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HEALTH RISK ASSESSMENT OF THE COMMERCIAL PENTABROMODIPHENYL ETHER PRODUCT IN THE UNITED STATES

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Introduction

A health risk assessment of the pentabromodiphenyl ether (pentaBDE; CAS No. 3254-81-9) commercial product was conducted as part of the United States Environmental Protection Agency (U.S. EPA) Voluntary Children's Chemical Evaluation Program Pilot (VCCEPP) to understand the potential health risks to children and prospective parents from all plausible sources using data from manufacturers and the published literature describing environmental levels in the United States [1]. The commercial pentaBDE product is made in the United States and used almost exclusively to flame retard flexible polyurethane foam (FPUF) used in bed mattresses and cushioning in upholstered products [2]. Mattress and cushion FPUFs contain 2-3% and 3-5%, respectively, of the commercial product. Scrap material from FPUF manufacturers have been used as padding beneath carpets, which could contain up to 3-5% of the flame retardant.

In this first tier of the three-tier VCCEPP process, hazard information was combined with screening-level exposure models to evaluate all plausible pathways by which children and adults might potentially be exposed in the workplace and in the home, school, office, and ambient environments. The study summarized here was the subject of a Peer Consultation Panel convened by Toxicology Excellence for Risk Assessment (TERA) in June 2003 [2].

Hazard Assessment

The current commercial pentaBDE product used in the U.S. is composed of a mixture of brominated diphenyl ether (BDE) congeners, including primarily tetraBDE (≅ 34%), pentaBDE (≅ 55%), and hexaBDE (≅ 12%) congeners. The predominate congeners include 2,2',4,4',5-pentaBDE (BDE-99) and 2,2',4,4'-tetraBDE (BDE-47), as well as lesser amounts of 2,2',3,4,4'-pentaBDE (BDE-85), 2,2',4,4',6-pentaBDE (BDE-100), 2,2',4,4',5,6-hexaBDE (BDE-154), and 2,2',4,4',5,5'-hexaBDE (BDE-153). The BDE constituents of the commercial pentaBDE product are not readily biodegradable, highly lipophilic, bind tightly to organic matter, do not volatilize appreciably, and are relatively immobile in soil. Metabolism studies in rats suggest that approximately 86% of the product is bioavailable by the oral route of exposure [3]. The results of a human skin absorption study suggest that 3% is bioavailable through dermal contact [4]. Bioavailability by the inhalation route has not been well studied.

The available toxicology data suggest that the commercial pentaBDE product is not acutely toxic to humans or animals by the oral, dermal, or inhalation routes of exposure [5, 6]. It does not induce

skin sensitization in guinea pigs, and has not been determined to be genotoxic in the Ames *Salmonella*, *Saccharomyces cerevisia* or in human lymphocytes *in vitro* [7]. In chronic and subchronic toxicity studies, the most prominently observed endpoints in animal bioassays are in the liver and include induction of enzymes that function in xenobiotic metabolism and microscopic observations characteristic of adaptive responses to enzyme induction, including increased liver weights and microscopic changes such as increased size of the hepatocytes and cytoplasm described as "ground glass" in appearance. Disruption of thyroid hormone (3,3',5,5'-tetraiodothyronine, or T_4) levels has been reported (T_3 levels have not been affected) [8]. In reproductive/developmental toxicity studies in rats and mice, no effects on pregnancy or standard developmental endpoints have been reported at maternal doses up to 30 mg/kg/day [8, 9] or 200 mg/kg/day [10]. Changes in neurobehavioral measures have been reported in some, but not all, studies of rats or mice exposed to pentaBDE shortly after birth [9, 11, 12].

Theoretical daily intakes calculated using screening-level exposure models were compared to three non-cancer health effect benchmark values. Changes observed in thyroid T_4 levels and the incidence of thyroid hyperplasia in rats were used to develop screening toxicity values for comparison to levels of exposure for children of all ages and prospective parents. The biological significance of these endpoints in the rat relative to human health is uncertain; therefore, this comparison is regarded as very protective of human health. Using benchmark dose (BMD) modeling and data from four studies [5, 8, 13, 14] the results of BMD modeling at the 90% confidence limit ($BMDL_{10}$) associated with decreased T_4 levels ranged from 9.04 mg/kg/day to 78 mg/kg/day. The $BMDL_{10}$ for thyroid hyperplasia ranged from 4 mg/kg/day in male rats to 9.6 mg/k/day in female rats. Applying a 100-fold uncertainty factor to the lowest $BMDL_{10}$ (4 mg/kg/day for thyroid hyperplasia), a screening toxicity value for thyroid hyperplasia was 0.04 mg/kg/day.

The second screening toxicity benchmark (changes in T_4 levels) was based on data from Zhou et al. [8] in the fetus or neonate exposed *in utero*. Using BMD modeling, the $BMDL_{10}$ was 10.3 mg/kg/day for data from PND 4 and 2.2 mg/kg/day for data from PND 14. By applying a 30-fold uncertainty factor, the resulting toxicity values calculated for changes in T_4 homeostasis were 0.1 and 0.07 mg/kg/day, respectively. The lower value was used in the Tier 1 assessment.

Liver enzyme induction as a possible indicator of liver effects, which was identified as the basis for U.S. EPA's oral non-cancer reference dose (RfD; 0.002 mg/kg/day) [15], *a priori* was not considered an adverse human health endpoint; however, this endpoint and the U.S. EPA RfD were used in the assessment to provide an upper-bound estimate of the potential health hazards. There is no evidence to suggest that the alteration of liver enzyme function due to exposure to the commercial pentaBDE product will result in an adverse effect on children or reproduction in adults. Further discussion is provided elsewhere [2].

Exposure Assessment

Theoretical upper-bound daily intakes were calculated for adults and children in different age bins (<1, 1-2, 3-5, 6-8, 9-11, 12-14, and 15-18 years) in accordance with U.S. EPA exposure assessment guidance [16] and using hypothetical exposure models developed for three scenarios: exposures in the workplace, exposures in the indoor home/school/office environments, and exposures associated with ambient environmental levels (e.g., via direct and indirect contact with soil, inhalation of airborne household dust and outdoor particulates, ingestion of meat, dairy, vegetable food products, recreationally caught fish, and ingestion of human breast milk by infants). Mouthing of FPUF cushions treated with the commercial pentaBDE product was

modeled for children less than 5 years old. Exposure point concentrations represented either the 95th percentile upper confidence limit of the mean or the maximum of the available U. S. environmental data.

Total daily intakes by children and adults through all plausible exposure routes are summarized in Figure 1. The contribution of different exposure pathways to the total daily intake by children from ages 0 to 18 years old is shown in Figure 2. The results of the screening-level exposure assessment indicated that the highest hypothetical exposures occurred in children <1 year, 1-2 years and 3-5 years old. With the exception of exposures in the workplace, calculated daily intakes for adults were well below the three screening toxicity benchmarks. In the workplace, hypothetical daily intakes exceeded the U.S. EPA RfD value if vapor inhalation occurred at the air saturated vapor limit (an assumption used in the absence of workplace air monitoring data) and dermal protection measures were not used to limit skin contact and hand-to-mouth contact. The use of protective equipment would significantly lower exposures in the workplace.

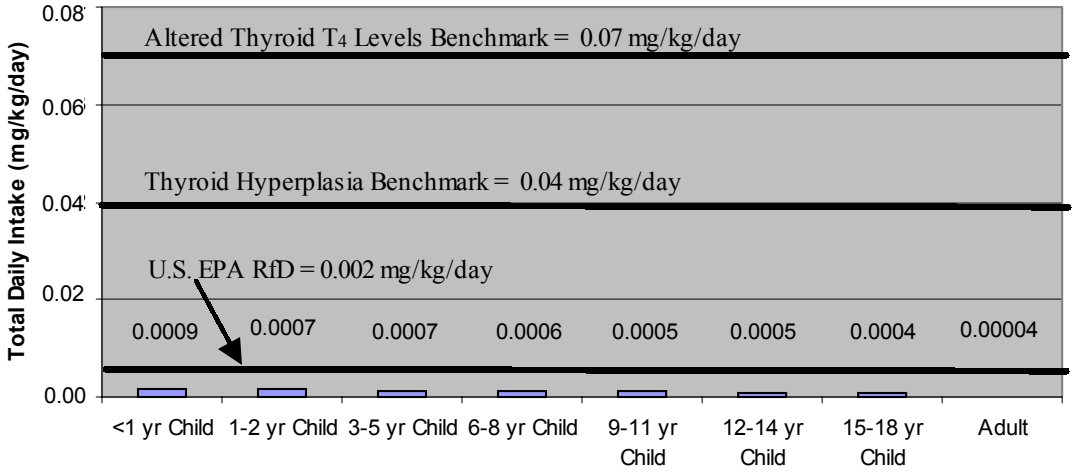

Figure 1. Theoretical total daily intake of the commercial pentaBDE product by children and adults through all plausible routes of exposure in the home/school/office and ambient enviroments in the U.S.

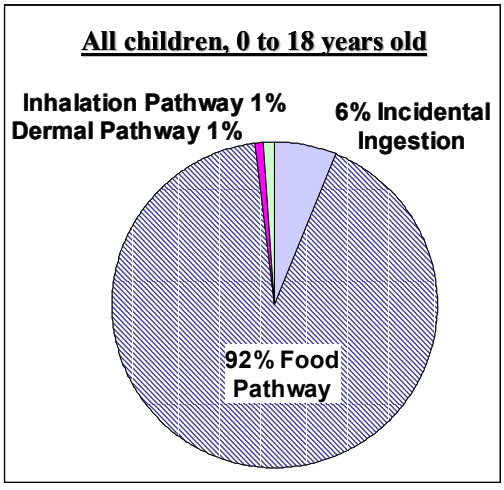

Figure 2. Relative contribution of different exposure pathways to the total daily intake of the commercial pentaBDE product by children from ages 0 to 18 years old.

Conclusions

The conservative approach to the exposure modeling in this VCCEPP Tier 1 assessment most likely over estimates actual exposures and hazard. The use of a probabilistic approach such as that used by Wenning [17] would be useful to identify the key exposure and hazard assumptions that could be evaluated further in Tier 2 or Tier 3 VCCEPP activities. For example, one large source of uncertainty in the assessment was the lack of source-specific exposure data on lower BDEs in the United States. Consequently, what are believed to be worst-case exposure estimates were used. While it does not appear that the levels of BDE's reported in the published literature exceed thresholds that potentially adversely affect human health, mechanistic studies would improve the understanding of the effects of BDEs on thyroid function, neurobehavorial responses and developmental effects in laboratory animals. These data would further enhance the understanding of the potential effects of the environmentally relevant BDE constituents of the commercial pentaBDE product on children.

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