PRELIMINARY EVALUATION OF HUMAN HEALTH RISK ASSOCIATED WITH EXPOSURE TO PBDES IN THE UNITED STATES

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Introduction

Polybrominated diphenyl ethers (PBDEs) have historically been added to a variety of consumer products to increase their resistance to fire. Over the past decade, investigators have reported the occurrence of adverse effects in rodents following exposure to PBDEs. This in turn has resulted in increased attention on characterizing potential sources of exposure to PBDEs and their concentrations in humans. As such, a wealth of data are now available characterizing PBDE body burdens in the United States. Most notable is the extensive PBDE biomonitoring data evaluated as part of the National Health and Nutrition Examination Survey (NHANES)[1]. This data was recently reported[1] and provides a robust dataset for characterizing exposure to PBDEs in the U.S. However, to date, it has been difficult to interpret the meaning of the measured concentrations in various media and human tissues due to the lack of applicable toxicity benchmarks for the various PBDEs. Given the concerns about the rising levels of PBDEs in various media, it is critical that human health risks be assessed to put the measured levels into perspective.

In December of 2006, the USEPA released draft toxicological reviews for BDEs 47, 99, 153 and 209[2]. Each of the draft assessments provided a toxicity benchmark for evaluation of noncancer effects associated with exposure(a reference dose (RfD) which is an estimate of daily exposure that is likely to be without an appreciable risk of deleterious effects during a lifetime). In addition, because BDE 209 was the only congener with data available evaluating carcinogenic effects, the toxicological assessment for BDE 209 included a toxicity benchmark for evaluating potential carcinogenic effects (a cancer slope factor [CSF], which is an upper bound on the estimate of risk per mg/kg-day of oral exposure). In traditional human health risk assessments in the U.S., these toxicological factors are applied to daily intake estimates to quantify theoretical health risk posed by exposure. Using the draft toxicity benchmarks for PBDEs, the objective of this study was to provide a preliminary evaluation (e.g., screening evaluation) of human health risks associated with exposure to PBDEs based on current estimates of intake in the U.S.

Materials and methods

Toxicological Values: The toxicological reviews were released by the USEPA in December 2006[2] and were subject to a peer review process to ensure that the science was used credibly, dose-response assessments were appropriately derived, and that the general characterization of toxicology associated with the compounds was accurately evaluated (note: finalized assessments had not been released as of May 2008). All RfD values were derived by first identifying a critical study and a principal effect for the point of departure (POD) in the calculations. Several uncertainty factors (UFs) were then applied in deriving the draft RfD.

BDE 47*: RfD*=1.2 x 10^{-4} mg/kg-day based on decreased habituation in mice in a neurobehavioral study reported by Eriksson et al 2001. Benchmark dose modeling was applied to this dataset to develop a POD (0.35 mg/kg). An UF of 3000 was then applied to develop the RfD (intraspecies variability (10), interhuman variability (10), extrapolation from subchronic to chronic (3), and database deficiencies (10).

BDE 99: RfD=1 x10^{-4} mg/kg-day based on rearing habituation in a neurobehavioral study reported by Viberg et al 2004. Benchmark dose modeling was applied to this dataset to develop a POD (0.32 mg/kg). An UF of 3000 was then applied (based on the UFs described for BDE 47) to develop the RfD.

BDE 153*:* RfD=1.5x10^{-4} mg/kg-day based on spontaneous motor behavior and learning ability in mice as reported by Viberg et al 2003. USEPA concluded that this was the only available study appropriate for dose-response . As

such, the USEPA relied on the NOAEL of 0.45 mg/kg as the POD. As for BDEs 47 and 99, an UF of 3000 was then applied to develop the RfD.
BDE 209 RfD=0.007 mg/kg-day based neurobehavioral changes in mice as reported by Viberg et al, 2003. USEPA relied on NOAEL of 2.22 mg/kg-day as the POD and applied UFs for interhuman variability (10), interspecies variability (10), and extrapolation from subchronic to chronic exposures (3). The oral CSF of $7x10^{-4}$ /mg/kg-day was based on neoplastic nodules or carcinomas (combined) in the liver of male rats in a two-year bioassay conducted by the National Toxicology Program (NTP).

Evaluation of Risk
The peer-reviewed literature was surveyed for studies that identified or calculated estimates of daily intake for non-occupational exposure to PBDEs in the U.S (note: estimates of intake were taken directly from the manuscript, underlying data was not thoroughly evaluated). If necessary, the previously reported estimates were converted to daily intakes based on a standard body weight (mg PBDE/kg bw-day, 70 kg for adults, 30 for children). Daily intake was estimated by study authors for the NHANES dataset[1] by summing the geometric means for BDE congeners 47, 99, 100 and 153 and then multiplying that sum by 0.177[3] to derive intake from body burden for PBDEs (note: 0.177 was identified as the factor that relates human PBDE body burden to daily intake). Quantitative estimates of non-cancer risk (i.e., hazard index, HI) were calculated by dividing the estimated intake by the oral RfDs, while estimates of cancer risk were calculated by multiplying the intake by the oral CSF. In most cases, intakes were reported based on a "sumPBDE" basis rather than congener-specific basis. For these calculations, it was assumed that all PBDEs were equipotent and the most conservative RfD was applied in the non-cancer risk equation. For the evaluation of theoretical carcinogenic risk, it was also assumed that all congeners were equipotent to BDE 209. This screening-level assessment is only representative of theoretical risks and should not be applied to other countries given that the PBDE body burden and exposure scenarios vary by country.

Results and discussion:
Theoretical estimates of non-cancer risk associated with exposure to ∑PBDEs from all routes of exposure are compared in Figure 1a. Generally, when the HI is less than 1, it is reasonable to assume that exposure is not likely to pose a health risk. These results indicate that for adults experiencing exposure equivalent to the central tendency, the HI was far less than 1 when it was assumed that all PBDEs were equipotent to BDEs 47 and 99. For children and upper-end adult exposures, the HI was approximately 0.5. A similar approach was utilized for the evaluation of carcinogenic risk (i.e., it was assumed that all PBDEs were equipotent to BDE 209). In accordance with this conservative approach, the theoretical risk associated with exposure to PBDEs in the U.S. is 10^{-8} or lower (a level which is well below risk levels generally considered to be acceptable by the USEPA [10^{-4} to 10^{-6}], Figure 1b). Two studies were available which reported congener-specific estimates of intake; risk estimates based on these congener-specific intakes are shown in Table 1. Based on congener-specific intakes provided by Lorber[4], estimates of risk were low for both children and adults. However, in Hays and Pyatt's[5] evaluation of aggregate exposure to 209 in children, non-cancer hazard indices were >1 when intakes based on upper-end exposures were utilized (note: the estimated intakes were modeled based on concentrations of 209 that had an average and maximum value of 0.96 and 33.6 ng/g lipid, respectively).

Theoretical risks associated with dietary exposure were also evaluated. In this analysis, results indicated that estimates of excess cancer risk were $\leq 10^{-4}$ and most estimates of hazard were well below 1 (data not shown). However, two exceptions associated with high-end exposure estimates for infants resulted in HI values of 3 and 5. Several studies were available which evaluated exposure to PBDEs from dust. Resulting risk estimates indicated that excess carcinogenic risk was below 10^{-6}; however, upper-end estimates of intake were associated with a noncancer HI>1 (Table 3).

The authors recognize that there is a great deal of uncertainty in this evaluation of risk resulting from exposure to PBDEs Rather than providing definitive estimates of risk, the objective of this study was to provide perspective on

the potential theoretical risk based on toxicity benchmarks developed by US regulatory agencies. Such evaluations can be used to help guide future research. For many of the studies selected for analysis, different numbers of congeners were reported (several of which did not include BDE 209), and several studies did not report congener-specific intakes. This scenario underscores the importance for future investigators to report congener-specific data. As such, one of the major sources of uncertainty in this preliminary analysis involves the assumption that all PBDEs are equipotent to the most potent congener evaluated by the USEPA. Given the conservatism inherent in this assumption, it is likely that noncancer risk has been overestimated in this preliminary analysis. Furthermore, many of the studies reporting intakes relied on very conservative (and often upper-end) exposure variables (e.g., ingestion rates, modeled concentrations vs. measured, etc.). Additionally, the oral cancer slope factor for BDE 209 was based on an endpoint that may be questionable given current criteria for evaluating and classifying pathological changes in rodents. The NTP is currently evaluating the carcinogenicity of the lower brominated mixtures; the results will provide valuable information regarding the assessment of potential carcinogenicity for congeners other than BDE 209. Furthermore, these estimates of risk are generally based on modeled estimates of intake and may not be representative of intake for highly exposed individuals. And perhaps most importantly, robust toxicity studies are not yet available for all PBDE congeners.

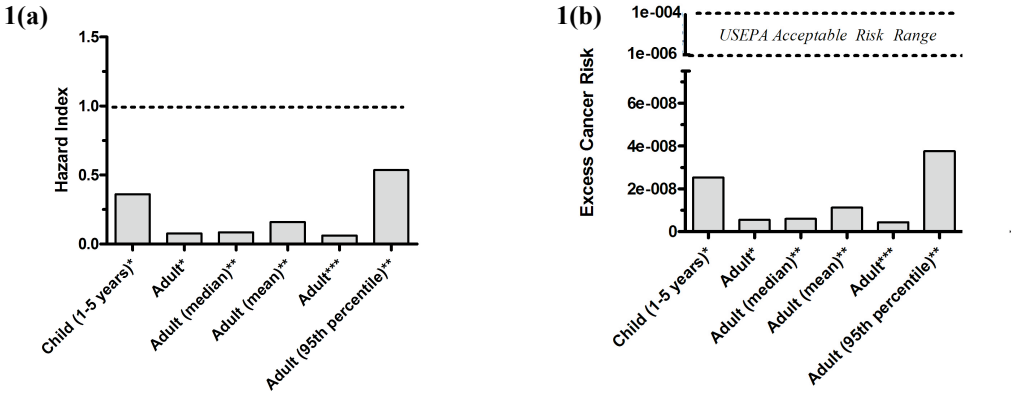

Figure 1. Theoretical noncancer (a) and cancer (b) risk estimates calculated from previously reported intakes for ∑PBDEs from all routes of exposure. Intake values taken from *Lorber 2008, **McDonald 2006, *** NHANES.

Taken together, these preliminary estimates indicate that BDEs 47 and 99 were associated with higher estimates of theoretical risk than BDEs 153 or 209 and that risks were greatest for infants and children as compared to adults. In all scenarios evaluated, the theoretical risks associated with exposure to PBDEs were within acceptable risk ranges for both carcinogenic and non-carcinogenic effects for adults. However, risk estimates associated with upper-end exposures in children and infants exceeded a hazard index of 1 in some cases, suggesting further investigation and congener-specific analyses of these exposure scenarios. Given the increasing evidence demonstrating that exposure to dust is likely an important route of exposure for humans, and that children have the highest likelihood to ingest dust, it is important to more fully characterize this exposure scenario on a congener-specific basis, as well as evaluate the potential toxicity associated with this exposure route.

References:

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Table 1. Congener-specific estimates of theoretical risk from all routes of exposure.

Reference	Exposure Scenario (as described by study authors)	Congener Evaluated	Hazard Index	Carcinogenic Risk
Lorber 2008	child, 1-5 years	209	0.001	6.90E-09
	adult	209	0.000	1.48E-09
	child, 1-5 years	47	0.092	na
	adult	47	0.020	na
	child, 1-5 years	99	0.102	na
	adult	99	0.022	na
	child, 1-5 years	153	0.005	na
	adult	153	0.001	na
Hays and Pyatt 2006	child, aggregate exposure (mid-range)	209	0.171	8.40E-07
	child, aggregate exposure (upper-end)	209	55.714	2.73E-04

Table 2. Theoretical risk estimates associated with exposure to PBDEs via dust. *As reported by Stapleton et al 2008[8].

Study (description of exposure route)	Congener(s)	Exposure Scenario	Hazard Index	Carcinogenic Risk
Allen et al 2008 (dust ingestion*)	17, 28/33, 47, 49, 66, 75 100, 99, 85/155, 154, 153, 138, 183, 196, 197, 203, 206, 207, 208, 209	50th percentile, child, assume IR =100mg/day	0.246	1.72E-08
		95th percentile, child, assume IR =100mg/day	6.233	4.36E-07
		50th percentile, adult, assume IR=10mg/day	0.011	7.40E-10
		95th percentile, adult, assume IR=10mg/day	0.267	1.87E-08
Lorber 2008 (soil/dust ingestion)	9 (28, 47, 99, 100, 138, 153, 154, 183, 209)	adult	0.051	3.58E-09
		child 1-5 years	0.239	1.67E-08
	47	adult	0.012	na
	99	adult	0.015	na
	153	adult	0.001	na
	209	adult	0.0002	1.05E-09
	47	child 1-5 years	0.054	na
	99	child 1-5 years	0.069	na
	153	child 1-5 years	0.004	na
	209	child 1-5 years	0.001	4.89E-09
Stapleton et al 2005 (dust ingestion*)	17, 28/33, 71, 47, 66, 100, 99, 85, 154, 153, 138, 156, 184, 183, 191, 190, 197, 196, 207, 206, 208, 209	50th percentile, child, assume IR =100mg/day	0.197	1.38E-08
		95th percentile, child, assume IR =100mg/day	0.600	4.20E-08
		50th percentile, adult, assume IR=10mg/day	0.008	5.90E-10
		95th percentile, adult, assume IR=10mg/day	0.026	1.80E-09
Stapleton et al 2008 (hand to mouth ingestion of dust)	17, 28/33, 47, 49, 66, 85/155, 99, 100, 138, 153, 154, 183, 209	50th percentile, child >48 months	0.460	3.22E-08
		95th percentile, child >48 months	2.030	1.42E-07
		50th percentile, adult	0.022	1.54E-09
		95th percentile, adult	0.097	6.77E-09