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ATSDR's Guidance Values for Polybrominated Biphenyls (PBBs) and Polybrominated Diphenyl Ethers (PBDEs)

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Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) is a U.S. public health agency with a mission to prevent exposure and adverse human health effects and diminished quality of life associated with exposure to hazardous substances from waste sites and unplanned releases to the environment. Health-based guidance values, specifically ATSDR's minimal risk levels (MRLs) and environmental media evaluation guides (EMEGs), play an important role in assessing 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 released to the public (1). In this document, ATSDR derived MRLs for oral exposure to PBBs and PBDEs.

PBBs and PBDEs are brominated organic compounds used as flame retardant additives in plastics, textiles, and other materials. As additives, they are physically mixed into product applications, rather than chemically bound. Therefore, they have the potential to migrate from the plastic matrix into the environment. Commercial production of PBBs was discontinued in the United States in 1976, but production of PBDEs has continued to the present. Concern for the possible health effects of PBDEs has heightened recently due to evidence that these chemicals are ubiquitously distributed with levels in the environment, biota, and humans tissues and breast milk that are continually increasing.

PBBs and PBDEs are each classes of structurally related brominated hydrocarbons in which 2-10 bromine atoms are attached to the molecular structure of biphenyl for PBBs or diphenyl ether for PBDEs. Three commercial PBB mixtures were manufactured: hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl. Limited data are available on health effects of commercial decabromobiphenyl and octabromobiphenyl mixtures; however, the hexabromobiphenyl mixtures FireMaster BP-6 and FireMaster FF-1 have been extensively tested. Three commercial PBDE mixtures have been and continue to be produced: decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether. DecaBDE has accounted for more than 80% of PBDE usage. The main source of human exposure to PBBs and PBDEs is the diet. Therefore, the derivation of health based guidance values (i.e., MRLs) for oral exposures is very important from the perspective of public health.

Materials and Methods

ATSDR's guidance values for PBBs and PBDEs were based on robust databases summarized in the 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).

Results and Discussion

Polybrominated Biphenyls - Oral MRLs

$ An MRL of 0.01 mg/kg/day has been derived for acute oral exposure (14 days or less) to PBBs.

The acute oral MRL was based on a NOAEL for decreased serum levels of thyroid T_4 hormone identified in groups of 8–11 male rats that were treated with 0, 1, 3, or 6 mg/kg/day doses of an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days (5). The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (component factors of 10 for animal to human extrapolation and 10 for human variability). Levels of serum T_4 were significantly ($p<0.05$) reduced at ∃3 mg/kg/day, indicating that the lowest dose (1 mg/kg/day) is the NOAEL. Decreased serum T_4 is considered adverse due to unequivocal evidence from numerous studies that the thyroid is a target of PBBs with a spectrum of effects, including decreases in serum T_3 and T_4 hormone, thyroid enlargement, effects in the follicular cells (e.g., reduced size, hyperplasia with columnar appearance and papillary projections), and accumulation of colloid droplets (for more information see 1).

Intermediate- and chronic-duration oral MRLs were not derived because serious developmental and reproductive effects were observed in monkeys that had been exposed to PBBs for durations that spanned the intermediate and chronic categories at the lowest dose tested in the database. This dose (0.012 mg/kg/day) caused increased menstrual cycle duration and implantation bleeding after 6–7 months of exposure and fetal deaths (fetal abortion and stillbirth) after .1 year of exposure in monkeys, with surviving infants having decreased birth weight and decreased postnatal weight gain (6, 7,).

Polybrominated Diphenyl Ethers - Oral MRLs

Due to the lower toxicity and lower potential for environmental degradation and bioaccumulation of decaBDE in comparison to the octaBDE and pentaBDE mixtures, MRLs for PBDEs are based on health effects data for the lower-brominated mixtures.

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

The acute oral MRL is based on a NOAEL of 1 mg/kg/day for reduced serum levels of thyroid T_4 hormone in fetal rats that were exposed to octaBDE on days 4–20 of gestation (8). The MRL was derived by dividing the NOAEL by an uncertainty factor of 30 (component factors of 10 for animal to human extrapolation and 3 for human variability). A component factor of 10 was not used for human variability because the MRL is based on effects observed in a sensitive subgroup. Thyroid hormone levels were determined in Long-Evans rats that were administered a technical pentaBDE mixture (DE-71) in corn oil by gavage from gestation day (Gd) 6 through postnatal day

(Pnd) 21, except for Pnd 0 (day of birth). Dams were sacrificed on Gd 20 and Pnd 22 and offspring were sacrificed on Gd 20 and Pnd 4, 14, 36, and 90). Study end points included serum total T_4 and T_3 concentrations measured at each age point.

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

The intermediate oral MRL is based on a LOAEL of 2 mg/kg/day for minimal liver effects in rats that were exposed to pentaBDE for 90 days (9). The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (component factors of 3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability). Groups of 30 male and 30 female Sprague-Dawley rats were exposed to pentaBDE (commercial mixture DE-71) in the diet at dosage levels of 0, 2, 10, or 100 mg/kg/day for up to 90 days. Hepatocytomegaly was observed in males at 2 mg/kg/day and both sexes at ∃10 mg/kg/day. The hepatocytomegaly was similar in incidence and severity after 4 and 13 weeks of exposure, was dose-related with respect to severity (some affected hepatocytes had vacuoles that likely contained lipid), and was still observed in males at ∃10 mg/kg/day and females at 2 and 100 mg/kg/day at 24 weeks postexposure (in lessened severity and incidence). A chronic-duration oral MRL was not derived for PBDEs due to insufficient data.

There are three-dimensional structural differences in PBBs and PBDEs that can influence the relative behavior of the chemicals in biological systems. Consequently, although there are some similarities in the health effects of PBBs and PBDEs, it cannot be assumed that corresponding PBDE and PBB congeners necessarily have the same toxicological and toxicokinetic characteristics. PBBs and PBDEs also share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly polychlorinated biphenyls (PCBs), chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (10, 11, 12). The toxicity of PCBs and PBBs is commonly classified as either “dioxin-like” or “non-dioxin-like” based on evidence that dioxin-like congeners act through the same Ah-receptor initial mechanism involved in 2,3,7,8-TCDD toxicity. The mechanism(s) of toxicity for non-dioxin-like PCB and PBB congeners is less clearly elucidated, but also may involve receptors (e.g., the estrogen receptor, the ryanodine receptor, and others). For PBDEs, the introduction of the ether bridge precludes clearly classifying the congeners as either “dioxin-like” or “non-dioxin-like”. Available studies of structure-induction properties, structure-affinity binding properties, and structure-toxicity properties suggest that some *ortho* substituted (non-dioxin-like) PBDE congeners can exhibit stronger affinity for the Ah receptor and exhibit stronger dioxin-type toxicity than their corresponding non-*ortho* substituted (dioxin-like) analogs (13, 14). This is contrary to what is expected for the corresponding PCB and PBB congeners, and has been attributed to the greater distance between the two biphenyl rings in PBDE congeners, relative to PCBs and PBBs. In other words, introduction of *ortho* substitutions into PBDEs or PCDEs does not create a spatial impediment for the two phenyl rings to assume a semi-flat position with respect to each other as it does for PCBs or PBBs. This has implications not only for dioxin-type toxicities, but also for non-dioxin-type toxicities. For example, mono- and diortho-substituted PCBs exhibit neurotoxic properties, and structure-activity relationships have been established for various neurological end points (12). Although this has not been adequately examined for PBBs and PBDEs, it is reasonable to speculate that mono- and diortho-substituted PBDEs might not necessarily follow

the potency rankings of mono- and diortho-substituted PCBs and PBBs. The assumption that PBBs and PBDEs share many toxicological characteristics with PCBs also does not consider geometrical differences due to the higher atomic weight and considerably larger molecular volume of bromine compared to chlorine (15). These differences contribute to dissimilar physical/chemical properties that can influence the relative toxicokinetics and toxicities of the chemicals.

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

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