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

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Introduction

A health risk assessment of the octabromodiphenyl ether (octaBDE; CAS No. 32536-52-0) 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]. Commercial octaBDE product is currently made in the U.S. and used almost exclusively to flame retard acrylonitrile-butadiene styrene (ABS) used in the plastic industries to manufacture casings for computers and electronic equipment. 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 commercial octaBDE product made in the U.S. (Great Lakes DE-79™) is composed of a mixture of brominated diphenyl ether (BDE) congeners, including pentaBDE (≅ 0.5%), hexaBDE (≅ 12%), heptaBDE (≅ 45%), octaBDE (≅ 33%), nonaBDE (≅ 10%), and decaBDE (≅ 0.7%). The BDE constituents of the commercial octaBDE product are not readily biodegradable, highly lipophilic, bind tightly to organic matter, do not volatilize appreciably, and are relatively immobile in soil. Few data in the literature describe the bioavailability of the commercial octaBDE product or its constituents in either animals or humans. Based on the available animal data, it is conservatively estimated that 50% and 3% of the predicted exposure concentrations of the commercial octaBDE product are absorbed by oral and dermal routes of exposure, respectively. The dermal absorption value was based on the results of a human skin absorption study [3]. Inhalation of respirable (<10 micron) particulate containing the commercial mixture is possible in product and ABS manufacturing workplaces; however, bioavailability by this route of exposure is not known.

The available toxicology data suggest that the commercial octaBDE product is not acutely toxic to humans or animals by the oral, dermal, or inhalation routes of exposure [4, 5]. 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* [6]. Among the chronic and subchronic toxicity studies available for the commercial octaBDE product, 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 have been reported. Developmental toxicity studies in rats showed decreases in maternal and fetal body weights [2].

Theoretical daily intakes calculated using screening-level exposure models were compared to three non-cancer health effect benchmark values. A reproductive/developmental effects benchmark value was derived from the NOAEL for maternal toxicity, evidenced by decreased fetal body weight observed in rodent studies [7]. The application of uncertainty factors for inter- and intra-species extrapolation to the results of benchmark dose (BMD) modeling at the 95% confidence level ($BMDL_5$ = 8.7 mg/kg/day) resulted in a health effect benchmark value of 0.09 mg/kg/day.

The thyroid has been identified as a target tissue in subacute and subchronic rodent studies. The results of BMD at the 90% confidence limit ($BMDL_{10}$) for potential effects on the thyroid was derived using data from three different subchronic studies [8, 9, 10] ranged from 3.3 mg/kg/day in males and 1.7 mg/kg/day in females to 76 mg/kg/day in either sex. For estimates of intake primarily by the oral route, the $BMDL_{10}$ derived from Zhou et al. [8] was used in conjunction with the application of a 100-fold uncertainty factor. These findings are likely relevant for human health assessment, especially in children, and differences in sensitivity to small changes in thyroid hormone levels should be considered quantitatively. The resulting health effect benchmark value was 0.09 mg/kg/day, which is comparable to the value calculated for maternal toxicity.

Liver enzyme induction as an indicator of liver effects, which was identified as the basis for U.S. EPA's oral non-cancer reference dose (RfD; 0.003 mg/kg/day) [11], *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 associated with exposure to the commercial octaBDE product will result in an adverse effect on reproduction in humans. The U.S. EPA RfD was based on increased hepatic enzyme induction in Sprague Dawley rats [12]. In Carlson [12], there were no microscopic changes in the liver of rats in a low dose series (up to 2.4 mg/kg/day); however, a high dose series (up to 19.15 mg/kg/day) was not examined microscopically. The enzymes induced in rodents were those potentially involved in endogenous and xenobiotic metabolism, not enzymes indicative of cellular damage in the liver (e.g., SGOT, SGPT, sorbital dehydrogenase were unchanged, even at high doses) and other tissues. In a similar study, the microscopic changes observed in the liver of rats exposed to much higher doses (up to 575 and 751 mg/kg/day for males and females, respectively) were considered adaptive changes [10], consistent with enzyme induction [13], with the exception of vacuolation observed in the 751 mg/kg/day females. It is likely that only these adaptive changes would have been observed in the livers of the high-dose series in Carlson [12]; if those tissues had been examined microscopically, a higher NOAEL and RfD are possible.

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 risk assessment guidance [14, 15] 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 plastic surfaces composed of ABS treated with the commercial octaBDE product was modeled for children less than 5 years old. Exposure point concentrations represented either the 95th percentile upper confidence limit on the mean or, for more limited data sets, the maximum of the available U.S. environmental data.

Total daily intakes by adults and children through all plausible exposure routes are summarized in Figure 1. The results of the screening-level exposure assessment indicated that the highest hypothetical exposures occurred in children, and were associated with ambient environmental exposures, specifically consumption of different foods by <1, 1-2, and 3-5 year old children. With the exception of adult exposures in the workplace, calculated daily intakes were below the three screening toxicity benchmark values. In the workplace, hypothetical daily intakes exceeded the U.S. EPA RfD value; inhalation and dermal contact were the predominant exposure routes. Worker exposure estimates assumed no workplace protective measures were used to limit respiratory and dermal exposures and the exposure limit for workplace air levels set by Great Lakes Chemical Corporation (0.14 mg/m^3, 8-hour time-weighted average) was exceeded. Exposures and associated health hazards in the workplace would be substantially lower, if respiratory and dermal protection measures are considered in this assessment.

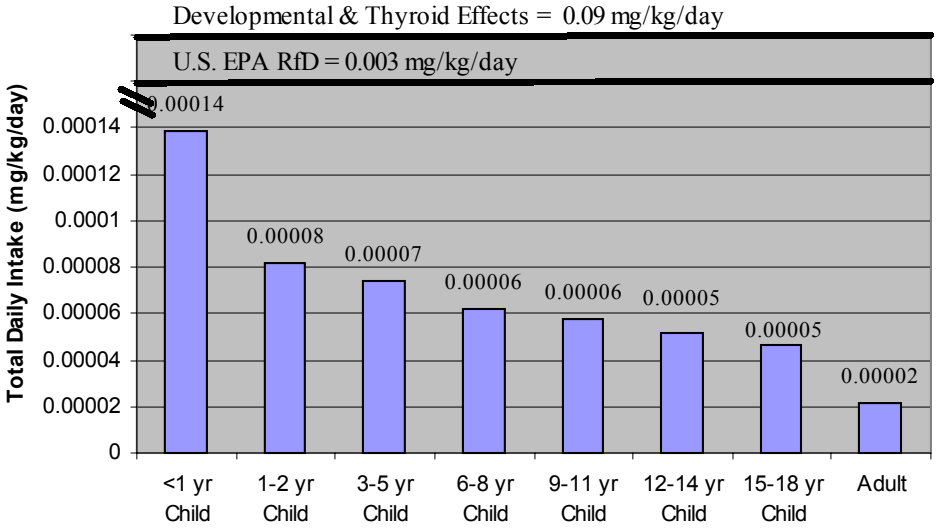

Figure 1. Theoretical total daily intake of the commercial octaBDE product by children and adults through all plausible routes of exposure in the home/school/office and ambient enviroments in the U.S.

Conclusions

While existing data do not allow for accurate quantification of exposures to children and prospective parents, the conservative nature of the screening-level exposure estimates in this VCCEPP Tier 1 assessment most likely over estimate actual exposures and hazard. The exposure

and hazard information and assumptions used in this Tier 1 assessment were intended to provide conservative, upper-bound estimates of exposure and hazard. The use of probabilistic methods such as that used by Wenning [16] would be useful to identify the key exposure and hazard assumptions that could be evaluated further in Tier 2 or Tier 3 VCCEPP activities. While it does not appear that the levels of BDEs 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, neurobehaviorial responses, and developmental effects in laboratory animals. These data would further enhance the understanding of the potential health effects posed by environmentally relevant BDE constituents of the commercial octaBDE product.

Finally, while there may be data gaps in the available exposure information, there does not appear to be any critical data gaps. For example, while environmental monitoring data for octaBDE product-related congeners, particularly in food products and human breast milk, represent a data gap in the Tier 1 assessment, the large margins of safety calculated in the Tier 1 assessment suggest that additional studies may not be warranted to meet the goals of the VCCEPP.

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