APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs)
[lower-brominated diphenyl ethers]
CAS Numbers: 32536-52-0 (octaBDE)
Date: March 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 2
Species: Rat

Minimal Risk Level: 0.006 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Great Lakes Chemical Corporation. 2000. A 90-day inhalation toxicity study of octabromodiphenyl oxide in albino rats, dated 04/04/02. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0574171-1.

Experimental design: This is an unpublished study in which a commercial octaBDE product (Lot No. 9525DA23B, bromine content 78.7%, composition and purity not otherwise specified) 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 (filtered 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 level groups were 2.0, 2.7, and 2.8 microns; 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 thyroids) were performed following exposure termination.

Effects noted in study and corresponding doses: Hepatic, nasal, lung, thyroid, and ovarian effects were observed. The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at $\geq$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 (minimal), 0/10, 3/10 (all minimal), and 10/10 (6 minimal, 2 mild, 2 moderate) in males, and 0/10, 0/10, 3/10 (all minimal), and 6/10 (3 minimal, 3 mild) in females. 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 goblet cell hypertrophy (minimal or mild) were slightly increased in nasal level II of both sexes at $\geq$1.1 mg/m^3; incidences in 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. 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 induced at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10 (2 mild, 1 minimal), 5/10 (all minimal), 5/10 (all minimal), and 10/10 (5 minimal, 3 mild, 2 moderate) in males, and 0/10, 5/10 (all minimal), 2/10 (all minimal), and 10/10 (1 minimal, 7 mild, 2 moderate) in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10 (both minimal), and 10/10 (5 minimal, 4 mild, 1 moderate) in males, and 0/10, 1/10 (minimal), 1/10 (minimal), and 10/10 (2 minimal, 5 mild, 3 moderate) in females. 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.

Other findings included some hematological alterations in 202 mg/m^3 females that were not considered to be exposure-related (slightly increased mean activated partial thromboplastin time, and decreased mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration without effects on red blood cell counts, hematocrit, or hemoglobin levels). Serum chemistry evaluations showed that cholesterol was significantly increased (66.2% more than controls, $p<0.01$) in 202 mg/m^3 females, but the magnitude of the elevation was not considered toxicologically significant. Some other statistically significant serum chemistry alterations (increased mean globulin and total protein, decreased albumin/globulin ratio) also occurred in the 202 mg/m^3 females, but were not considered exposure-related due to small magnitudes of changes and lack of similar findings in the males.

Dose and end point used for MRL derivation: 1.1 mg/m^3

[X] NOAEL [ ] LOAEL

Considering the unclear adversity of minimal severity goblet cell hypertrophy, lack of clear dose-related increasing trends for incidence and severity of this nasal effect, identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the NOAEL for effects on thyroid hormones is the most appropriate basis for derivation of the MRL.

Uncertainty factors used in MRL derivation:

[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability
[X] 3 modifying factor for incomplete database

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

Was a conversion used from intermittent to continuous exposure? The NOAEL was adjusted to continuous exposure as follows: 1.1 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 0.196 mg/m^3

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The human equivalent NOAEL ($NOAEL_{HEC}$) was calculated from the duration-adjusted NOAEL ($NOAEL_{ADJ}$) using EPA RfC methodology as follows:

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

The RDDR for the extrathoracic region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate the RDDR of 2.7: 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 180 g.

Based on these values, the MRL for lower brominated diphenyl ethers is derived as follows:

$$MRL = NOAEL_{HEC} \div (UF \times MF) = 0.53 \div (30 \times 3) = 0.006 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: This is the only intermediate-duration inhalation study of PBDEs.

The thyroid is a sensitive target of lower-brominated BDEs in orally exposed animals. A LOAEL for reduced serum T_4 hormone levels in rat dams that were exposed to 2,2',4,4',5-pentaBDE (BDE 99) (Kuriyama et al. 2007) was used as a co-critical end point for the basis for the acute oral MRL for lower-brominated BDEs. This study is supported by numerous studies that report reduced serum T_4 levels in adult, nonpregnant mice and rats following acute exposure to commercial pentaBDE mixtures (Bromkal 70, Bromkal 70-5 DE, DE-71), and the commercial octaBDE mixture DE-79, or 2,2',4,4'-tetraBDE (BDE 47), indicating significant reductions of 19–92% following gavage exposure at doses ≥10 and ≥0.8 mg/kg/day in rats and mice, respectively, for 1–14 days (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001;Hoppe and Carey 2007; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001). In developing animals, numerous studies have reported decreased serum T_4 and/or T_3 levels in pups after gestational and lactational exposure to commercial pentaBDE mixtures (DE-71, Bromkal 70-5 DE), BDE 99, or BDE 47 at doses as low as 0.3 mg/kg/day in rats and 452 mg/kg/day in mice (Blanco et al. 2013; Bondy et al. 2011, 2013; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Kuriyama et al. 2007; Miller et al. 2012; Poon et al. 2011; Shah et al. 2011; Skarman et al. 2005; Szabo et al. 2009; Wang et al. 2011a; Zhou et al. 2002).

Hepatic effects observed in critical study also support the selected point of departure (POD), as a dose-related increased centrilobular hepatocellular hypertrophy was observed in males and females exposed to octaBDE at concentrations ≥16 mg/m^3; however, this end point was not selected as a co-critical effect, as the increase in incidence was only significant at 202 mg/m^3 (Great Lakes Chemical Corporation 2000).

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs)
[lower-brominated diphenyl ethers]
CAS Numbers: 60348-60-9 (2,2',4,4',5-pentaBDE)
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 24, 60, 63
Species: Rat

Minimal Risk Level: 0.00006 ($6x10^{-5}$) [X] mg/kg/day [ ] ppm [ ] mg/m^3

References: Kuriyama SN, Talsness CE, Grote K, et al. 2005. Developmental exposure to low dose PBDE 99: effects on male fertility and neurobehavior in rat offspring. Environ Health Perspect 113(2):149-154.

Talsness CE, Shakibaei M, Kuriyama SN, et al. 2005. Ultrastructural changes observed in rat ovaries following in utero and lactational exposure to low doses of a polybrominated flame retardant. Toxicol Lett 157(3):189-202.

Kuriyama SN, Wanner A, Fidalgo-Neto AA, et al. 2007. Developmental exposure to low-dose PBDE-99: Tissue distribution and thyroid hormone levels. Toxicology 242(1-3):80-90.

Experimental design: In the first study (Kuriyama et al. 2005), pregnant rats (16–20/group) were given a single dose of 2,2',4,4',5-pentaBDE (BDE 99, 98% purity) at 0, 0.06, or 0.3 mg/kg via gavage in peanut oil vehicle on GD 6. Dams were allowed to deliver, and litter size was not artificially altered. Emergence of postnatal reflexes and developmental landmarks (eruption of incisors, fur development, eye opening, and testes descent) was evaluated in all pups (163–200/group). Locomotor activity was evaluated over 24-hour periods on PNDs 36 and 71 in one male and female per litter (16–20 litters/group). F1 male offspring were sacrificed as adults (~PND 140, 12 males/group) and the thymus, spleen, liver, testis, epididymis, seminal vesicle, and ventral prostate were weighed. The right testis and caudal epididymis were retained for spermatid and sperm counts and morphology, respectively. Additionally, blood was collected for analysis of testosterone and LH levels. In 15–19 F1 males/group, reproductive function was assessed at ~PND 150. F1 males were mated with untreated females in a 1:1 ratio for 14 days. The ability of males to impregnate unexposed females was assessed, and pregnant dams were sacrificed on GD 21 for assessment of the number of implantations, resorptions, and fetuses in the F2 generation. Uterine and fetal weight was recorded, and fetuses were sexed and examined for external anomalies. In a separate group of F1 males, male sexual behavior was assessed in 20 males/group at ~PND 160. F1 males were mated with untreated females in estrus (1:1) and the sexual behavior of each mating was recorded for 20 minutes.

In the second study (Talsness et al. 2005), pregnant rats (14–17/group) were exposed to BDE 99 according to the exposure protocol for Study 1. The F1 offspring were weaned on PND 22. The female offspring were necropsied in estrus (based on vaginal cytology) on approximately PND 90. Histological evaluation of the ovary (10/group), uterus (5–7/group), and vagina (5–9/group) was performed. Ovarian follicles were counted in 10 ovaries from each group. One ovary from one female offspring in each group was analyzed by transmission electron microscopy. Twenty virgin F1 females per group were mated with non-exposed males to evaluate fertility. The F1 dams were sacrificed on GD 21 and the uterus was excised. The uterine and F2 fetal weights and the number of implantations, resorptions, and fetuses were

determined. The F2 fetuses were examined for external anomalies and when present, they were stained and examined for skeletal anomalies.

In the third study (Kuriyama et al. 2007), pregnant rats (15–20/group) were exposed to BDE 99 according to the exposure protocol for Study 1. On PND 1, approximately half of the dams (8–10/group) and their offspring were sacrificed. Liver samples were collected for enzyme activity (EROD, UDPGT) and blood was collected for determination of thyroid hormones (T_3, free-T_3, T_4, free-T_4). In pups, blood and liver tissue were pooled by gender on a litter basis. On PND 14, 2 pups/sex/litter (7–11 litters/group) were sacrificed, and liver samples and blood were collected for analysis. On PND 22, remaining dams (7–11/group) and 2 pups/sex/litter were sacrificed, and liver samples and blood were collected for analysis.

Effects noted in study and corresponding doses:

Study 1 (Kuriyama et al. 2005): No exposure-related effects were observed for the age at fur development or eye opening, testes descent, or the ability to master the rotating rod test. However, significant delays in the eruption of incisors in F1 pups and the development of the cliff-drop aversion reflex were observed in F1 males in the 0.3 mg/kg group, compared with controls. Total activity, time spent active, the duration of activity per active phase, and the total activity per active phase were all significantly increased in F1 offspring on PND 36 in the 0.3 mg/kg group, compared with controls. On PND 71, the increased total activity and time spent active persisted in the 0.3 mg/kg group, and was also significantly increased in the 0.06 mg/kg group. In the group sacrificed on PND 140, no exposure-related changes were observed in body weight, liver weight, or thymus weight; however, absolute spleen weight was significantly increased by 9% in the 0.06 and 0.3 mg/kg groups, and relative spleen weight was significantly increased by 12% in the 0.06 mg/kg group. Compared with controls, significantly altered male reproductive organ weights at PND 140 included a 10 and 11% decrease in relative testes and epididymis weight, respectively, in the 0.3 mg/kg group and a 5% decrease in relative epididymis weight in the 0.06 mg/kg group; no significant changes were observed in absolute organ weights. In both dose groups, the number of spermatids and sperm and daily sperm production were significantly decreased, compared with controls. No exposure-related effects were observed for sperm morphology. No changes were observed in serum testosterone or LH levels. Despite sperm alterations, no significant exposure-related effects were observed in male reproductive function or the majority of male sexual behaviors. The only significantly altered male sexual behavior was a 32% decrease in the percent of males with two or more ejaculations.

Study 2 (Talsness et al. 2005): No statistically significant, exposure-related histological changes were observed at the light microscopic level in the ovary, uterus, or vagina of female offspring, and no exposure-related effects were observed in the number of ovarian follicles. However, multiple ultrastructural changes were noted in the ovaries of PND 90 female offspring from dams exposed to 0.06 or 0.3 mg/kg, including destruction of the surface of the serosal epithelial cells, necrosis, and numerous vesicular structures with dense granular material within the cytoplasm. Additional changes observed in the 0.3 mg/kg group included degenerative changes and aggregates of small and large vesicles filled with homogeneously dense granular material in the cytoplasm and clumped chromatin within the condensed nucleus. No exposure-related changes were found for F1 female pregnancy rate, total implantation sites, implantation sites/dam, F2 fetuses/gravid dam, or total number of live F2 fetuses. However, the resorption rates were 12 and 15% in the 0.06 and 0.3 mg/kg groups, respectively, compared with the control rate of 9%. Statistics were not reported; however, the resorption rates in the exposed rats were also reportedly increased compared with historical controls (average control resorption rate=5.4%, with rates up to 10% considered to be within normal limits). In addition, the percentage of litters with resorptions was higher in the exposed females, being 47% in the control group and 69 and 72% in the 0.06 and 0.3 mg/kg groups, respectively. In F2 pups, mean fetal weight was significantly increased by 5% in the 0.06 mg/kg group, but not in the 0.3 mg/kg group, compared with controls. Three fetuses from different litters in the 0.3 mg/kg/day group showed skeletal anomalies (tail, skull, vertebrae); however,

this incidence of anomalies in 3/18 litters is not significantly elevated compared with the control incidence of 0/19 (Fisher's exact test, performed for this review).

Study 3 (Kuriyama et al. 2007): Serum T_4 levels were significantly decreased by 23–33% in the 0.06 and 0.3 mg/kg dams, sacrificed on PND 1. No changes were observed in T_3, free-T_3, or free-T_4 at PND 1 or any thyroid hormone levels at PND 22 in dams. In pups, no dose-related changes were observed at PND 1 or 14. At PND 22, serum T_4 was significantly decreased by in F1 males and females and serum free-T_4 was significantly decreased in F1 females from the 0.3 mg/kg group (19–23% reductions). Hepatic EROD activity was significantly decreased in PND 22 dams from the 0.3 mg/kg group; no other changes in hepatic enzyme activity were observed in dams. In F1 offspring, hepatic UDPGT activity was significantly increased in females at PND 1 and EROD activity was significantly elevated in males at PND 22; no other changes in hepatic enzyme activity were observed in F1 offspring.

Dose and end point used for MRL derivation: 0.06 mg/kg

[ ] NOAEL [X] LOAEL

Collectively, these studies indicate a LOAEL of 0.06 mg/kg for endocrine effects in F0 dams (reduced serum T_4) and reproductive and neurobehavioral effects in F1 adult offspring (impaired spermatogenesis, ultrastructural changes in ovaries, increased resorptions in F1 females mated to unexposed males, and increased spontaneous motor activity). A NOAEL was not identified.

Uncertainty factors used in MRL derivation:

[X] 10 for extrapolation from a LOAEL to a NOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage studies).

Was a conversion used from intermittent to continuous exposure? Not applicable (single exposure studies).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL:

Support for reproductive effects in F1 animals as a co-critical end point: In a companion study to the critical studies described above, pregnant rats (8/group) were administered 2,2´,4,4´-tetrabromodiphenyl ether (BDE 47, 98% purity) at 0, 0.14, or 0.7 mg/kg via gavage in peanut oil vehicle on GD 6 (Talsness et al. 2008). As observed in pentaBDE-exposed F1 females, ultrastructural changes (accumulation of vesicular structures with homogeneously dense granular material in the cytoplasm of the stromal cells, large vacuoles) were observed in the ovaries of F1 females from both dose groups on PND 100. No exposure-related changes were observed in F1 female fertility or F2 litter parameters. F1 males were not evaluated for developmental reproductive effects following tetraBDE exposure.

Support for altered open-field activity in F1 animals as a co-critical end point: Alterations in open-field activity have been consistently reported in mice exposed to BDE 99 at doses ≥0.8 mg/kg on PND 3 or 10 and evaluated at 2–8 months of age, characterized by decreased activity during the first 20-minute period

followed by increased activity during the third 20-minute period (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Sand et al. 2004; Viberg et al. 2002, 2004a, 2004b). These findings indicate an initial decrease in activity, but also a lack of habituation to new surroundings. The study authors noted that this nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) has also been reported in adult mice neonatally exposed to certain PCB congeners. Several other 1-day exposure studies have reported similar findings in rats and mice following exposure to various lower-brominated PBDEs. Decreased spontaneous activity and/or impaired habituation was observed in rats exposed to BDE 99 at 8 mg/kg on PND 10, mice exposed to 2,2',4,4',5,5'-hexaBDE (BDE 153) at ≥0.45 mg/kg on PND 10, mice exposed to BDE 47 at 10.5 mg/kg on PND 10, mice exposed to the 2,2',3,4,4',5',6-heptaBDE (BDE 183) at 15.2 mg/kg on PND 3, and mice exposed to the 2,2',3,4,4',5,5',6-octaBDE (BDE 203) at 16.8 mg/kg on PND 3 or 10 (Eriksson et al. 2001; Viberg et al. 2003a, 2005, 2006). Increased vertical activity was significantly increased at 4 months, but not at 2 months, in mice exposed to BDE 47 at ≥1 mg/kg on PND 10; no changes were observed in horizontal activity or habituation (Gee and Moser 2008). No changes in open-field behavior were observed in mice exposed to BDE 183 at 15.2 mg/kg or 2,2',3,3',4,4',5,5',6-nonaBDE (BDE 206) at 18.5 on PND 10 (Viberg et al. 2006).

Additional neurobehavioral changes observed in the studies described above included learning and memory impairments in the Morris water maze or radial arm maze in mice exposed to BDE 99 at 0.8 mg/kg on PND 10, mice exposed to BDE 153 at ≥0.9 mg/kg on PND 10, and mice exposed to BDE 203 at 16.8 mg/kg on PND 10, and in rats exposed to BDE 47 at ≥1 mg/kg on PND 10 (Fischer et al. 2008; He et al. 2009, 2011; Viberg et al. 2003a, 2006).

Support for decreased serum T_4 in F0 dams as a co-critical end point: Numerous studies report reduced serum T_4 levels in adult, nonpregnant mice and rats following acute exposure to commercial pentaBDE mixtures (Bromkal 70, Bromkal 70-5 DE, DE-71), the commercial octaBDE mixture DE-79, or BDE 47. Significant reductions of 19–92% have been reported following gavage exposure at doses ≥10 and ≥0.8 mg/kg/day in rats and mice, respectively, for 1–14 days (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001;Hoppe and Carey 2007; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001).

Toxicokinetic considerations: Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs)
[lower-brominated diphenyl ethers]
CAS Numbers: 5436-43-1 (2,2',4,4'-tetraBDE)
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 164
Species: Rat

Minimal Risk Level: 0.000003 ($3x10^{-6}$) [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Zhang Z, Zhang X, Sun Z, et al. 2013b. Cytochrome P450 3A1 mediates 2,2',4,4'-tetrabromodiphenyl ether-induced reduction of spermatogenesis in adult rats. PLoS ONE 8(6):e66301. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0066301. August 14, 2014.

Experimental design: Male rats (20/group) were administered 2,2',4,4'-tetrabromodiphenyl ether (BDE 47; ≥98.7%) at 0, 0.001, 0.03, or 1 mg/kg/day via gavage in corn oil 6 days/week for 8 weeks. Twenty-four hours after the final BDE 47 treatment, rats were sacrificed. Testes were fixed for histological analysis and labeling of apoptotic cells or prepared for analysis of sperm production. Daily sperm production was estimated by dividing the total number of mature spermatids per testis by 6.1 (i.e., the days of the seminiferous cycle that the spermatids are present in the seminiferous epithelium). Testicular samples were examined for ROS and mRNA expression of apoptosis related proteins (ser15, ser473, p53, PTEN, AKT, BAD, caspase 3, FAS, FASL). Serum levels of E2, FSH, LH, and testosterone were measured.

Effects noted in study and corresponding doses: Histological examination of the testes showed a significant increase in the number of multinucleated giant cells (arising from spermatocytes that aborted meiosis) at ≥0.03 mg/kg/day and abundant vacuolar spaces in the seminiferous epithelium at 1 mg/kg/day (quantitative data not reported). Additionally, the number of apoptotic cells was significantly increased by 1.9- and 3-fold in the testes of rats from the 0.03 and 1 mg/kg/day groups, respectively, and the mRNA levels of several apoptosis genes were elevated in a dose-related manner. Daily sperm production was significantly decreased by 23% in the 1 mg/kg/day group, compared with controls. Serum testosterone was significantly decreased by ~34, 53, and 62% in the 0.001, 0.03, and 1 mg/kg/day groups, respectively, compared with controls. No exposure-related changes were observed in serum E2, FSH, or LH levels. Testicular ROS levels were significantly elevated at 1 mg/kg/day, compared with controls.

Dose and end point used for MRL derivation: 0.001 mg/kg/day

[ ] NOAEL [X] LOAEL [ ] $BMDL_{1SD}$

BMD modeling was performed on the serum testosterone data to assess suitability of this approach for determining the POD. Since testosterone data were presented graphically, GrabIt! software was used to extract the means and standard deviations. The data are shown in Table A-1.

Table A-1. Digitally Extracted Serum Testosterone Levels Following Exposure to BDE 47 (Zhang et al. 2013b)

Dose (mg/kg)	Mean testosterone level (ng/mL)	Standard deviation (ng/mL)
0	9.8	0.8
0.001	6.5	1.6
0.03	4.6	1.1
1	3.7	1.5

Modeling was performed using the reference benchmark response (BMR) of 1 standard deviation change from the mean (1SD). Results are shown in Table A-2 and Figure A-1.

Table A-2. Modeling Results for Decreased Serum Testosterone Levels Following Exposure to BDE 47 (Zhang et al. 2013b)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg)	$BMDL_{1SD}$ (mg/kg)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Exponential (model 2)[d]	<0.0001	0.14	<0.0001	-3.34	0.20	3.96	108.73	0.54	0.32
Exponential (model 3)[d]	<0.0001	0.14	<0.0001	-3.34	0.20	3.96	108.73	0.54	0.32
Exponential (model 4)[d]	<0.0001	0.14	0.11	0.00	0.00	1.13	66.79	0.0003	0.0002
Exponential (model 5)[d]	<0.0001	0.14	N/A	0.00	0.00	1.13	68.79	0.0003	0.0002
Hill[d]	<0.0001	0.14	0.18	0.02	-0.10	1.00	66.09	0.0002	0.0001
Linear[e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45
Polynomial (2-degree)[e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45
Polynomial (3-degree)[e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45
Power[d,e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BDE = brominated diphenyl ether; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation

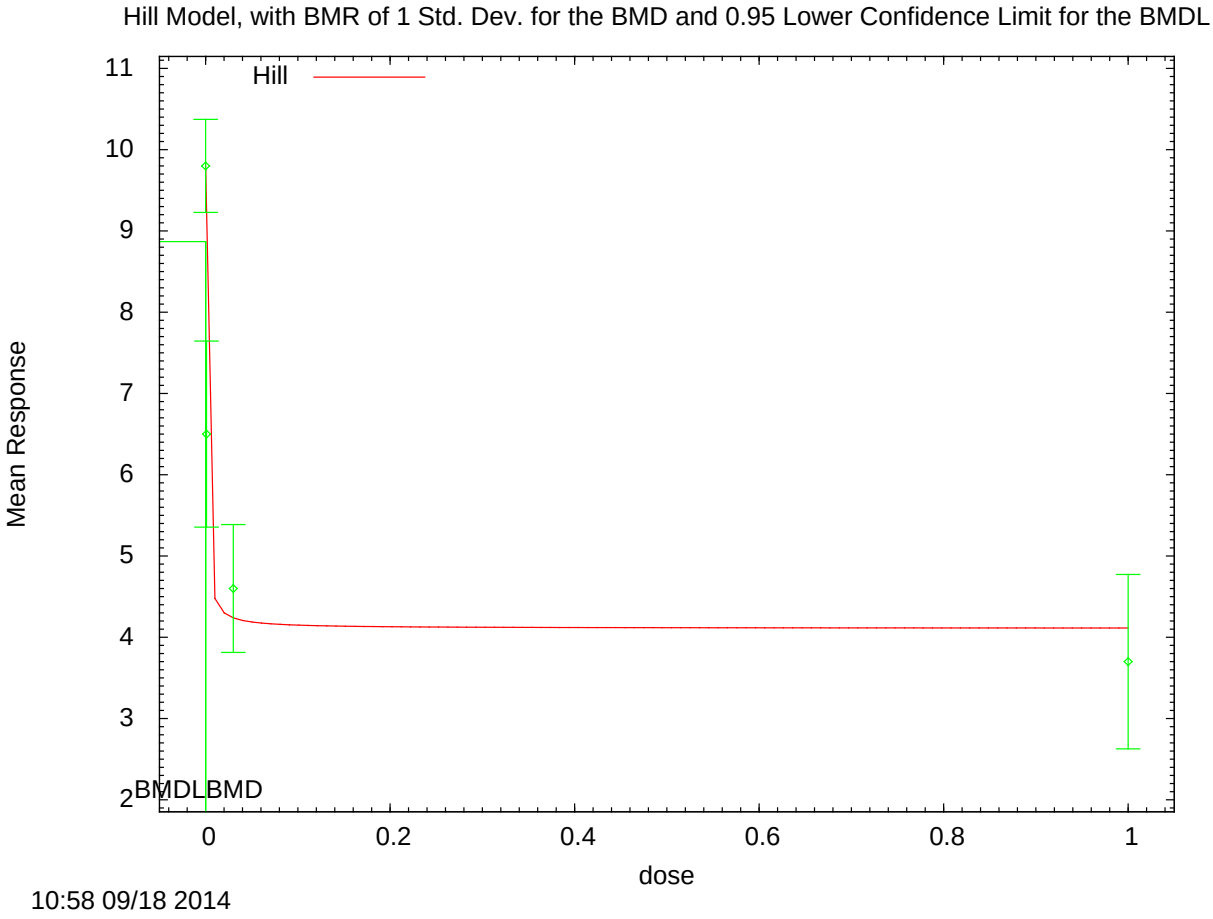

Figure A-1. Fit of Hill Model to Data for Decreased Serum Testosterone Levels Following Exposure to BDE 47 (Zhang et al. 2013b)

Goodness-of-fit statistics indicate inadequate fit to the data for all models except the Exponential 4 and Hill models, which were considered unsuitable for use in MRL derivation because they did not provide reliable information about the shape of the dose-response curve. For example, using the BMR of 1SD, the BMD, which should be within the range of the data points for best model performance, is a full order of magnitude lower than the lowest dose used in the study. When an alternate BMR of 50% change from the mean (50RD) was used in order to get the BMD within the range of observation, the BMDL calculation failed (data not shown). The observed instability in the BMD and BMDL calculations indicates that the model is not suitable for use in MRL derivation.

In the absence of a suitable model, the minimal LOAEL of 0.001 mg/kg/day for decreased serum testosterone was chosen as the POD for MRL derivation; no NOAEL was identified. The change in testosterone is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, this statistically significant reduction in serum testosterone is considered an early indication of damage to the male reproductive system, considering the additional effects observed at ≥0.03 mg/kg/day (histological lesions in testes, sperm effects).

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage study).

Was a conversion used from intermittent to continuous exposure? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: One additional rat study and a mouse study reported histopathological changes in the testes following intermediate-duration exposure to tetraBDE at ≥0.03 mg/kg/day; neither study evaluated serum testosterone levels (Huang et al. 2015; Wang et al. 2013). In the rat study, a NOAEL of 0.001 mg/kg/day and a LOAEL of 0.03 mg/kg/day were identified for increased epithelial thickness and spermatocyte apoptosis in the testes of males exposed to BDE 47 for 8 weeks via gavage (Huang et al. 2015). In the mouse study, a NOAEL of 0.0015 mg/kg/day and a LOAEL of 0.045 mg/kg/day were identified for germ cell loss and increased apoptosis in the testes of males exposed to BDE 47 for 30 days via gavage (Wang et al. 2013). Testis sections in control and 0.0015 mg/kg/day groups were normal. In the 0.045, 0.15, and 30 mg/kg/day groups, "some" seminiferous tubules exhibited complete germ cell loss and had a Sertoli cell-only phenotype (no incidence data reported). No exposure-related changes were observed in Leydig cells. The TUNEL assay showed a significant, dose-related increase in the number of apoptotic cells. Quantitative data were not reported; however, from the qualitative figures, it appears that apoptotic cells were observed at doses ≥0.045 mg/kg/day.

No other study evaluated testicular histopathology or serum testosterone levels in male laboratory animals following exposure to tetraBDE (BDE47). Following intermediate exposure to other congeners, no changes in testicular histology were observed in rats exposed to commercial pentaBDE mixtures (Bromkal 70-5 DE; DE-71) at gavage doses up to 250 mg/kg/day for 15–28 days (Becker et al. 2012; Oberg et al. 2010), commercial penta- or octaBDE mixtures (DE-71, unspecified octa mixture) at dietary doses up to 750 mg/kg/day for 28–90 days (IRDC 1976, 1977; WIL Research Laboratories 1984), or a dietary PBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) at doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012). However, testicular apoptosis was not evaluated in any of these studies. Serum testosterone was significantly decreased by 40–45% in rats exposed once to BDE 99 at 0.06 or 1.2 mg/kg (Alonso et al. 2010). Other studies evaluating serum testosterone levels after intermediate-duration exposure to lower-brominated PBDEs mixtures (DE-71, dietary PBDE mixture described above) did not report exposure-related decreases (Becker et al. 2012; Ernest et al. 2012; Stoker et al. 2005). These data suggest that individual congeners (BDE 47, BDE 99) may have a greater capacity to alter serum testosterone levels than PBDE mixtures.

One-generation studies of the BDE 47 congener reported developmental effects at ≥0.03 mg/kg/day, including:

- Impaired spatial learning in the Barnes maze in PNW 8 offspring of mouse dams fed cornflakes dosed with BDE 47 from pre-mating day 28 through PND 21 (Koenig et al. 2012).

- Decreased center-field activity in an open field (indicating increased anxiety) in PND 60 female offspring from mouse dams fed cornflakes dosed with BDE 47 from pre-mating day 28 through PND 21 (Ta et al. 2011).

- Decreased pre-weaning weight, decreased pup vocalizations on PNDs 8–10, and decreased sociability on PND 72 in female offspring of mouse dams exposed to BDE 47 via gavage from pre-mating day 28 through PND 21 (Woods et al. 2012)

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Polybrominated Diphenyl Ethers (PBDEs) [decabromodiphenyl ether (decaBDE)]
CAS Numbers:	1163-19-5
Date:	February 2017
Profile Status:	Final
Route:	[ ] Inhalation [X] Oral
Duration:	[X] Acute [ ] Intermediate [ ] Chronic
Graph Key:	12
Species:	Mouse

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm [ ] mg/m^3

References: Johansson N, Viberg H, Fredriksson A, et al. 2008. Neonatal exposure to deca-brominated diphenyl either (PBDE 209) causes dose-response changes in spontaneous behavior and cholinergic susceptibility in adult mice. Neurotoxicology 29:911-919.

Buratovic S, Viberg H, Fredriksson A, et al. 2014. Developmental exposure to the polybrominated diphenyl ether PBDE 209: Neurobehavioural and neuroprotein analysis in adult male and female mice. Environ Toxicol Pharmacol 38(2):570-585.

Experimental design: In the first study (Johansson et al. 2008), neonatal male mice (3–4 litters/group) were given single doses of 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209, 98% purity) at 0, 1.34, 2.22, 13.4, or 20.1 mg/kg via gavage in a 20% fat emulsion vehicle (1:10 mixture egg lecithin and peanut oil) on PND 3. Mice were observed for clinical signs of toxicity and body weight was measured at PND 3 and PNW 4. Spontaneous motor behavior (locomotion, rearing, total activity) was evaluated in an open field at 2 months (10 mice/group) and 4 months (16 mice/group). Motor activity was measured during a 60-minute period, divided into three 20-minute intervals. Nicotine-induced behavior was evaluated at 4 months following single subcutaneous injections of 80 µg nicotine/kg (8/group) or 10 mL 0.9% NaCl/kg (8/group). Anxiety was assessed at 4 months using the elevated plus maze.

In the second study (Buratovic et al. 2014), neonatal male mice (6 litters/group; 31–40 males and 23–34 females per group) were administered 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209, >95% purity) at doses of 0, 1.34, 5.76, or 13.4 mg/kg via gavage in a 20% fat emulsion vehicle (1:10 mixture egg lecithin and peanut oil) on PND 3. Mice were observed for clinical signs of toxicity and body weight changes throughout the study (no further details were provided). Spontaneous motor behavior (locomotion, rearing, total activity) was evaluated in an open field at 2 months (18/sex/group). Motor activity was measured during a 60-minute period, divided into three 20-minute intervals. Directly after spontaneous motor evaluation, 9/sex/group were injected with a cholinergic agent (0.25 mg/kg paraoxon in males, 80 µg/kg nicotine in females), while the other 9/sex/group were injected with 0.9% saline, for evaluation of cholinergic-induced locomotion. At 4 months, spontaneous behavior was assessed again in the saline-injected animals only (9 males/group at all doses and 9 females/group in the control and high-dose group only). Learning and memory was assessed using the Morris water maze at 5 and 7 months in 13–15 males from the 0, 5.76, and 13.4 mg/kg groups only (the same mice were evaluated at each time point). Male and female mice were sacrificed at 7 months. The cerebral cortex and hippocampus from control and high-dose males and females were removed and processed for neuroprotein analysis using Western blot.

Effects noted in study and corresponding doses:

Study 1 (Johansson et al. (2008): No clinical signs of toxicity or body weight effects were observed. At 2 months, significantly decreased locomotion, rearing, and total activity were observed during the first 20-minute interval of the open field assessment in mice exposed to ≥2.22 mg/kg, compared with controls. However, during the third 20-minute interval, when activity should decrease due to habituation, locomotion, rearing, and total activity were significantly increased in mice exposed to ≥13.4 mg/kg. None of the end points measured were significantly altered at 1.34 mg/kg. At 4 months, significantly decreased locomotion, rearing, and total activity were observed during the first interval of the open field assessment in mice exposed to ≥2.22 mg/kg, compared with controls. During the third interval, significantly increased locomotion, rearing, and total activity were observed in mice exposed to ≥2.22 mg/kg. Additionally, total activity, but not rearing or locomotion, was significantly decreased during the first 20-mintue interval in the 1.34 mg/kg group; no significant changes were observed during the third interval in the 1.34 mg/kg group. Statistical analysis shows that habituation ability declined in mice exposed to ≥2.22 mg/kg from 2 to 4 months of age. At 4 months, nicotine exposure caused significantly decreased activity during the first interval in mice exposed to ≥13.4 mg/kg, compared with saline-injected mice from the same decaBDE exposure group. This finding is the opposite of the expected increase in activity due to nicotine exposure, which was observed in controls and lower dose decaBDE groups. During third interval, mice exposed to ≥13.4 mg/kg and nicotine showed impaired habituation. No exposure-related effects were observed in the elevated plus maze assessment.

Study 2 (Buratovic et al. 2014): No clinical signs of toxicity or body weight effects were observed. In spontaneous activity assessment, a dose-related decrease in locomotion, rearing, and total activity was observed during the first 20 minutes of open field testing in a novel environment at 2 months. Decreases were significant at all doses tested in both sexes; however, findings were only dose-related for total activity. However, during the third 20-minute interval, when activity should decrease due to habituation, locomotion, rearing, and total activity were significantly increased in males and females at ≥5.76 mg/kg. At 2 months, cholinergic agents caused decreased activity during the first interval in mice exposed to ≥5.76 mg/kg, compared with saline-injected mice from the same decaBDE exposure group. This finding is the opposite of the expected increase in activity due to paraoxon or nicotine exposure, which was observed in controls and low-dose decaBDE groups. During the third interval, mice exposed to ≥5.76 mg/kg and cholinergic agent showed impaired habituation. At 4 months, total activity during the first 20 minutes was still significantly decreased at all doses in males, and locomotion and rearing were significantly decreased in males in the mid- and high-dose groups only; all three parameters were significantly decreased in high-dose females (other doses not evaluated). All three parameters were significantly increased in high-dose males and females during the third 20-minute period, indicating decreased habituation; locomotion and rearing were also slightly, but significantly, increased in mid-dose males. In the Morris water maze, initial learning was comparable between exposed and control mice at 5 and 7 months. However, latencies to find the escape platform during the reversal learning phase (learning to find the escape platform in a new location after initial training) were significantly longer in mid- and high-dose males at 5 and 7 months (other exposure groups not assessed). After sacrifice, significant increases in protein levels of CaMKII, Gap-43, and Tau were observed in the cortex and hippocampus in male mice and increased levels of Tau were observed in the cortex and hippocampus of female mice. No changes in synaptophysin were observed.

Dose and end point used for MRL derivation: 1.34 mg/kg

[X] NOAEL [ ] LOAEL

In the first study (Johansson et al. 2008), a NOAEL of 1.34 mg/kg and a LOAEL of 2.22 mg/kg were determined for the nonhabituating profile (i.e., decreased activity early in the test period and increased

activity late in the test period). The singular finding of decreased total activity during the first 20-minute interval at 4 months in the 1.34 mg/kg group was not considered sufficient to establish a LOAEL of 1.34 mg/kg. The nonhabituating profile, which is a common effect observed with developmental PBDE exposure (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Sand et al. 2004; Viberg et al. 2002, 2003a, 2004a, 2004b), was considered to be a stronger basis for a NOAEL/LOAEL determination. BMD modeling was performed on the habituation ratio (activity during the last 20-minute interval/activity during the first 20-minute interval) at 2 and 4 months reported by Johansson et al. (2008) to assess suitability of this approach for determining the POD. However, none of the models provided an adequate fit with constant or nonconstant variance.

In the second study (Buratovic et al. 2014), a NOAEL of 1.34 mg/kg and a LOAEL of 5.76 mg/kg were determined for the nonhabituating profile (i.e., decreased activity early in the test period and increased activity late in the test period). Similar to the Johansson et al. (2008) study, the finding of decreased total activity during the first 20-minute interval at 2 and 4 months in the 1.34 mg/kg group was not considered sufficient to establish a LOAEL of 1.34 mg/kg. The nonhabituating profile was considered to be a stronger basis for a NOAEL/LOAEL determination, and additional neurological effects (impaired learning, altered response to cholinergic agents) support a LOAEL of 5.76 mg/kg. The quantitative habituation ratio was not reported by Buratovic et al. (2014); therefore, BMD modeling was not performed for this study.

Uncertainty factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage study).

Was a conversion used from intermittent to continuous exposure? Not applicable (single exposure study).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: In a similar study, decreased spontaneous activity and impaired habituation were also observed in 2- and 6-month-old mice exposed to BDE 209 at doses ≥2.22 mg/kg on PND 3 (lowest dose tested) (Viberg et al. 2003b). These effects were not observed if exposure was on PND 10 or 19 at doses up to 20.1 mg/kg (Viberg et al. 2003b). Additionally, decreased spontaneous activity was observed in 2-month-old rats following exposure to BDE 209 doses ≥6.7 mg/kg on PND 3 (lowest dose tested) (Viberg et al. 2007). At 20.1 mg/kg, impaired habituation and decreased nicotine-induced behavior were also observed. This nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) is consistent with neurobehavioral alterations observed following early postnatal exposure to lower-brominated PBDEs and has been reported in adult mice neonatally exposed to certain PCB congeners (see Acute MRL Worksheet for lower-brominated PBDEs for more details).

Additional neurodevelopmental effects observed in mice following acute exposure to BDE 209 from PND 2 to 15 at 20 mg/kg/day via micropipette include delayed ontogeny of reflexes, increased locomotion in males at PND 70, and learning impairment and impulsivity at 16 months, but not at 3 months (Rice et al. 2007, 2009). In rats, impaired learning was observed in Morris water maze in PND 25 rat offspring of dams exposed to BDE 209 from GD 1 to 14 at doses ≥30 mg/kg/day via gavage (Chen et al. 2014).

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs) [decabromodiphenyl ether (decaBDE)]
CAS Numbers: 1163-19-5
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 29
Species: Rat

Minimal Risk Level: 0.0002 ($2x10^{-4}$) [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Zhang Z, Sun ZZ, Xiao X, et al. 2013a. Mechanism of BDE 209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. Arch Toxicol 87(8):1557-1567.

Experimental design: Adult male rats were administered 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether (BDE 209) at 0, 0.05, 1, or 20 mg/kg/day daily via gavage in corn oil for 8 weeks. Rats were observed for clinical signs of toxicity and body weights were measured every 3 days. Rats were fasted for 24 hours after the final gavage treatment, and then sacrificed. Body weights and heart, spleen, lung, kidney, and liver weights were recorded. Blood was collected for clinical chemistry analysis (serum total cholesterol, triglycerides, glucose, insulin, and TNF-α) and determination of plasma markers of oxidative stress (MDE, GSH, and SOD). Liver samples from three rats in the control and low-dose (0.05 mg/kg/day) groups were collected for microarray analysis (Affymetrix GeneChip), and gene ontogeny category, pathway, gene-act-network and gene co-expression analyses were conducted. Quantitative real-time-PCR was performed to quantitate gene expression to validate the gene expression data obtained from microarray analysis.

Effects noted in study and corresponding doses: No clinical signs of toxicity or body weight effects were observed. The relative liver weight was significantly decreased at 1 and 20 mg/kg/day by 9% (absolute liver weights were not reported). No changes were observed in relative weights of heart, spleen, lung, or kidney. No exposure-related changes were reported in serum cholesterol or triglyceride levels. Serum glucose levels were significantly increased by 12, 18, and 21% in 0.05, 1, and 20 mg/kg/day groups, compared with controls. Serum insulin was significantly decreased by 50–60% at 1 and 20 mg/kg/day. Subsequent to this finding, the pancreas was evaluated histologically. Consistent with the insulin findings, morphological changes at 1 and 20 mg/kg/day included blurred boundaries among pancreatic islet cells (quantitative data not reported). Plasma SOD activity was significantly decreased in all exposed groups and plasma GSH was significantly decreased at 1 and 20 mg/kg/day. Serum TNF-α was significantly increased at 1 and 20 mg/kg/day.

BDE 209 induced 1,257 liver gene transcript changes, and 18 canonical pathways were significantly enriched. Four of them were involved in immune diseases, including autoimmune thyroid disease, graft-versus-host disease, allograft rejection, and T1DM. Subsequently, gene act network and gene coexpression network found that some major histocompatibility complex molecules and TNF-α were involved in the T1DM pathway.

Dose and end point used for MRL derivation: 0.05 mg/kg/day

[ ] NOAEL [X] LOAEL [ ] $BMDL_{1SD}$

BMD modeling was performed on the serum glucose data to assess suitability of this approach for determining the POD. Modeling was performed using the reference BMR of one standard deviation change from the mean (1SD), as well as an alternate BMR of 20% change from the mean (RD20). The alternate BMR of RD20 was identified by the reference value range for rat glucose levels, which varies ~20% around the mean (reference mean [range] = 118.1 mg/dL [77–141 mg/dL]; Charles River Laboratories 1998). Results are shown in Table A-3 and Figure A-2.

Table A-3. Modeling Results for Increased Serum Glucose Levels Following Exposure to BDE 209 (Zhang et al. 2013a)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg)	$BMDL_{1SD}$ (mg/kg)
Constant variance									
Exponential (model 2)[d]	0.0006	0.71	0.0009	2.09	-0.10	-2.66	46.79	18.09	11.79
Exponential (model 3)[d]	0.0006	0.71	0.0009	2.09	-0.10	-2.66	46.79	18.09	11.79
Exponential (model 4)[d]	0.0006	0.71	0.33	0.00	0.00	0.68	35.65	0.04	0.01
Exponential (model 5)[d]	0.0006	0.71	N/A	0.00	0.00	0.68	37.65	0.04	0.01
Hill[d,e]	0.0006	0.71	0.41	-0.01	0.08	-0.61	35.37	0.03	0.006
Linear[f]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
Polynomial (2-degree)[f]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
Polynomial (3-degree)[f]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
Power[d,e]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
								BMD_{RD20} (mg/kg)	$BMDL_{RD20}$ (mg/kg)
Hill[d,f]	0.0006	0.71	0.41	0.54	NA	-0.61	35.37	21.84	0.05

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. With constant variance model applied, the only models that provided adequate fit to the means were the Exponential (model 4) and the Hill models. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Hill model).
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BDE = brominated diphenyl ether; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = exposure concentration associated with 10% extra risk); NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); RD = relative deviation; SD = standard deviation

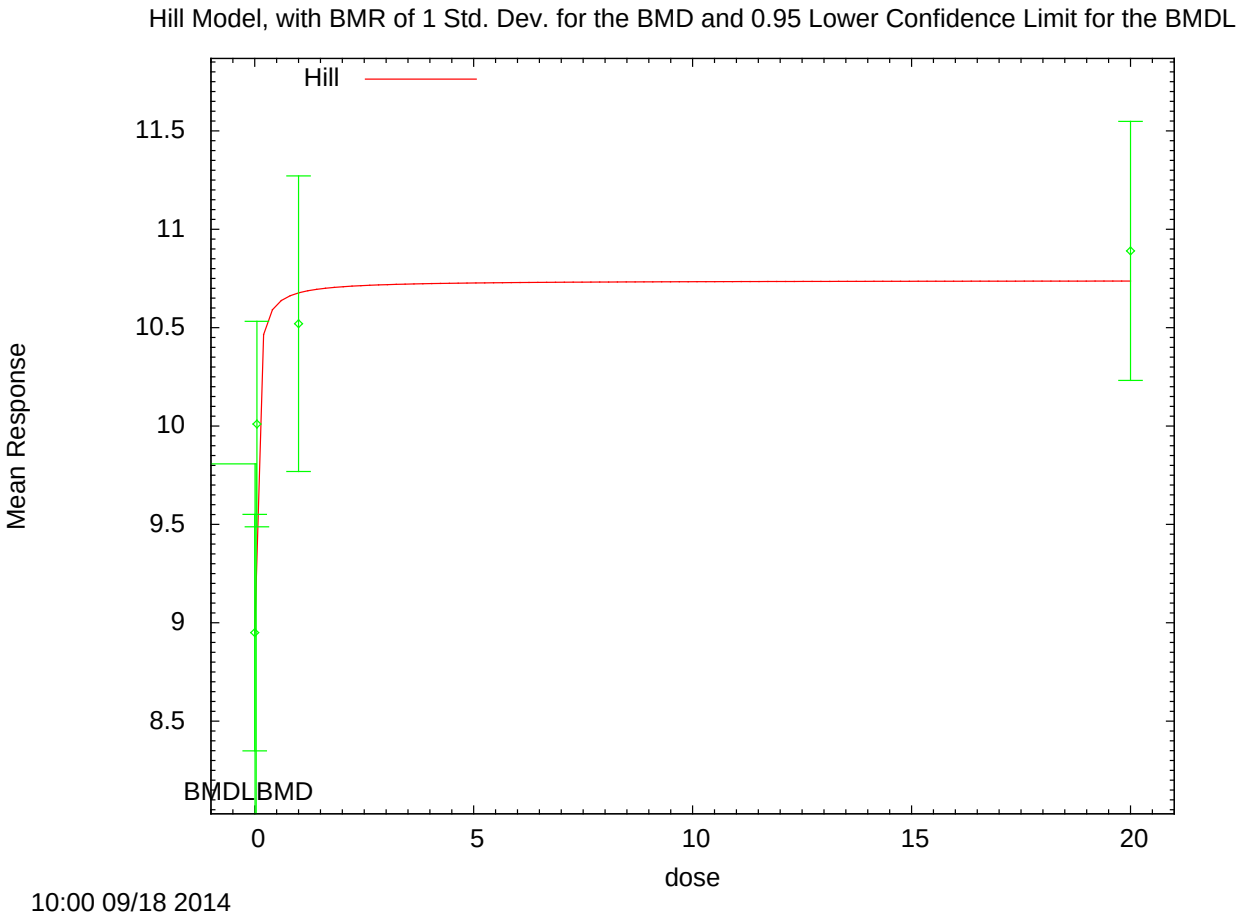

Figure A-2. Fit of Hill Model to Data for Increased Serum Glucose Levels Following Exposure to DecaBDE (Zhang et al. 2013a)

Goodness-of-fit statistics indicate inadequate fit to the data for all models except the Exponential 4 and Hill models, which were considered unsuitable for use in MRL derivation because they did not provide reliable information about the shape of the dose-response curve. For example, using the reference BMR of 1SD change from the mean, the ratio of BMD:BMDL is 5 for the Hill model (0.03/0.006) and 4 for the Exponential Model 4 (0.04/0.01). These values are quite high and suggest that the data do not permit accurate estimation of the BMDL. Using the BMR of RD20 for the Hill model, the ratio was much higher still (21.84/0.05=437). The fact that this ratio changes so much with BMR underscores the instability in the BMDL estimates using this model.

In the absence of a suitable model, the minimal LOAEL of 0.05 mg/kg/day based on a 12% increase in serum glucose was chosen as the POD for MRL derivation. The change in glucose is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, the increase in serum glucose is considered to be part of a spectrum of effects indicative of altered insulin homeostasis and toxicity to the pancreas, including decreased serum insulin and morphological changes in pancreatic islet cells observed at ≥1 mg/kg/day, following BDE 209 exposure.

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage study).

Was a conversion used from intermittent to continuous exposure? Not applicable (doses administered daily).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The association between PBDE-exposure and diabetes has been evaluated in a few human studies. An analysis of cross-sectional NHANES data showed a significant increase in risk of diabetes associated with serum levels of BDE 153 (but not BDE 28, BDE 47, BDE 99, or BDE 100; BDE 209 was not assessed), although the risk was higher with exposure to 50–75th percentile BDE 153 levels than >75th percentile BDE 153 levels (Lim et al. 2008). Serum BDE 153 concentrations (but not BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, or BDE 154) were also shown to be significantly associated with increased odds of developing gestational diabetes in a cohort of 258 pregnant women; again, BDE 209 was not assessed (Smarr et al. 2016). However, other cross-sectional and prospective studies found no relationship between serum PBDE concentrations and diabetes in an adult cohort from Wisconsin (Turyk et al. 2015), an elderly cohort in Finland (Airaksinen et al. 2011), or an elderly cohort in Sweden (Lee et al. 2011).

Only one other animal study evaluated the pancreas following decaBDE exposure. In rats exposed to BDE 209 via gavage for 28 days at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day, slight or moderate insulitis was observed in the Langerhan's islets of the "majority of samples," but findings were not exposure-related (Van der ven et al. 2008a). Similarly, no exposure-related effects were observed for serum glucose levels (Van der ven et al. 2008a). The only other study evaluating serum glucose levels after decaBDE exposure instead reported reduced serum glucose levels in male rats exposed to 20 mg/kg/day of a dietary PBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) for 70 days (Ernest et al. 2012). The observed decreased glucose levels could be due to the pentaBDE component, as male rats exposed to the commercial pentaBDE mixture DE-71 at doses of 0.27–200 mg/kg/day for 28 days also showed decreased glucose levels; study authors did not report the lowest dose at which glucose levels were significantly lower in male rats, but they reported a BMD_{10RD} of 179.55 mg/kg/day and a $BMDL_{10RD}$ of 66.7 mg/kg/day (Van der ven et al. 2008b). Other effects occurred at doses 4–40-fold higher than the observed pancreatic and related effects:

- A LOAEL of 2 mg/kg/day was identified for transient histopathological effects in the liver of male offspring and kidney of female offspring of rat dams exposed to BDE 209 from GD 10 to PND 21 (no NOAEL identified) (Fujimoto et al. 2011).

- A LOAEL of 10 mg/kg/day was identified for hepatocytic swelling in the liver, vacuolization in the interstitial cells of testes, and sperm damage in PND 71 male offspring of mouse dams exposed to BDE 209 from GD 0 to 17 (no NOAEL identified) (Tseng et al. 2008, 2013).

- A LOAEL of 20 mg/kg/day was identified for decreased anxiety in mice treated with BDE 209 by daily gavage for 15 days (no NOAEL identified) (Heredia et al. 2012).

- A LOAEL of 20.1 mg/kg/day was identified for altered hippocampal electrophysiology in rats exposed to BDE 209 from GD 1 to PND 41, PNDs 1–21, or PNDs 22–41 (no NOAEL identified) (Xing et al. 2009).

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

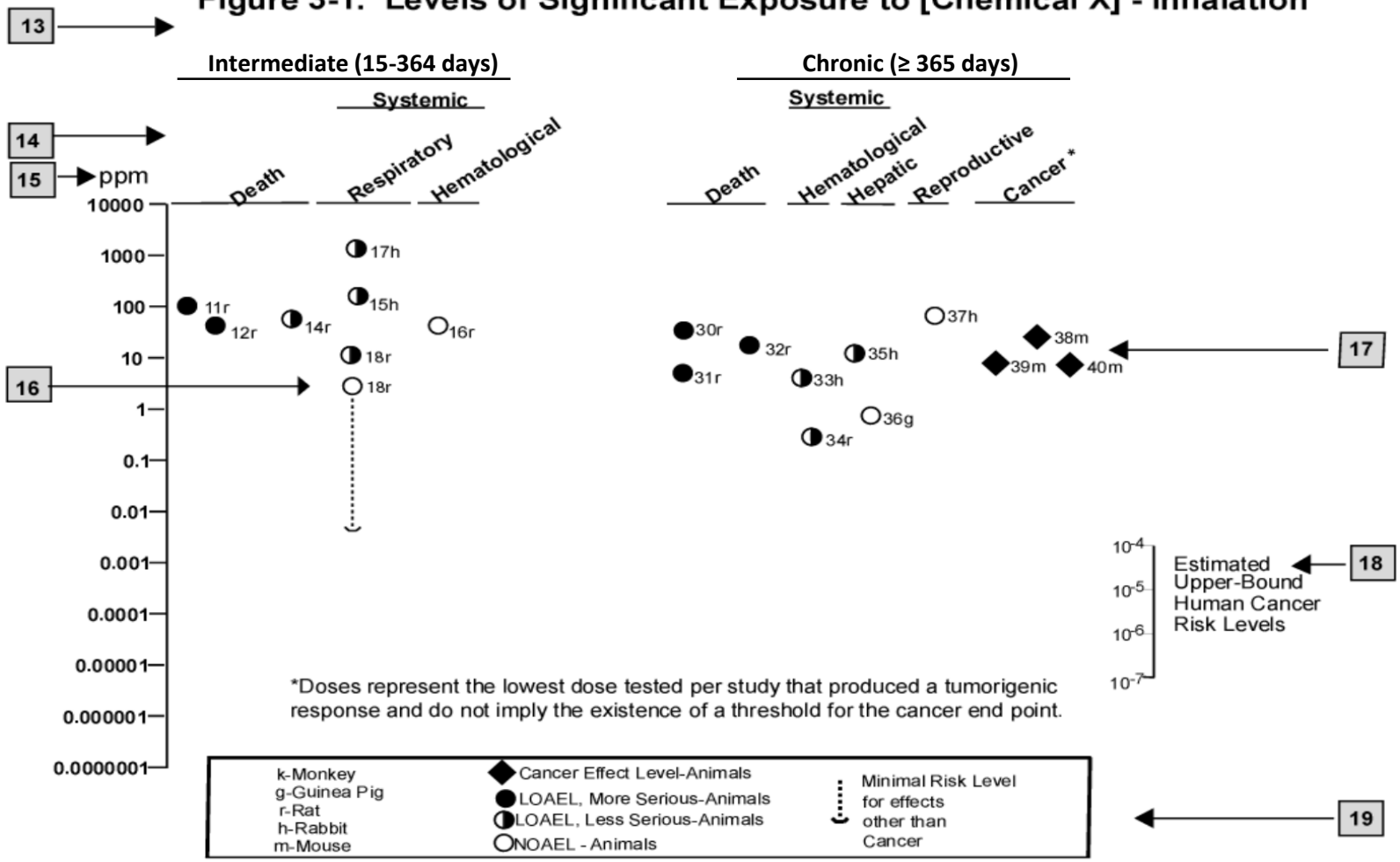
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result