MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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November 25, 2015

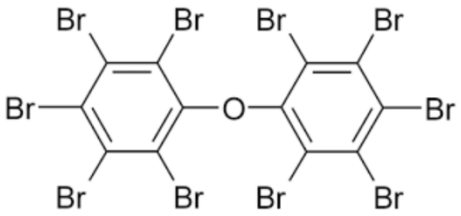
To: File for Decabromodiphenyl Ether (CAS No. 1163-19-5)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Updates

The Initial Threshold Screening Level (ITSL) for decabromodiphenyl ether (DBDPE) is 25 µg/m^3 with 24-hr averaging time. The Initial Risk Screening Level (IRSL) for DBDPE is 5 µg/m^3 and the Secondary Risk Screening Level (SRSL) is 50 µg/m^3; both with annual averaging time.

Molecular Structure of DBDPE:



Summary of Non-Cancer Animal Studies (from EPA, 2008)

The effect of DBDPE on spontaneous motor behavior of NMRI male mice was investigated in adult animals exposed as neonates to a single oral dose of DBDPE (Viberg et al., 2003). Male mice were given on postnatal day (PND) 3 or 19 single doses of 0, 2.22, or 20.1 mg/kg body weight DBDPE (>99% purity) in a fat emulsion. Ten-day-old mice received 0, 1.34, 13.4, or 20.1 mg/kg. The spontaneous behavior test (measuring locomotion, rearing, and total activity) was conducted in 10 male mice randomly selected from three to five litters in each treatment group at 2, 4, and 6 months of age. The behavior variables were measured for a 60 minute period, divided into three consecutive 20 minute periods. Treatment with DBDPE caused no clinical signs of toxicity at any time during the experimental period. The only effect noted in mice exposed to 2.22 mg/kg was a significant decrease in total activity in the first 20 minute test period compared with the controls at 2 months of age. Mice exposed neonatally up to 20.1 mg/kg on either PND 10 or 19 did not show any significant differences in any of the variables after 2, 4, or 6 months, compared with controls. The authors indicated that the absence of effects on spontaneous activity in mice treated on PNDs 10 and 19 suggests that there is a critical window for the induction of the observed behavioral disturbances. The NOAEL in this study was 2.22 mg/kg, and the lowest-observed-adverse-effect level (LOAEL) was 20.1 mg/kg for significant changes in spontaneous motor behavior and decreased habituation capability for locomotion, rearing, and total activity, worsening with increasing age.

Rice et al. (2007) examined the effects on developmental milestones, sensorimotor behaviors, serum thyroxine (T4) levels, and locomotor activity in male and female C57BL6/J mice administered DBDPE (99.5% purity) from a micropipette in doses of 0, 6, or 20 mg/kg-day from PNDs 2-15. There were no delays in postnatal developmental milestones (pinna detachment, incisor eruption, eye opening, vaginal opening, or testes descent) from DBDPE treatment in male or female mice. The authors developed a special functional observational battery (FOB) to examine a series of home-cage, reflexive, and sensorimotor behaviors, measured on PND 14, 16, 18, or 20. Three of the FOB endpoints were affected by DBDPE exposure at 6 and 20 mg/kg-day: palpebral reflex, forelimb grip, and struggling behavior during handling. Locomotor activity declined over the course of the 2-hour assessment in PND 70 males and females in the control and treated groups. However, the rate of decline was significantly different in male mice exposed to 6 and 20 mg/kg-day compared with control animals, an effect that was most pronounced in the high-dose males during the first 1.5 hours of the 2-hour activity session. The LOAEL in this study was 6 mg/kg-day, the lowest dose tested, for decrease in the percent of male and female pups performing the palpebral reflex, increased struggling behavior of male mice, decreased T4 levels in male mice, and effects on locomotor activity of male mice on PND 70.

In a 2-year study, male and female F344/N rats were exposed to DBDPE (94-97% purity) at doses of 0, 1,120, or 2,240 mg/kg-day for male rats and 0, 1,200, or 2,550 mg/kg-day for female rats (NTP, 1986). Exposure to DBDPE in the diet did not cause compound-related effects on survival or any significant effects on body weight or food consumption. However, treatment resulted in several nonneoplastic changes in high-dose males, including thrombosis and degeneration of the liver, fibrosis in the spleen, and lymphoid hyperplasia in the mandibular lymph nodes. Based on these results, a NOAEL for systemic toxicity was 1,120 mg/kg-day, and the LOAEL was 2,240 mg/kg-day. Female rats appeared to be less sensitive to the systemic toxicity of DBDPE, and the NOAEL in female rats was 2,550 mg/kg-day, the highest dose tested.

Derivation of the Reference Dose (RfD)

EPA (2008) based the RfD on a mouse study by Viberg et al. (2003) where a single dose of DBDPE was given on postnatal day (PND) 3 or 19 in single doses of 0, 2.22, or 20.1 mg/kg body weight. The No-Observed-Adverse-Effect-Level (NOAEL) in this study was 2.22 mg/kg, and the Lowest-Observed-Adverse-Effect Level (LOAEL) was 20.1 mg/kg for significant changes in spontaneous motor behavior and decreased habituation capability for locomotion, rearing, and total activity, worsening with increasing age. EPA applied a total uncertainty factor (UF) of 300 to the NOAEL to derive the RfD.

RfD = NOAEL/(10x10x3)
RfD = 2.2 mg/kg/300
RfD = 0.0073 mg/kg x 1000µg/mg
RfD = 7 µg/kg

EPA (2008) applied a 10-fold UF_A to account for laboratory animal to human interspecies differences. A default intraspecies UF_H of 10 was applied to account for variations in susceptibility within the human population (intrahuman variability). A

threefold UF_S was used to adjust for exposure duration. EPA (2008) stated that the UF_S was viewed as a dosing duration adjustment rather than simply a comparison of the effects of a subchronic to a chronic exposure. A threefold UF_S was applied because the critical study dosed the animals only once within the hypothesized critical window.

Pursuant to Rule 232(1)(b) the ITSL can be derived from the RfD as follows:

$$ITSL = RfD \times 70kg/20m^3$$
$$ITSL = 7\ \mu g/kg \times 70kg/20m^3$$
$$ITSL = 25\ \mu g/m^3$$

Pursuant to Rule 323(2)(b) the averaging time is 24-hours. A 24-hr averaging time was applied based on the nature and duration of the key study and the ITSL value derivation.

Derivation of the Initial Risk Screening Level and Inhalation Unit Risk for Cancer
The details of the derivation of the OSF are described in US EPA (2008); excerpts are provided below:

Oral Slope Factor: 7×10^{-4} per mg/kg-day
Dose-Response Data (Carcinogenicity, Oral Exposure)
Tumor Type: Liver neoplastic nodules or carcinoma (combined)
Test Species: Male F344/N rats
Route: Oral, diet
Reference: NTP (1986)
Extrapolation Method: Multistage model with linear extrapolation from the point of departure (LED12)

Summary of National Toxicology Program (NTP, 1986) as quoted by US EPA (2015)

Groups of male and female F344/N rats were exposed to decaBDE (94-97% purity) in the diet at doses of 0, 1,120, or 2,240 mg/kg-day for male rats and 0, 1,200, or 2,550 mg/kg-day for female rats (NTP, 1986). No clinical signs of toxicity were observed in the treated rats. Statistically significant increases in the incidence of neoplastic nodules in the liver were observed at both treatment doses in males and at the high dose in females, providing some evidence of carcinogenicity of decaBDE. The incidence of hepatocellular carcinomas was low in male and female rats.

At the time the NTP (1986) study was conducted, the term neoplastic nodule was used to describe abnormal cellular masses in the livers of rats, characterized by loss or distortion of normal cellular architecture (Maronpot et al., 1986). Some of those nodules would now be described as benign hepatocellular adenomas in rats (Wolf and Mann, 2005). However, there is no complete equivalency between the neoplastic nodule of the past and hepatocellular adenoma term of today. Some of the neoplastic nodules from the NTP (1986) study might now be classified as foci of cellular alteration or hyperplasia rather than adenomas (Maronpot et al., 1986). Adenomas and foci of cellular alteration are considered to be preneoplastic lesions, whereas hyperplastic lesions represent secondary nonneoplastic changes (Maronpot et al., 1986). The assumption that the hepatic neoplastic nodules from the NTP (1986) bioassay are

equivalent to hepatic adenomas under the current NTP lexicon is a conservative interpretation of the data.

Groups of male and female B6C3F1 mice were administered decaBDE (94-97% purity) in the diet at doses of 0, 3,200, or 6,650 mg/kg-day in male mice and 0, 3,760, or 7,780 mg/kg-day in female mice. No clinical signs of toxicity were observed in the treated mice. The combined incidence of hepatocellular adenomas or carcinomas in male mice significantly increased at low dose and increased marginally at high dose. In the thyroid gland, significant increases in the incidence of follicular cell hyperplasia, considered by many as a precursor to thyroid tumors, was observed in males but not in females. Thyroid gland follicular cell adenomas or carcinomas (combined) were slightly, but not significantly, increased in treated mice of both sexes over the corresponding control mice.

The oral slope factor is derived from the LED_{12}, the 95% lower bound on the exposure associated with a 12% extra cancer risk, by dividing the risk (as a fraction) by the LED_{12}, and represents an upper bound, continuous lifetime exposure risk estimate: LED_{12}, lower 95% bound on exposure at 12% extra risk = 178 mg/kg-day. The slope of the linear extrapolation from the LED_{12} = 0.12/178 mg/kg-day = 0.0007 per mg/kg-day. ED_{12}, central estimate of exposure at 12% extra risk = 263 mg/kg-day. The slope of the linear extrapolation from the ED_{12} = 0.12/263 mg/kg-day = 0.0005 per mg/kg-day.

Drinking Water Concentrations and Incidence Levels from NTP (1986) (from US EPA, 2015)

Administered dose (mg/kg-day)	Human equivalent dose[a] (mg/kg-day)	Incidence of liver neoplasticnodules and carcinomas (combined)
0	0	2/50 (4%)
1120	305	8/50 (16%)
2240	608	15/49 (31%)

[a] A body weight $(bw)^{3/4}$ scaling factor was used to convert the administered dose in the rat study to human equivalent dose (HED):
HED=administered dose x (body weight of animal/body weight of human)$^{0.25}$.
Body weight of human is assumed to be 70 kg. Body weights of rats were calculated from reported weekly body weight data.

The Oral Slope Factor (OSF) of 7 x10^{-4} per mg/kg-day was calculated by U.S. Environmental Protection Agency (US EPA, 2008). The Inhalation Unit Risk were calculated from the OSF of 7 x10^{-4} per mg/kg-day, pursuant to Rule 231(3)(f)(ii) as follows:

IUR = OSF x 20m^3/70kg x 1 mg/1000 µg
IUR = (7 x10^{-4} per mg/kg-day) x 20m^3/70kg x 1 mg/1000µg
IUR = 2E-7 per µg/m^3

The IRSL and SRSL were calculated from the IUR as follows:

IRSL = 1E-6/IUR SRSL = 1E-5/IUR
IRSL = 1E-6/2E-7 per µg/m^3 SRSL = 1E-5/2E-7 per µg/m^3
IRSL = 5 µg/m^3 SRSL = 50 µg/m^3

The IRSL of 5 µg/m^3 and the SRSL of 50 µg/m^3 have annual averaging time.

References

Maronpot, RR; Montgomery, CA; Boorman, GA; et al. (1986) National Toxicology Program nomenclature for hepatoproliferative lesions of rats. Toxicol Pathol 14(2):263-273.

NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of decabromodiphenyl oxide (CAS No. 1163-19-5) in F344/N rats and B6C3F1 mice (feed studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 309. Available from the National Institute of Environmental Health Sciences, Research Triangle Park, NC, and online at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr309.pdf.

Rice, DC; Reeve, EA; Herlihy, A; et al. (2007) Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. Neurotoxicol Teratol 29:511-520.

US EPA. 2008. 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209) (CASRN 1163-19-5). U.S. Environmental Protection Agency. Integrated Risk Information System. June 2008. Downloaded 11/25/2015 from http://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0035_summary.pdf

Viberg, H; Fredriksson, A; Jakobsson, E; et al. (2003) Neurobehavioral derangements in adult mice receiving decabromodiphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicol Sci 76:112-120.

Wolf, DC, Mann, PC (2005) Confounders in interpreting pathology for safety and risk assessment. Toxicol Appl Pharmacol 202:302-308.