
Laboratory animals and *in vitro*	
Acute toxicity	**Lowest oral LOAEL** (mouse) = 2.22 mg/kg-bw (male mice, 10–16 per group, single gavage on PND 3), based on changes in spontaneous behaviour, decreased activity (hypoactivity) when introduced to a novel environment and poorer habituation (with relative hyperactivity with increased time in the novel environment), as assessed at 2 and 4 months (Johansson et al. 2008).
Repeated-dose toxicity	**Lowest oral LOAEL** = 40 mg/kg-bw per day, based on increased malonyldialdehyde levels and decreased superoxide dismutase levels in brain tissue of adult mice subjected to oral gavage of decaBDE for 15, 30 or 60 days at doses of 0, 0.1, 40, 80 or 160 mg/kg-bw per day. To analyze self-repair, mice were allowed to recover for 20, 40 or 60 days after the 60-day exposure period. Acetylcholinesterase activity was decreased at 80 and 160 mg/kg-bw per day. As the same effects were observed in mice subjected to a self-repair experiment (i.e., no changes observed in levels of acetylcholinesterase, superoxide dismutase or malonyldialdehyde), the authors concluded that these changes caused permanent nervous system damage (Liang et al. 2010a). **Other oral LOAEL** = 60 mg/kg-bw per day (male and female rats, five of each sex per group, gavage for 28 days), based on slight centrilobular hypertrophy in the liver of males and evidence for decreasing thymus and brain weights in females (estimated CEDs of 75 and 125 mg/kg-bw per day, respectively). The LOAEL of 60 mg/kg-bw per day was the highest dose tested in this study. Note: A BMD approach was used to estimate CEDs associated with 10% changes from controls for several parameters. These values did not correspond with actual doses tested. Although lower CEDs were determined for increased seminal vesicle weight (CED = 1.5 mg/kg-bw per day) and decreased epididymis weight (4 mg/kg-bw per day) in males, the opposite direction of change in these two organs, which are functionally connected to each other, suggests that the changes observed were adaptive rather than adverse. Also, reduced CYP17 activity in females (CED = 0.51 mg/kg-bw per day) was not considered to be adverse, because cholesterol production was unaffected and there was no supporting evidence of an effect on CYP17 in males (Van der Ven et al. 2008a). [Additional new studies: Tseng et al. 2006, 2008] No **dermal** or **inhalation** repeated-dose toxicity data were identified.
Developmental toxicity (general)	**Lowest LOAEL** = 10 mg/kg-bw per day, based on effects on sperm chromatin DNA integrity (denaturation induction and fragmentation index), sperm hydrogen peroxide generation and decreases in serum T_3 in male offspring following gavage of mice dams on days 0–17 of pregnancy with 0, 10, 500 or 1500 mg/kg-bw per day of decaBDE, with evaluation of male offspring only on PND 71. At 1500 mg/kg-bw per day, anogenital distance was decreased, and swelling of hepatocytes, effects on hepatic enzymes (weak but statistically significant increase in S9 EROD activity) and mild changes in thyroid glands were observed (all in male pups); absolute testis weight was decreased, sperm-head abnormalities and significant testicular histopathology (many interstitial cells and seminiferous tubules with severe vacuolization and almost complete loss of spermatozoa and spermatids) were also observed. No maternal toxicity was observed (Hsu et al. 2006; Tseng et al. 2008, 2011). [Additional new developmental studies: Tseng et al. 2006; Rice et al. 2007] In a specialized study of possible immunotoxic effects, female rats were given decaBDE by

Endpoint	Lowest effect level/results
	gavage from day 10 of gestation until PND 21. The offspring showed B-cell activation and reduced NK cells at maternal dose levels of 5 mg/kg-bw per day and above, as assessed on day 21 (Teshima et al. 2008) [**LOAEL** = 5 mg/kg-bw per day]. [Additional new immunomodulatory developmental studies: Watanabe et al. 2008, 2010; Zhou et al. 2010]
Developmental neurotoxicity	**Lowest oral LOAEL** (mouse) = 2.22 mg/kg-bw (male mice, 10–16 per group, single gavage on PND 3), based on changes in spontaneous behaviour, decreased activity (hypoactivity) when placed in a novel environment followed by relative hyperactivity with time in the novel environment, indicative of a reduced capability to habituate, as assessed at 2 and 4 months (Johansson et al. 2008). Pregnant rats were fed diet containing decaBDE at doses of 0, 10, 100 or 1000 ppm from gestation day 10 to PND 20, and pup parameters were determined on PND 20 and postnatal week 11. The LOAEL was 0.7–2.4 mg/kg-bw per day (10 ppm, equivalent to 0.7, 1.5 and 2.4 mg/kg-bw per day on gestation days 10–20, PNDs 1–9 and PNDs 10–20, respectively), based on increased liver weight and liver cell hypertrophy in male pups and increased cytoplasmic eosinophilia in renal proximal tubules of the kidney in female pups. At the higher dose levels (7–23 and 66–224 mg/kg-bw per day, corresponding to 100 and 1000 ppm, respectively), decreases in the corpus callosum area and in 20,30-cyclic nucleotide 30-phosphodiesterase activity in the cingulated deep cortex in the pup brain were observed at postnatal week 11, indicating white matter hypoplasia in oligodendrocytes, whereas at 1000 ppm, thyroid hormones (serum T_3 and T_4) were decreased in males, with hypertrophy of thyroid follicular cells in both sexes. There were no effects on maternal or offspring reproductive parameters (Fujimoto et al. 2011). Mice offspring from 11–13 litters per treatment group were gavaged on PNDs 2–15 (14 days) with decaBDE at doses of 0, 6 or 20 mg/kg-bw per day. At 6 mg/kg-bw per day and above, there were effects on palpebral reflex (age 14 days), struggling behaviour (age 20 days), grip strength (age 14 and 16 days) and locomotor activity (age 70 days) and a dose-related reduction in serum T_4 level in males. Learning behaviour was impaired at 20 mg/kg-bw (ages 70 days and 1 year). There were no effects on growth or postnatal developmental milestones, anogenital distance or crown–rump length (Rice et al. 2007). Mice offspring from 11–13 litters per treatment group (littermates of those used in Rice et al. 2007) were gavaged on PNDs 2–15 (14 days) with decaBDE at 0, 6 or 20 mg/kg-bw per day. Animals underwent behavioural training and testing at the ages of 70 days or 16 months on three behavioural tasks: fixed-ratio schedule of food reinforcement, fixed-interval schedule and light–dark visual discrimination. At 16 months of age, littermates of both sexes exposed to the high dose performed less efficiently than controls in the fixed-interval schedule, there was altered performance on the fixed-ratio schedule (slope earned reinforcements not as steep as the other groups), and they performed poorly in the light–dark visual discrimination task (learned the task more slowly, made fewer errors on the first response choice of a trial but more preservative errors after an initial error and had lower latencies to respond compared with controls), suggestive of an inability to respond appropriately to the consequences of previous choices. Mice at 70 days of age performed only minimally differently from controls for all tests (Rice et al. 2009). [Additional new developmental neurotoxicity studies: Cressey et al. 2006; Viberg et al. 2007, 2008; Viberg 2009; Hardy and Stedeford 2008; Jiang et al. 2008; Tseng et al. 2008; Wu et al. 2008; Kim et al. 2009; Xing et al. 2009] The following study was conducted according to OECD and US EPA guidelines for

Endpoint	Lowest effect level/results
	developmental neurotoxicity: Pregnant rats were dosed from gestation day 6 to lactation day 21 with commercial DecaBDE (97.5% decaBDE plus 2.5% nonaBDE) at doses of 0, 1, 10, 100 or 1000 mg/kg-bw per day. Neurobehavioural tests of pups (startle response, learning and memory) were conducted on PNDs 20, 22, 60 and 62, whereas motor activity tests were conducted on PNDs 13, 17, 61, 120 and 180, and neuropathology and morphometric analyses were performed on pups sacrificed on PNDs 21 and 72. The numbers of pups found dead between PNDs 0 and 21 were increased in the 100 and 1000 mg/kg-bw per day groups (25 and 28, respectively, compared with 15 in the control group), and the number missing and presumed cannibalized was increased at 1000 mg/kg-bw per day (7 vs. 1 in the controls), although the authors stated that "the deaths were not considered related to treatment." No treatment-related changes were observed in clinical observations, startle response, or learning and memory tests. In the motor activity tests on pups, cumulative total mean counts of locomotor patterns were statistically lower in the 1000 mg/kg-bw group compared with normal controls; ambulatory counts in the first 10-min time block in the 1000 mg/kg-bw group were statistically higher on PND 180 compared with a nicotine-treated control group; cumulative total counts of locomotor activity were lower at PNDs 60 and 120 compared with a saline-treated control group; and both total cumulative and total ambulatory counts were statistically lower on PND 180 compared with the saline-treated control group. However, the authors stated that these were all within the laboratory's historical control ranges. No changes in neuropathology were observed in pups sacrificed at weaning or on PND 72. In regards to brain morphometry, on PND 21, mean thickness of the pons was decreased in males, and mean distance between layers of pyramidal neurons in the hippocampus was decreased in females at 1000 mg/kg bw per day. At PND 72, hemisphere height and cortex vertical thickness were lower in males at 1000 mg/kg-bw per day. Again, the authors stated that these values were within historical control ranges. Although the authors tried to explain away the effects observed in pups at 1000 mg/kg-bw per day as being within historical control values and an increased number of deaths at 100 and 1000 mg/kg-bw per day as not being related to treatment, these arguments are considered to be weak, as several different parameters were affected, historical control data were not provided in the supplementary data and significant differences in a number of motor activity parameters all occurred at the same time point (PND 180). Additionally, the authors provided no explanation for the increased number of missing pups at 1000 mg/kg-bw per day (Biesemeier et al. 2011a) [**LOAEL** = 100 mg/kg-bw per day, based on increased number of pup deaths at 100 and 1000 mg/kg-bw per day, as well as increased number of missing pups and effects on motor activity and brain morphometry in pups at 1000 mg/kg-bw per day].

Abbreviations: BMD, benchmark dose; bw, body weight; CED, critical effect dose; CYP, cytochrome P450; DNA, deoxyribonucleic acid; EROD, ethoxyresorufin-*O*-deethylase; LOAEL, lowest-observed-adverse-effect level; NK, natural killer; PND, postnatal day; S9, 9000 × *g* rat liver supernatant; T_3, triiodothyronine; T_4, thyroxine

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