ATSDR's Guidance Values for Polybrominated Diphenyl Ethers (PBDEs) - Update

Hana Pohl[1], Stephen Bosch[2]

[1]Agency for Toxic Substances and Disease Registry
[2]Syracuse Research Corporation

Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR), a U.S. public health agency, derives health-based guidance values called minimal risk levels (MRLs) to assess the public health implications of low-level exposures to substances found at hazardous waste sites. ATSDR's Toxicological Profile for Polybrominated Biphenyls (PBBs) and Polybrominated Diphenyl Ethers (PBDEs) was recently finalized and released to the public[1]. In this document, ATSDR derived MRLs for exposure to PBBs and PBDEs. The acute-duration MRL for oral exposure to PBBs of 0.01 mg/kg/day and the acute- and intermediate-duration MRLs of 0.03 mg/kg/day and 0.007 mg/kg/day, respectively, for oral exposure to PBDEs that previously were presented to this forum[2], remained unchanged following public comments on the draft toxicological profile. The availability of new data enabled ATSDR to derive intermediate-duration inhalation MRLs for inhalation exposure to lower brominated PBDEs and oral exposure to decaBDE. Based on the public comments, ATSDR has considered evaluation of decaBDE separately from the lower brominated PBDEs. Important differences exist between the chemistry and toxicity of decaBDE and those of lower brominated PBDEs. DecaBDE seems to be largely resistant to environmental degradation, whereas octa- and pentaBDE commercial mixture components are likely to undergo differential partitioning and transformation which results in higher occurrence of tetra- and penta-BDEs in environmental samples. Tetra- and pentaBDE congeners are also the main PBDEs in human tissues such as blood, adipose, and breast milk. The preferential accumulation of the lower brominated PBDEs is likely due to their relatively easy absorption, and partitioning and retention in lipid-rich tissues. In contrast, decaBDE is very poorly absorbed (~1% or less of an oral dose) and rapidly eliminated (~99% of the dose within 72 hours). Further, decaBDE is significantly less toxic than lower brominated PBDEs mixtures. For example, intermediate-duration oral studies in rats showed that commercial octa- or pentaBDE mixtures were hepatotoxic at doses as low as 2-10 mg/kg/day, whereas high purity commercial decaBDE caused no hepatotoxicity at doses as high as 8,000-9,500 mg/kg/day[1].

Materials and Methods

ATSDR's guidance values for PBBs and PBDEs were based on robust databases summarized in a toxicological profile for these chemicals (1). The methodology for deriving ATSDR's guidance values and the use of uncertainty factors in the process have been described in detail in several publications[2,3,4]. If data are available, MRLs can be derived for inhalation and oral exposures of acute- (up to 14 days), intermediate- (15-364 days), and chronic- (365 days or more) durations.

Results and Discussion

Inhalation MRL for Lower Brominated PBDEs • An MRL of 0.006 mg/m^3 has been derived for intermediate-duration inhalation exposure (15-364 days) to lower brominated PBDEs. The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 1.1 mg/m^3 for changes in thyroid hormones in rats that were intermittently exposed to octaBDE for 13 weeks[6]. This is an unpublished industry sponsored study in which a commercial octaBDE product (bromine content 78.7%) was administered to groups of 10 male and 10 female rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (air only), 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3. Changes in nasal Goblet cells were increased at 202 mg/m^3, but showed no clear dose-related increasing trends for incidence or severity. Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly increased in incidence at 202 mg/m^3. Thyroid hormone assessments, however, showed exposure-related decreases in mean thyroxine (total T4) at

≥16 mg/m^3 in both sexes, and increases in TSH (thyroid-stimulating hormone) 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 T3 changes. Considering the questionable adversity of minimal severity nasal Goblet cell hypertrophy, lack of clear dose- related increasing trends for incidences and severity of this nasal effect, clear identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in serum levels of thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the effects on thyroid hormones are the most appropriate basis for estimation of an intermediate-duration inhalation MRL. The MRL of 0.006 mg/m^3 was derived by dividing the $NOAEL_{HEC}$ of 0.53 mg/m^3 by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability) and a modifying factor of 3 (for an incomplete database reflecting a single study in one species). The $NOAEL_{HEC}$ was calculated using the following equations: $NOAEL_{ADJ}$ = 1.1 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 0.196 mg/m^3 $NOAEL_{HEC} = NOAEL_{ADJ}$ x RDDR = 0.196 mg/m^3 x 2.7 = 0.53 mg/m^3 The RDDR (regional deposited dose ratio) for the extrathoracic (ET) region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate the RDDR: MMAD (mass median aerodynamic diameter) of 2.0 µm with a mean GSD (geometric standard deviation) (sigma g) of 3.37, default human body weight of 70 kg, and a default female F344 rat body weight of 0.18 kg.

Oral MRL for Decabromodiphenyl Ether ·An MRL of 10 mg/kg/day has been derived for intermediate -duration oral exposure (15 -364 days) to decaBDE. The MRL was derived based on a NOAEL of 1,000 mg/kg/day for developmental toxicity in rats exposed to decaBDE for 19 days during gestation [7]. The MRL was estimated by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). A commercial decaBDE product was administered to groups of 25 mated female Sprague -Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days 0 through 19 [7]. Each female was sacrificed on gestation day 20 and necropsied. End points examined included maternal clinical observations, maternal body weight/weight gain and food consumption, maternal gravid uterine and liver weights, maternal gross lesions, total number of corpora lutea, uterine implantations, early and late resorptions, viable and nonviable fetuses, and fetal weight and sex. Fetuses were examined grossly (all fetuses), evaluated for skeletal/cartilaginous malformations and ossification variations (approximately half of each litter), and evaluated for visceral malformations (remaining fetuses). No treatment -related effects on any maternal or fetal end points were observed, indicating that 1,000 mg/kg/day was the NOAEL for maternal and developmental toxicity. Supporting results were obtained from an intermediate -duration systemic toxicity study. In this study, a commercial decaBDE was fed to F344 rats in estimated doses of 496 -8,000 mg/kg/day and to B6C3F1 mice in estimated doses of 589 - 9,500 mg/kg/day for 13 weeks [8]. Comprehensive histological examination was performed following the exposure. The highest doses were considered NOELs in both species. The developmental study was chosen for the MRL derivation because developmental endpoints were not studied at higher doses [8]. EPA Reference doses (RfDs) for decaBDE, octaBDE, and pentaBDE are 0.01, 0.03, and 0.002 mg/kg/day, respectively [9]. The apparent difference between the EPA's (0.01 mg/kg/day) and ATSDR's (10 mg/kg/day) guidance values for decaBDE is caused by the availability of new relevant data. The EPA 's RfD was last updated in 1995 and was based on a NOAEL (highest dose tested in the database at that time) of 1 mg/kg/day in rats following a 2 year exposure via their diet [10]. An uncertainty factor of 100 was used "in lieu of specific data" for the chemical. In contrast, ATSDR 's MRL was based on more recent data demonstrating the low toxicity of the decabrominated congener as described above. If extrapolated across duration of exposure, this intermediate -duration MRL of 10 mg/kg/day, would become a chronic exposure MRL of 1 mg/kg/day. This value is equal to the NOAEL from the 2year study[10].

References

1. ATSDR. 2004. Toxicological Profile for PBBs and PBDEs Atlanta, Georgia: Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services (www.atsdr.cdc.gov).

2. Pohl HR, Bosch S. 2003. 23nd International Symposium on Halogenated Environmental Organic Pollutants and Persistent Organic Pollutants, Boston, USA, vol. 61, pp. 211-214.

3. ATSDR 1996. Minimal risk levels for priority substances and guidance for derivation. Federal Register 61

(101):25873-25882.

4. Pohl HR, Abadin H, Regul Toxicol Pharmacol, 1995, 22 (2):180-188.

5. Pohl HR, Smith-Simon C, Hicks H. 1998. Regul Toxicol Pharmacol 28:55-60.

6. Great Lakes Chemical Corporation. 2001. Initial Submission Letter and Support; dated 05/25/01. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0574171-1[unpublished study].

7. Hardy ML, Schroeder R, Biesemeier J, et al. 2002. Int J Toxicol 21:83-91.

8. NTP. 1986. NTP technical report on the toxicology and carcinogenesis studies of decabromodiphenyl oxide in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program.

9. IRIS 2004. Integrated Risk Information System. http://www.epa.gov/iris. Sept 01, 2004.

10. Kociba RJ, Frauson LO, Humiston CG, et al. 1975. J Combust Toxicol 2(4):267-285.