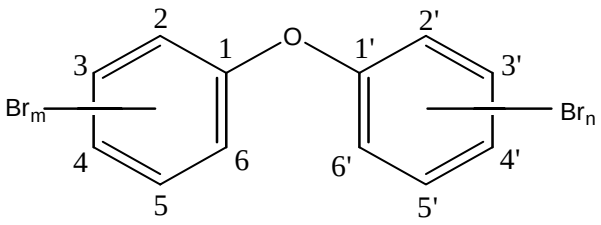
4. RELEVANCE TO PUBLIC HEALTH—PBDEs

4.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBDEs IN THE UNITED STATES

Polybrominated diphenyl ethers (PBDEs) are brominated organic compounds used as flame retardant additives in plastics, textiles, and other materials. As additives, they are physically mixed into product applications, rather than chemically bound. Therefore, they have the potential to migrate from the plastic matrix into the environment when conditions are ideal. Production of PBDEs began in the 1970s and has continued to the present. Concern for the possible health effects of PBDEs has heightened recently due to evidence that components of pentabromodiphenyl ether (pentaBDE) commercial mixtures are ubiquitously distributed at very low levels in the environment, biota, human tissues, and breast milk. Body-burden data indicate that the general population is exposed to low levels of primarily lower brominated (e.g., tetra- and penta-) BDEs. For example, the median concentrations of BDE 47, BDE 153, BDE 183, BDE 209, and total PBDEs (sum of four congeners) were 0.63, 0.35, 0.17, <1, and 2.2 ng/g lipid weight, respectively. DecaBDE was found at levels above the limit of quantification (1 pmol/g lipid). Environmental concentrations of lower brominated PBDEs (i.e., tetraBDE and pentaBDE) appear to be leveling off in Europe, but appear to be increasing in certain areas in Canada and the United States, although data are too sparse to make broad statements regarding trends. The concentration of total PBDEs in air ranges from 5.5 pg/m^3 in rural environments to 52 pg/m^3 in urban air. Because PBDEs are hydrophobic in nature, this class of compounds has not been detected in water to any significant extent. Environmental concentrations of higher brominated commercial mixtures (e.g., decabromodiphenyl ether or decaBDE) are principally concentrated in soils and sediment near industrial point sources.

PBDEs are classes of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the molecular structure (i.e., diphenyl ether). Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBDEs. There are 209 different molecular combinations, or congeners, that are possible for PBDEs, although only a limited number exist in commercial mixtures. Based on the number of bromine substituents, there are 10 homologous groups of PBDE congeners (monobrominated through decabrominated), with each homologous group containing one or more isomers. The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo-congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 isomers, respectively. The general chemical structure of PBDEs is shown below:



where m + n = 1–10

Due to the ether linkage and the position and number of bromine atoms, there are important three-dimensional differences in the structures of PBDEs that can influence the molecules' receptor interactions and toxicological properties as discussed in Section 5.5, Mechanisms of Action. In general, PBDEs are not expected to have the same array of three-dimensional conformations as either PBBs or polychlorinated biphenyls (PCBs).

People are environmentally exposed to PBDEs of different congeneric composition than the source commercial mixtures, which have specific congeneric compositions. People are also environmentally exposed to lower brominated PBDEs (e.g., tetra- and penta- brominated congeners) due to differential partitioning and transformation of the individual congeners in the environment, including transformation in food animals. Additionally, as discussed in Section 5.4, because PBDEs are lipophilic and some congeners are not readily metabolized, they are likely to be retained in the body for long periods of time (years).

Three commercial PBDE mixtures have been and continue to be produced: decaBDE, octaBDE, and pentaBDE. DecaBDE has accounted for more than 80% of world PBDE usage. The composition of commercial decaBDE is ≥97% decaBDE, with the remainder mainly nonabromodiphenyl ether (nonaBDE). Commercial octaBDE is a mixture of congeners ranging from hexabromodiphenyl ether (hexaBDE) to nonaBDE, and mixtures of pentaBDE are comprised of tetrabromodiphenyl ether (tetraBDE) to hexaBDE congeners. Congeners with less than four bromine atoms are generally not found in commercial PBDEs. The main isomers in the commercial pentaBDE product are 2,2',4,4',5-penta-bromodiphenyl ether (i.e., 2,2',4,4',5-pentaBDE or BDE 99; see Section 6-1) and 2,2',4,4'-tetrabromo-diphenyl ether (i.e., 2,2',4,4'-tetraBDE or BDE 47; see Section 6-1). DecaBDE seems to be largely resistant to environmental degradation. However, there is very little information on the environmental degradation of decaBDEs and the data that exist are controversial. Octa- and pentaBDE commercial mixture components, that have a total of four or less bromines, likely undergo differential partitioning

(e.g., bioconcentration in aquatic organisms) and possibly some type of transformation process (e.g., photodegradation) as well. The octa- and pentaBDE mixture components have more readily yielded the predominance of lower-brominated tetra- and penta-congeners, particularly BDE 47, BDE 99, and 2,2',4,4',6-pentaBDE (i.e., 2,2',4,4',6-pentaBDE or BDE 100; see Section 6.1), which have been detected in environmental and human tissue samples (including breast milk). Most studies indicate that levels of lower brominated BDEs in body fluids are a factor of 10–100 higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe). The main source of human exposure to lower brominated PBDE congeners may be from dietary intake, particularly from foods with high fat content (e.g., fatty fish). Lower-brominated tetra- and penta- congeners have been detected in air samples, including those taken from remote areas, indicating that inhalation may also be a potential exposure route for the general population.

4.2 SUMMARY OF HEALTH EFFECTS

Information is available on the potential health effects of all three classes of commercial PBDE products, i.e., decaBDE (also referred to as DBDPO), octaBDE, and pentaBDE. As subsequently discussed, the toxicity of decaBDE is generally much less pronounced than for octa- and pentaBDE commercial products following acute and repeated-dose exposures. This dissimilar toxicity is likely related to the preferential accumulation of lower brominated congeners in the body, due to their greater partitioning and retention in lipid-rich tissues and lower rates of metabolism and elimination relative to decaBDE. In particular, in comparison with the lower brominated mixtures, oral studies in rats found that decaBDE is minimally absorbed (0.3–2%), has a relatively short half-life (<24 hours), and is rapidly eliminated via fecal excretion (>99% in 72 hours). These toxicokinetic differences appear to be related to the number and location of bromines on the diphenyl oxide molecule, and correlate with environmental monitoring data indicating that decaBDE has low bioaccumulation potential. Three-dimensional differences in molecular structure might also contribute to the dissimilar toxicity between congeners (see discussions in Section 4.3 and Section 5.5.2).

The preponderance of health effects data on PBDEs is from studies of orally exposed laboratory animals. Based on the information summarized below and detailed in Chapter 5 (Health Effects), the animal data indicate that decaBDE is much less likely than lower brominated PBDEs to cause health effects in humans, and that main targets of concern for lower brominated PBDEs in humans are the liver, thyroid, and neurobehavioral development. Intermediate- and chronic-duration oral studies in rats and mice found that penta- and octaBDE commercial mixtures caused effects mainly in the liver and thyroid, particularly

enlargement and histological alterations in both organs and changes in serum levels of thyroid hormones. Little information is available on potential neurotoxic effects of PBDEs. PBDEs have not been tested for neurotoxicity using comprehensive test batteries, and most studies used a single dose level of a single congener. Mild impairments in spontaneous motor behavior and learning and memory were found in mice that were exposed to single low doses of 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), and/or 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209) during perinatal and/or early postnatal periods and tested later in life. Concern for neurodevelopmental toxicity of PBDEs is further raised by the documented effects of lower brominated commercial mixtures on thyroid hormone homeostasis, and critical involvement of thyroid hormones in central nervous system development.. Several acute-duration studies with commercial pentaBDE mixtures and the single congener, 2,2',4,4'-tetraBDE (BDE 47), suggest that immune suppression might be another important health end point for lower brominated BDEs, although comprehensive immunological evaluations have not been performed on any congener or commercial mixture. Information on the reproductive toxicity of PBDEs is limited to a one-generation study of a low-purity decaBDE product (77.4% decaBDE, 21.8% nonaBDE, 0.8% octaBDE) in rats that found no exposure-related functional effects. Developmental toxicity studies have shown no evidence of teratogenicity of penta- and octaBDEs in rats and rabbits, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses, have occurred. No fetotoxic or teratogenic effects were induced in rats exposed to high, but not maternally toxic, doses of commercial decaBDE. Information on the carcinogenicity of PBDEs is limited to one chronic oral study of decaBDE and one chronic oral study of lower-brominated PBDEs. The decaBDE study found that lifetime exposure to a high-purity commercial product decaBDE caused neoplastic changes in the liver, including neoplastic nodules in rats and hepatocellular adenomas and carcinomas in mice. Equivocal increases in thyroid gland follicular cell tumors were also observed in mice. The study of lower brominated PBDEs used a former commercial product containing 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE. No neoplastic effects occurred in rats exposed to this mixture for approximately 2 years, but the power of this study to detect carcinogenic effects is limited by very low dose levels and testing of only one species. The weight of available genotoxicity evidence indicates that PBDEs are not genotoxic. Dermal application studies in rabbits showed that decaBDE, octaBDE, and pentaBDE were nonirritating to intact skin and caused some erythematous and edematous responses in abraded skin. DecaBDE was not a skin sensitizer in humans and octaBDE and pentaBDE were nonsensitizing in guinea pigs, indicating that the PBDEs did not cause delayed contact hypersensitivity.

Thyroid Effects. Limited information is available on thyroid effects in PBDE-exposed humans. There are suggestive occupational data as shown by effects that included increased serum thyroid

stimulating hormone (TSH), low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers in workers exposed to decaBDE and/or unspecified PBBs. Due to the mixed nature of the exposure, the possible effects cannot be solely attributed to either chemical. There was no clear association between plasma levels of BDE 47 and thyroid hormone levels (free and total T_3 and T_4, TSH, free testosterone, follicle-stimulating hormone, lutenizing hormone, and prolactin) in men who consumed varying amounts of fatty fish from the Baltic Sea. Based on evidence in animals as summarized below, the thyroid is particularly sensitive to lower brominated PBDEs and a possible target of toxicity in exposed humans.

Thyroid effects, which mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia, were consistently observed in rats and mice orally exposed to lower brominated commercial PBDE mixtures. Accompanying changes in serum TSH levels were not found, and the depression of serum T_4 seems to involve enhanced metabolic formation of hydroxylated metabolites of PBDEs, which bind with high affinity to thyroid transport proteins. Acute duration studies showed decreases in serum T_4 in rats exposed to ≥10 mg/kg/day octaBDE or ≥30 mg/kg/day pentaBDE for 4 days and in rats and mice exposed to ≥18 mg/kg/day pentaBDE for 14 days. Effects observed in intermediate-duration studies included thyroid hyperplasia in rats exposed to ≥8 mg/kg/day octaBDE for 30 days and reduced serum T_4 in rats exposed to ≥10 mg/kg/day pentaBDE for 90 days. Exposure to pentaBDE on gestation day 6 through postnatal day 21 caused serum T_4 reductions at 30 mg/kg/day in maternal rats and ≥10 mg/kg/day in their fetuses and neonatal offspring. Intermediate-duration exposure to a 77% decaBDE/22% nonaBDE commercial mixture caused thyroid hyperplasia in rats at doses ≥80 mg/kg/day for 30 days. Chronic (103-week) exposure to a high-purity (≥97%) commercial decaBDE mixture did not induce thyroid histopathological changes in rats at ≤2,550 mg/kg/day, although follicular cell hyperplasia was increased in mice exposed to 2,240 mg/kg/day of the same commercial product.

The extent that PBDEs affect circulating levels of T_4 or T_3 might vary with species and rats are often regarded as more sensitive than humans. The main basis for this opinion seems to be studies showing that PBDEs affect binding of thyroid hormones to transthyretin (TTR), the primary transport protein in rats. Because TTR is not the major transport protein in humans, the findings have been interpreted as evidence that humans will be less sensitive than rats to thryoid effects of PBDEs. As discussed in Section 5.5.3, the greater sensitivity of rats is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; the latter being, in part, related to the absence of thyroid binding globulin (TBG) in rats. Whereas TTR is the major thyroid hormone binding protein in rats, TBG is the main binding protein in humans and most other mammals.

However, although TTR is not the main transport protein in human serum, it is the principal protein involved in transport of T_4 to the brain in both rats and man. Therefore, without specific evidence that rats are more sensitive to PBDEs than humans, and considering the importance of TTR for the transport of thyroid hormones in the human brain, it is misleading to assume that PBDEs are unlikely to affect thyroid function in humans, or that humans are less sensitive to these effects than rats.

Neurological Effects. A limited amount of information is available on neurological effects of commercial PBDE mixtures. No clinical signs of neurotoxicity or neurohistopathology were observed in rats or mice exposed to commercial decaBDE in dietary doses as high as 16,000–19,000 mg/kg/day for 14 days, 8,000–9,000 mg/kg/day for 13 weeks, or 2,550–7,780 mg/kg/day for 103 weeks. Although the high doses and extended exposure durations provided opportunities for the induction and/or development of clinical signs, the study is limited by lack of testing for subtle behavioral changes and neuro-developmental effects. A commercial pentaBDE mixture was evaluated for several behavioral end points in offspring of rats that were perinatally exposed to 1–100 mg/kg/day by gavage on gestation day (GD) 6 through postnatal day (PND) 21. Evaluation of the offspring as adults showed no alterations in motor or sensory development as assessed by motor activity, habituation, and auditory startle response, although suggestive decreases in fear conditioning were observed.

Neurobehavioral effects of individual PBDE congeners were evaluated in mice that were exposed during perinatal and/or early postnatal periods to 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), or 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209). Most of these studies used similar single oral dose experimental designs and evaluated spontaneous motor behavior and swim maze performance at 2–6 months of age. The findings collectively indicate that the nervous system is a target of particular PBDE congeners during a defined critical phase of neonatal brain development, as shown by mild impairments in spontaneous motor behavior and learning and memory in older mice. One study used a different experimental design in which mice were exposed to BDE 99 from GD 6 to PND 21, and evaluated using a variety of somatic (body weight gain, hair growth, day of eyelid and ear opening, day of incisor eruption) and neurobehavioral (righting reflex, forelimb stick grasping reflex, forelimb placing reflexes, negative geotaxis, screen grasping and climbing, pole grasping, ultrasonic vocalizations, homing test) end points during PNDs 2–22, as well as spontaneous activity end points on PNDs 22–120. Findings were suggestive of delayed sensorimotor development and altered spontaneous behavior. Based on the limited available information (most of the studies were reported as abstracts), and considering the known effects of lower brominated PBDEs on thyroid hormone homeostasis and the

critical role that thyroid hormones play in development of the central nervous system, neurobehavioral development is a potential effect of concern for lower brominated PBDEs in humans.

Hepatic Effects. The hepatotoxic potential of lower brominated PBDE mixtures is well-documented in animals by oral exposure. The spectrum of observed hepatic effects includes microsomal enzyme induction, liver enlargement, and degenerative histopathologic alterations that progress to tumors. Repeated dietary exposure to PBDEs typically caused liver enlargement with or without degenerative changes, and effects were generally dose-related in incidence and severity, more frequent and pronounced in males than females, and more severe with octaBDE and pentaBDE than decaBDE. For example, subchronic oral studies in rats showed that commercial pentaBDE mixtures were hepatotoxic at doses ≤10 mg/kg/day. Increased liver weight and hepatocellular enlargement with vacuolation occurred in rats exposed to commercial pentaBDE doses as low as 2–9 mg/kg/day for 4–13 weeks. Increased incidences of degeneration and necrosis of individual hepatocytes were observed 24 weeks following exposure to ≥2 mg/kg/day of commercial pentaBDE for 90 days in rats. In contrast, high purity commercial decaBDE caused no liver pathology in rats and mice at estimated doses as high as 2,000–8,000 and 2,375–9,500 mg/kg/day, respectively. High purity commercial decaBDE caused liver effects only following lifetime exposure to doses that were still very high. Exposure to 94–97% decaBDE for 103 weeks caused liver thrombosis and degeneration in rats at 2,240 mg/kg/day, and centrilobular hypertrophy and granulomas in mice at ≥3,200 mg/kg/day. No studies are available on hepatic effects of PBDEs in humans. Based on the evidence in animals, lower brominated PBDEs are potentially hepatotoxic in humans.

Immunological and Lymphoreticular Effects. Information regarding the immunosuppressive potential of PBDE mixtures is essentially limited to evidence from acute-duration oral studies of pentaBDE in animals. The plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days; single doses as high as 500 mg/kg had no effect. In the same study, exposure to up to 72 mg/kg/day had no effect on natural killer cell (NKC) activity. *In vitro* production of IgG immunoglobulin from pokeweed mitogen-stimulated splenocytes was reduced in mice exposed to 36 mg/kg/day pentaBDE for 14 days. Other 14-day studies in mice found no changes in natural killer cell activity to murine YAC-1 target cells at ≤72 mg/kg/day or numbers of splenic and thymic lymphocyte subsets at ≤36 mg/kg/day, although 18 mg/kg/day of the single congener BDE 47 caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in spleen. Chronic ingestion of decaBDE caused splenic lesions (hematopoiesis, fibrosis, lymphoid hyperplasia) in rats exposed to ≥1,200 mg/kg/day for

103 weeks, indicating that it is considerably less immunotoxic than pentaBDE. No studies are available on immunological effects of PBDEs in humans. Due to the limited amount of data in animals, insufficient information is currently available to adequately characterize the human immunotoxic potential of PBDEs.

Developmental Effects. Oral developmental toxicity studies of deca-, octa-, and pentaBDE have shown no evidence of teratogenicity in animals. Gestational exposure to a high (1,000 mg/kg/day) but maternally nontoxic dose of decaBDE was fetotoxic in rats as shown by subcutaneous edema and delayed skull bone ossification; however, it is of note that this preparation was only 77% decaBDE. A later study of decaBDE, using a >97% pure compound, reported no maternal or fetal toxicity at doses up to 1,000 mg/kg/day. Commercial mixtures of octaBDE caused skeletal ossification variations in rats and rabbits at maternally toxic levels and other indications of fetotoxicity at lower doses. Effects of gestational exposure to octaBDE included minimally increased postimplantation loss in rats at ≥10 mg/kg/day, increased resorptions in rats at 25 mg/kg/day, and increased skeletal variations in rabbits at 15 mg/kg/day and rats at 50 mg/kg/day. No evidence of fetotoxicity was found in the only available study of pentaBDE in rats at maternally toxic doses ≤200 mg/kg/day. No studies are available on developmental effects of PBDEs in humans. Based on the evidence in animals, PBDEs are unlikely to cause developmental toxicity at expected levels of exposure.

Cancer. The only information regarding carcinogenicity of PBDEs in humans is available from a case-control study that found no clear association between risk of non-Hodgkin's lymphoma and exposure to BDE 47 in a small group of Swedish men and women.

For most PBDEs, including pentaBDE and octaBDE, animal studies of carcinogenic effects are not available; cancer data on PBDEs in animals are limited to results of studies on commercial decaBDE products. In a bioassay conducted by the NTP, male and female rats were exposed to high purity commercial decaBDE (lots that were 96 or 94–97% pure) in the diet in low doses of 1,120 and 1,200 mg/kg/day, respectively, and high doses of 2,240 and 2,550 mg/kg/day, respectively, for 103 weeks. Male and female mice were similarly exposed to low doses of 3,200 and 3,760 mg/kg/day, respectively, and high doses of 6,650 and 7,780 mg/kg/day, respectively. Incidences of neoplastic nodules in the liver were significantly increased in the male and female rats, although the term neoplastic nodule is poorly defined and understood, and is no longer used by NTP to characterize hepatoproliferative lesions in rats. Incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in the male mice. Slightly elevated incidences of thyroid gland follicular cell adenoma or

carcinoma (combined) were additionally observed in exposed male mice, although the increases were not statistically significant. Carcinogenicity was additionally evaluated in rats that were exposed to 0.01, 0.1, or 1.0 mg/kg/day dietary doses of a 77.4% decaBDE mixture (containing 21.8% nonaBDPO and 0.8% octaDBDPO) for approximately 2 years. No exposure-related neoplastic changes were found, but the power of this study to detect carcinogenic effects is limited by the very low dose levels in comparison to those tested in the NTP bioassay.

Based on the limited evidence of carcinogenicity in animals in the NTP bioassay (significantly increased incidences of neoplastic liver nodules in rats and combined hepatocellular adenomas and carcinomas in mice), as well as the lack of human data, decaBDE has been classified in EPA Group C (possible human carcinogen) and IARC Group 3 (not classifiable as to its carcinogenicity to humans). EPA Group D classifications (not classifiable as to human carcinogenicity) were assigned to nona-, octa-, hexa-, penta-, tetra-, tri-, and *p,p'*-diBDE based on no human data and no or inadequate animal data. The U.S. Department of Health and Human Services has not classified the carcinogenicity of any PBDE mixture.

4.3 MINIMAL RISK LEVELS (MRLs)

PBDEs share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly PBBs, PCBs, chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (Agency for Toxic Substances and Disease Registry 1994, 1998, 2000). However, although these chemicals are structurally similar in two dimensions, PBDEs (and PCDEs) differ from the other classes on a three-dimensional basis. In particular, the oxygen bridge of the ether linkage in the diphenyl oxide molecule increases the distance between the biphenyl rings. This apparently reduces steric interactions between *ortho* substituents on the adjacent rings, such that the presence of *ortho* bromines is unlikely to present a barrier to rotation that would prevent the two aromatic rings from assuming a fully coplanar configuration (Chen et al. 2001; Hardy 2002b; Howie et al. 1990). In other words, the ether bridge makes PBDEs more noncoplanar in nature, and introducing *ortho* substitutions into PBDEs does not create a spatial impediment for the two phenyl rings to assume a semi-flat position with respect to each other, as it does for PBBs or PCBs. Therefore, for PBDEs, the influences of the ether bridge and bromine position preclude clearly classifying the congeners as either dioxin-like (coplanar) or nondioxin-like (noncoplanar). This has implications not only for dioxin-type toxicities, which are mediated by the Ah (aryl hydrocarbon) receptor (AhR) pathway (and therefore might not be a significant issue for PBDEs), but also for nondioxin-type effects. The assumption that PBDEs share many toxicological characteristics with PCBs also does not consider geometrical differences due to the higher

atomic weight and considerably larger molecular volume of bromine compared to chlorine (Hardy 2000, 2002b). These differences contribute to dissimilar physical/chemical properties that can influence the relative toxicokinetics and toxicities of the chemicals. The geometrical differences in bromine and chlorine also have implications for understanding the mechanism(s) of effects for nondioxin-like PBB congeners, which are not as well characterized as for PCBs. In particular, it cannot necessarily be assumed, on the basis of two-dimensional structure, that the mechanisms and effects for nondioxin-like PBBs and PCBs are similar.

People are environmentally exposed to PBDE mixtures of different congeneric composition than the original commercial PBDE products. Although the toxicity or potency of environmental mixtures of congeners consequently might be greater or less than that of the original commercial PBDE product, there are insufficient mixture toxicity data on which to directly base MRLs for environmental PBDEs. Due to the likelihoods that (1) multiple mechanisms (Ah-receptor-dependent mechanisms, Ah-receptor independent mechanisms, or both) may be involved in health effects induced by PBDEs, (2) different PBDE congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PBDEs with differing biological activities, as well as to the lack of a suitable approach for quantitatively evaluating joint toxic action from concurrent exposures to PBDEs, PBBs, PCBs, CDDs, and/or CDFs in the environment, data from commercial PBDE mixtures are used to develop MRLs for assessing health risks from environmental exposures to PBDEs.

There are important differences in the environmental chemistry and toxicity of decaBDE compared to lower brominated BDEs. DecaBDE seems to be largely resistant to environmental degradation, whereas octa- and pentaBDE commercial mixture components are likely to undergo differential partitioning and transformation, such that tetra- and pentaBDEs are the predominant congeneric forms that have been detected in the environment. Tetra- and pentaBDE congeners are also the main PBDEs in human tissues (blood, adipose, and breast milk), and BDE 47, BDE 99, and BDE 100 are particularly prevalent in both environmental and biological samples. The preferential accumulation of the lower brominated BDEs is likely due to their partitioning and retention in lipid-rich tissues; decaDBE does not appreciably partition into lipid-rich tissues and has higher rates of metabolism and elimination. These characteristics seem to be a function of both the number and location of bromines on the diphenyl oxide molecule. The tetra- and pentaBDEs appear to be relatively well absorbed, whereas the fully brominated decaBDE, a large poorly soluble molecule, is very poorly absorbed (≈1% or less of an oral dose) and rapidly eliminated (≈99% of the dose within 72 hours). Further, decaBDE is significantly less toxic than lower brominated BDE mixtures. For example, subchronic oral studies in rats showed that commercial octa- or pentaBDE

mixtures were hepatotoxic at doses as low as 2–10 mg/kg/day, while high purity commercial decaBDE caused no liver pathology at doses as high as 8,000–9,500 mg/kg/day (IRDC 1976, 1977; NTP 1986; WIL Research Laboratories 1984). Liver effects (thrombosis and degeneration) of commercial decaBDE in rats were only induced following lifetime exposure, and doses were still very high (2,240 mg/kg/day) (NTP 1986). A study in weanling rats showed that acute oral exposure to commercial decaBDE had no effect on thyroid hormones, while similar exposures to commercial octaBDE or pentaBDE mixtures caused decreases in serum T_4 and T_3 levels (Zhou et al. 2001). Similarly, acute postnatal oral exposure to pure decaBDE congener (BDE 99) was less potent than BDE 47, BDE 99, and 2,2',4,4',5,5'-hexaBDE (BDE 153) in inducing behavioral effects in adult mice (Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003b). Due to the dissimilar toxicity and environmental chemistry of decaBDE as discussed above, separate MRLs were derived for decaBDE and lower brominated mixtures.

Inhalation MRLs

Decabromodiphenyl Ether

No MRLs were derived for acute-, intermediate-, or chronic-duration inhalation exposure to decaBDE due to a lack of inhalation studies on this BDE congener.

Lower Brominated BDEs

Derivation of an acute-duration MRL for lower brominated BDEs is not recommended at this time due to insufficient information. The inhalation database for acute-duration exposure to PBDEs is essentially limited to two 14-day unpublished industry-sponsored studies of octaBDE in rats (Great Lakes Chemical Corporation 1978, 2000). Liver and nasal effect levels were identified in these studies, but are inappropriate bases for MRL estimation. As discussed below, derivation of an acute MRL is precluded by inconsistencies between the studies and a lack of suitable information on thyroid hormone levels or another sufficiently sensitive end point.

In the Great Lakes Chemical Corporation (1978) study, groups of five male and five female Charles River CD rats were whole-body exposed to dust of an unspecified commercial octaBDE mixture in mean analytical concentrations of 0, 0.6, 3.7, 23.9, or 165.2 mg/m^3 for 8 hours/day for 14 consecutive days. The average mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles were 3.5 µm and 2, respectively. Study end points included clinical signs (including observations for respiratory distress and nasal and ocular irritation), body weight and food consumption,

hematology (5 indices), blood chemistry (5 indices, thyroid hormones not assessed), urinalysis (10 indices), organ weights (5 organs including thyroid/parathyroid), gross pathology, and histology (21 tissues including nasal turbinates, trachea, lungs, and thyroid). The clinical laboratory tests were limited to rats in the control and two highest dose groups. The histological exams were limited to the control and highest dose groups, except for the liver, which was examined in all groups. Signs of increased respiration rate (rapid breathing) were observed by the end of each exposure period in rats exposed to ≥24 mg/m^3; this effect always disappeared by the following morning. Liver weight was significantly increased and hepatic lesions occurred in rats exposed to ≥3.7 mg/m^3. At 3.7 mg/m^3, the liver lesions consisted of very slight to slight, focal to multifocal cytoplasmic enlargement of the hepatocytes, accompanied by focal acidophilic degeneration of individual to small groups of cells. The liver lesions were similar in the higher dose groups except that that the hepatocyte enlargement was multifocal to diffuse in distribution, and the presence of focal, small to large areas of hepatocellular necrosis of very slight to marked degree. There were no exposure-related histological changes in other tissues.

The Great Lakes Chemical Corporation (2000) study is currently only available as a secondary summary. This study was summarized in a recent European Union Risk Assessment Report (EU 2003a), but a report is not currently available in the Toxic Substances Control Act Test Submissions (TSCATS) database. The only pertinent information in the TSCATS database (as of March 2004) is a notice that the study was initiated (Great Lakes Chemical Corporation 2000), strongly suggesting that the completed study was never submitted.

In the Great Lakes Chemical Corporation (2000) study, a commercial octaBDE product (bromine content 78.7%, not otherwise identified) was administered to groups of five male and five female Crl:CD(SD)IGS BR rats, by nose-only inhalation as a dust aerosol, in measured concentrations of 0 (air only), 1.0, 10, 110, or 250 mg/m^3 for 6 hours/day, 5 days/week, for 2 weeks. MMADs in the low to high level groups were 2.9, 3.2, 2.9, and 2.9 µm; GSDs were not reported in the available study summary. Clinical signs, body weight, food consumption, and survival were evaluated throughout the study. Hematology, serum chemistry, urine indices, and thyroid hormones were not assessed. Necropsies, organ weight measurements, and histological examinations were performed following exposure termination. The histological examinations included nasal cavity, larynx, trachea, lungs, liver, kidneys, adrenals, brain, spleen, testes, and ovaries, but excluded thyroid and heart. Exposure-related effects occurred in the liver and nasal cavity. Hepatic effects included increased mean absolute and/or relative liver weights at ≥10 mg/m^3 in males and ≥110 mg/m^3 in females, with the greatest increases at 110 and 250 mg/m^3 (21–

44%). Centribobular hypertrophy similarly occurred in the liver at ≥10 mg/m^3 in both sexes (100% incidences in all groups except 4/5 females at 10 mg/m^3). Nasal effects included minimal to mild Goblet cell hyperplasia and/or hypertrophy at ≥1 mg/m^3 in males and ≥10 mg/m^3 in females. The nasal Goblet cell hyperplasia/hypertrophy occurred in nasal levels II and III in males at 1 mg/m^3, and generally in nasal levels II–VI in both sexes at ≥10 mg/m^3. No changes were found in the remaining squamous, respiratory, and olfactory nasal epithelia, or other parts of the respiratory tract.

As detailed above, hepatocellular hypertrophy was found at concentrations at ≥3.7 mg/m^3 in the Great Lakes Chemical Corporation (1978) study and ≥10 mg/m^3 in the Great Lakes Chemical Corporation (2000) study. This liver effect was accompanied by some degenerative hepatocellular changes in the 1978 study, but this was not confirmed by the later study. Additionally, slight histological changes in nasal Goblet cells occurred at ≥1 mg/m^3 in the Great Lakes Chemical Corporation (2000) study, but there were no nasal effects in the earlier study. Interpretation of the significance and adversity of the liver and nasal alterations is complicated by the inconsistency of findings between the studies and other factors, including the small numbers of animals per study (five/sex/level) and different methods of inhalation exposure (whole-body versus nose-only). Additionally, a well designed 13-week study (Great Lakes Chemical Corporation 2001a, 2001b) found (1) hepatocellular hypertrophy, but no degenerative liver changes, at higher a minimum effect level (16 mg/m^3) than in both 14-day studies, and (2) no clearly exposure-related changes in nasal Goblet cells at concentrations below 202 mg/m^3 (study summarized in intermediate MRL section). Further, the adversity of the slight nasal Goblet cell changes, which were predominantly minimal in severity and possibly suggestive of very slight nasal irritation in both the 14-day and 13-week studies, is unclear.

The available information indicates that there are insufficient bases for considering the hepatic and nasal changes as adverse acute effects. More importantly, exposure to ≥16 mg/m^3 caused changes in serum levels of thyroid hormones (decreased T_3, increased TSH) in the 13-week study. Thyroid hormone levels were not determined in either of the 14-day studies. Therefore, due to the lack thyroid hormone data in the 14-day studies, as well as the lack of any clear lowest-observed-adverse-effect levels (LOAELs) for the other end points in the 14-day studies, particularly at exposures levels below the LOAEL for thyroid effects in the 13-week study, there is no sufficiently sensitive basis for derivation of an MRL for acute-duration exposure.

- An MRL of 0.006 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to lower brominated BDEs.

The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 1.1 mg/m^3 for changes in thyroid hormones in rats that were intermittently exposed to octaBDE for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Calculation of the MRL is detailed below.

The inhalation database for intermediate-duration exposure to PBDEs consists of one well-conducted 13-week study (Great Lakes Chemical Corporation 2001a, 2001b). This is an unpublished industry-sponsored study in which a commercial octaBDE product (bromine content 78.7%) was administered to groups of 10 male and 10 female Crl:CD(SD)IGS BR rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (air only), 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The mean MMADs in the low to high exposure groups were 2.0, 2.7, and 2.8 µm, and the corresponding mean GSDs were 3.37, 3.72, and 3.01. Clinical and physical signs, body weight, food consumption, and survival were evaluated throughout the study. Ophthalmic, hematology (11 indices), serum chemistry (18 indices), and serum thyroid hormone (TSH, total T_3, and total T_4) evaluations were performed near the end of the exposure period. Urinalyses were not conducted. Comprehensive necropies, organ weight measurements, and histological examinations (including respiratory tract and thyroid) were performed following exposure termination.

Hepatic, nasal, lung, thyroid, and ovarian effects were observed (Great Lakes Chemical Corporation 2001a, 2001b). The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and liver weight (absolute and relative) at 202 mg/m^3. Total incidences of centrilobular hepatocellular hypertrophy in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10, 0/10, 3/10, and 10/10 in males, and 0/10, 0/10, 3/10, and 6/10 in females; severity was predominantly minimal in all groups and was not dose-related. Changes in nasal Goblet cells were increased at 202 mg/m^3, but showed no clear dose-related increasing trends for incidence or severity. Total incidences of nasal Goblet cell hypertrophy were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3; incidences in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10 (all minimal), 9/10 (7 minimal, 2 mild), 6/10 (all minimal), and 10/10 (9 minimal, 1 mild) in males, and 2/10 (all minimal), 6/10 (all minimal), 4/10 (all minimal), and 8/10 (all minimal) in females. Nasal Goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10, all minimal severity, not increased in females). Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly increased in incidence at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10, 5/10, 5/10, and 10/10 in males, and 0/10, 5/10, 2/10, and 10/10 in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10, and 10/10 in males, and 0/10, 1/10, 1/10, and 10/10 in females. The severity of

both lesion types tended to increase from minimal to mild/moderate at 202 mg/m^3. Gross lung changes also occurred in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial and/or mediastinal lymph nodes. The lymph node effects correlated with the histological finding of granulomatous inflammation. There were no exposure-related gross or histopathological changes in the spleen, bone marrow, thymus, or other tissues, including thyroid. Thyroid hormone assessments, however, showed exposure-related decreases in mean thyroxine (total T_4) at ≥16 mg/m^3 in both sexes, and increases in TSH at ≥16 mg/m^3 in males and 202 mg/m^3 in females. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and were considered to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes. Qualitative histological evaluations of step sections of ovaries showed an absence of corpora lutea in 3/10 females at 202 mg/m^3, compared to 0/10 in the control and lower exposure groups. This 30% incidence was interpreted to be a treatment-related effect because an absence of corpora lutea was considered unusual in rats at 20 weeks of age.

Considering the questionable adversity of minimal severity nasal Goblet cell hypertrophy, lack of clear dose-related increasing trends for incidences and severity of this nasal effect, clear identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in serum levels of thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the effects on thyroid hormones are the most appropriate basis for estimation of an intermediate-duration inhalation MRL. The MRL of 0.006 mg/m^3 was derived by dividing the $NOAEL_{HEC}$ of 0.53 mg/m^3 by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability) and a modifying factor of 3 (for an incomplete database reflecting a single study in one species). The $NOAEL_{HEC}$ was calculated using the following equations:

$$NOAEL_{ADJ} = 1.1 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.196 \text{ mg/m}^3$$

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.196 \text{ mg/m}^3 \times 2.7 = 0.53 \text{ mg/m}^3$$

The RDDR for the extrathoracic (ET) region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate the RDDR: MMAD of 2.0 µm with a mean GSD (sigma g) of 3.37, default human body weight of 70 kg, and a default female F344 rat body weight of 0.18 kg. Additional information on the derivation of the intermediate-duration inhalation MRL for lower brominated BDEs is provided in Appendix A.

No MRL was derived for chronic-duration inhalation exposure to lower brominated BDEs due to a lack of chronic studies.

Oral MRLs

Decabromodiphenyl Ether

No MRL was derived for acute-duration oral exposure to decaBDE due to insufficient data. Information is available on effects of acute exposure on body and liver weights, microsomal enzyme induction in the liver, and serum thyroid levels in weanling rats (Carlson 1980b; NTP 1986; Zhou et al. 2001), but the database is limited by lack of LOAELs and/or sufficiently sensitive end points.

- An MRL of 10 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to decabromodiphenyl ether.

The MRL was derived based on a NOAEL of 1,000 mg/kg/day for developmental toxicity in rats exposed to decaBDE for 19 days during gestation (Hardy et al. 2002). The MRL was estimated by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability)..

A commercial decaBDPE product (97.34% DBDPO, 2.66% nonaBDE and octaBDE) was administered to groups of 25 mated female Sprague-Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days 0 through 19 (Hardy et al. 2002). Each female was sacrificed on gestation day 20 and necropsied. End points examined included maternal clinical observations, maternal body weight/weight gain and food consumption, maternal gravid uterine and liver weights, maternal gross lesions, total number of corpora lutea, uterine implantations, early and late resorptions, viable and nonviable fetuses, and fetal weight and sex. Fetuses were examined grossly (all fetuses), evaluated for skeletal/cartilaginous malformations and ossification variations (approximately half of each litter), and evaluated for visceral malformations (remaining fetuses). No treatment-related effects on any maternal or fetal end points were observed, indicating that 1,000 mg/kg/day was the NOAEL for maternal and developmental toxicity.

Only one intermediate-duration systemic toxicity study of high purity decaBDE has been conducted. In this study, a commercial decaBDE product (94–97% pure) was fed to F344 rats (10/sex/level) in estimated doses of 496–8,000 mg/kg/day, or B6C3F1 mice (10/sex/level) in estimated dietary doses of

589–9,500 mg/kg/day, for 13 weeks (NTP 1986). All animals were observed daily, weighed weekly, and necropsied at the end of the exposure period. Comprehensive histological examinations were performed, but limited to the control and high-dose groups. No hematology, clinical chemistry, or urine indices, or thyroid hormone levels, were evaluated. There were no compound-related clinical signs, deaths, body weight or food consumption changes, gross pathology, or histopathology, indicating that 8,000 and 9,500 mg/kg/day are intermediate-duration NOAELs for systemic toxicity in rats and mice, respectively. As discussed above, the NOAEL for developmental toxicity is 1,000 mg/kg/day (Hardy et al. 2002). Because doses of decaBDE higher than 1,000 mg/kg/day have not been tested for developmental toxicity, and the NTP (1986) study indicates that this dose is also a NOAEL for systemic toxicity, the 1,000 mg/kg/day developmental toxicity NOAEL is used as the basis for the MRL. Additional information on the derivation of the intermediate-duration oral MRL for decaBDE is provided in Appendix A.

No MRL was derived for chronic-duration oral exposure to decaBDE. Only one chronic study of high purity decaBDE has been conducted. In this study, a commercial decaBDE product (94–97% pure) was fed to F344 rats (50/sex/dose level) in dietary doses of 1,120/1,200 mg/kg/day (males/females) or 2,240/2,550 mg/kg/day, and B6C3F1 mice (50/sex/dose level) in doses of 3,200/3,760 mg/kg/day or 6,650/7,780 mg/kg/day, for 103 weeks (NTP 1986). Animals were examined daily for clinical signs. Body weights and food consumption were measured throughout the study, and comprehensive gross and histological examinations were performed on all animals in all dose groups, including those that were moribund or died during the study. No hematology, clinical chemistry, or urine indices, or thyroid hormone levels, were evaluated. Liver degeneration and thrombosis were significantly ($p<0.05$) increased in male rats at 2,240 mg/kg/day; respective incidences in the control, low, and high dose groups were 13/50, 19/50, and 22/50 for degeneration, and 1/50, 0/50, and 9/50 for thrombosis. The thrombosis was characterized by a near total occlusion of a major hepatic blood vessel by a dense fibrin coagulum. Neoplastic nodules in the liver were increased in males at ≥1,120 mg/kg/day and in females at 2,550 mg/kg/day in incidences that were dose-related and statistically significant, although no treatment-related increases in hepatocellular carcinomas were observed. Other effects in exposed rats included fibrosis of the spleen, lymphoid hyperplasia of the mandibular lymph nodes, and acanthosis of the forestomach at 2,240 mg/kg/day. In mice, histopathological changes occurred in 3,200 mg/kg/day in males in the liver (centrilobular hypertrophy and granulomas) and thyroid (follicular cell hyperplasia). An MRL was not derived because the lowest tested dose, 1,120 mg/kg/day in male rats, is a LOAEL for a liver lesion (neoplastic nodules) that is precancerous and associated with thrombosis in the same tissue.

Lower Brominated Diphenyl Ethers

- An MRL of 0.03 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to lower brominated diphenyl ethers.

The acute oral MRL is based on a NOAEL of 1 mg/kg/day for reduced serum levels of thyroid T_4 hormone in fetal rats that were exposed to pentaBDE on days 4–20 of gestation (Zhou et al. 2002). The MRL was estimated by dividing the NOAEL by an uncertainty factor of 30 (component factors of 10 for animal to human extrapolation and 3 for human variability). A component factor of 10 was not used for human variability because the MRL is based on effects observed in a sensitive subgroup. Thyroid hormone levels were determined in Long-Evans rats that were administered a technical pentaBDE mixture (DE-71) in corn oil by gavage from GD 6 through PND 21, except for PND 0 (day of birth) (Zhou et al. 2002). Dams were sacrificed on GD 20 and PND 22, and offspring were sacrificed on GD 20 and PNDs 4, 14, 36, and 90). Study end points included serum total T_4 and T_3 concentrations measured at each age point. The maternal exposure to pentaBDE caused reductions in serum total T_4 that were significantly ($p<0.05$) different from controls in dams at 30 mg/kg/day on GD 20 and PND 22 (48 and 44%, respectively, relative to controls), and in fetuses and offspring at ≥10 mg/kg/day on GD 20 (at least 15% reduced) and PNDs 4 and 14 (50 and 64% maximal in the 10 and 30 mg/kg/day groups, respectively). The effect on T_4 concentrations in the offspring was age-dependent as values returned to control levels by PND 36. There were no exposure-related effects on serum total T_3 concentrations in the dams or offspring at any time, although T_3 was not be measured in fetuses on GD 20 due to insufficient serum sample volume. The critical NOAEL of 1 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T_4 hormone levels in fetal rats that were exposed to pentaBDE (Zhou et al. 2002) are supported by a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day for reduced serum T_4 levels in weanling (28-day-old) rats that were exposed to octaBDE for 4 days (Zhou et al. 2001). Data from other acute-duration studies of PBDEs that support the selection of the critical NOAEL and LOAEL include a NOAEL of 2.5 mg/kg/day and LOAEL of 10 mg/kg/day for fetotoxicity in rats exposed to octaBDE for 10 days during gestation (Life Science Research Israel Ltd. 1987), a NOAEL of 5 mg/kg/day and LOAEL of 15 mg/kg/day for fetotoxicity in rabbits exposed to octaBDE for 13 days during gestation (Breslin et al. 1989), and LOAELs of 18 mg/kg/day for reduced serum T_4 in rats and mice exposed to pentaBDE for 14 days (Fowles et al. 1994; Hallgren et al. 2001). Additional information on the derivation of the acute-duration oral MRL for lower brominated BDEs is provided in Appendix A.

The human relevance of thyroid effects in rats is debatable. As discussed in the thyroid effects part of Section 4.2, mechanistic data indicate that humans are generally less sensitive than rodents because

(1) PBDEs likely affect thyroid function by displacing T_4 from serum-binding proteins in blood and by increasing liver metabolism of thyroid hormones, (2) the major plasma thyroid hormone transporter protein in rats, transthyretin (TTR), is only a minor binding protein in humans, and (3) a thyroid hormone binding globulin, not TTR, is the major transporter protein in humans (Blay et al. 1993; Capen 1997; Sinjari et al. 1998). The importance of the role of TTR in human thyroid homeostasis is unclear because, although it is not is the main transport protein in humans, TTR is necessary for thyroid hormone transport to the developing human fetus. Consequently, it is appropriate to use reduced serum T_4 in fetal rats as the critical effect for the MRL. Support for the relevance of this effect is provided by the lack of changes in thyroid hormones in the maternal animals at the dose that caused the effect on T_4 in the offspring.

- An MRL of 0.007 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to lower brominated BDEs.

The intermediate oral MRL is based on a LOAEL of 2 mg/kg/day for minimal liver effects in rats that were exposed to pentaBDE for 90 days (WIL Research Laboratories 1984). The MRL was estimated by dividing the LOAEL by an uncertainty factor of 300 (component factors of 3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability). Groups of 30 male and 30 female Sprague-Dawley rats were exposed to pentaBDE (commercial mixture DE-71) in the diet at dosage levels of 0, 2, 10, or 100 mg/kg/day for up to 90 days. Study end points included clinical signs, body weight, food consumption, hematology, clinical chemistry (including serum T_3 and T_4), urine indices, gross pathology, and selected organ weights (brain, gonads, heart, liver, kidneys, thymus, and thyroid). Histological examinations were performed on the liver, thyroid, thymus, kidney, and lung in all dose groups and in all tissues (comprehensive evaluation) at 0 and 100 mg/kg/day. Hepatocytomegaly was observed in males at 2 mg/kg/day and in both sexes at ≥10 mg/kg/day. The hepatocytomegaly was similar in incidence and severity after 4 and 13 weeks of exposure, was dose-related with respect to severity (some affected hepatocytes had vacuoles that likely contained lipid), and was still observed in males at ≥10 mg/kg/day and females at 2 and 100 mg/kg/day at 24 weeks postexposure (in lessened severity and incidence). Examinations at 24 weeks following exposure also showed an increase in individual hepatocytes with degeneration and necrosis, effects that were considered to be likely exposure-related and indicative of final loss of previously damaged cells. No NOAEL was identified because liver changes were observed at all dose levels. Nonhepatic effects included decreases in serum T_4 levels at ≥10 mg/kg/day and thyroid follicular cell hyperplasia at 100 mg/kg/day. Based on the observations of hypertrophy, mild degeneration, and slight necrosis, 2 mg/kg/day is considered to be a minimal LOAEL for liver effects. Data from other intermediate-duration studies that support selection of the 2 mg/kg/day minimal LOAEL include hepatic LOAELs of 5 mg/kg/day for cytomegaly (with vacuolation and necrosis

at higher doses) in rats exposed to octaBDE for 13 weeks (IRDC 1977), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976). Other relevant effect levels from intermediate-duration studies include a thyroid LOAEL of 10 mg/kg/day for reduced serum T_4 levels in fetuses and neonatal offspring of rats that were exposed to pentaBDE from GD 6 through PND 21 (Zhou et al. 2002). Additional information on the derivation of the intermediate-duration oral MRL for PBDEs is provided in Appendix A.

A chronic-duration oral MRL was not derived for lower brominated BDEs due to insufficient data. Only one chronic study of PBDEs other than high purity decaBDE has been conducted (Kociba et al. 1975; Norris et al. 1975b). In this study, Sprague-Dawley rats (25/sex/dose level) were fed a 77.4% pure commercial decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years. Evaluations that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. The highest NOAEL is 1 mg/kg/day (highest tested dose), but this NOAEL is not appropriate for MRL estimation due to insufficient sensitivity of the study. In particular, using the NOAEL of 1 mg/kg/day and an uncertainty factor of 100, a chronic oral MRL based on this study would be 5 times higher than the 0.002 mg/kg/day intermediate MRL. A similar pattern was observed for thyroid effects in the study used to derive the acute-duration oral MRL (Zhou et al. 2001) as summarized above. Due to the insufficiencies of the chronic data for MRL derivation, the intermediate oral MRL could be used as a value for chronic exposure.