Distribution of PBDE Levels Among U.S. Women: Estimates of Daily Intake and Risk of Developmental Effects

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Introduction

Levels of polybrominated diphenylethers (PBDEs) among residents of North America are approximately 40 to 70 times higher than those of individuals in Europe or Japan[1-3]. This disparity is likely a result of the fact that more than 95% of the world's use of the penta-BDE technical mixture (whose congeners are highly bioaccumulative) is in the Americas[4]. Recent data suggest that PBDE body burdens continue to rise in North American wildlife[5] and humans[6]. Five congeners (BDE-47, -99, -100, -153, and -154) predominate in human tissues, accounting for about 90% of the total PBDE body burden. PBDEs levels among individuals within a population vary widely, by approximately 50-fold. The reasons for this variability are not well understood, but likely relate to differences in exposure and host differences that affect uptake and elimination.

Like PCBs and dioxins, the PBDEs are long lived in the body, with estimated terminal half-lives of 2 to 7 years or more[7]. Half-lives of PBDEs in rats are dramatically shorter and range from about 15 to 75 days, depending on the congener. Thus, the same daily intake of PBDEs will result in steady state tissue concentrations that are roughly 20- to 100-fold higher in humans than rodents. The best way to extrapolate from rodents to humans is by comparing tissue concentrations (i.e., body burdens)[8].

The primary health concerns of PBDEs appear to be developmental effects, including harm to the developing brain[9-15] and reproductive organs[16-18].

The aim of this study is to estimate the distribution of PBDEs concentrations in serum, adipose tissue, and breastmilk among women residing in the United States (U.S.). This paper attempts to estimate a reasonable range of daily intake of PBDEs, using the U.S. body burden data. Finally, the paper examines potential health risks posed by the PBDEs by comparing tissue concentrations in humans to projected tissue concentrations in rodents resulting from studies of developmental neurotoxicity and reproductive effects.

Methods

Distribution of PBDE Concentrations in U.S. Women

PBDEs levels have been reported for individuals in 6 groups of women in the U.S. (Table 1). Combined data within each media, and for all media combined, were tested to see if they were lognormally distributed using a Chi-square goodness of fit test (Crystal Ball 2000, Decision Engineering, Inc.). The distributions are provided in Table 2.

Table 1. Studies Examining PBDE Levels in Individual U.S. Women

Study	She 2002[1]; Petreas 2003[2]	Petreas 2003[2,a]	Mazdai 2003[3]	Schecter 2003[19]	Sharp 2003[20]	NWEW 2004[21]
Pop.	California	California	Indiana	Texas	U.S.	Washington
N	32	50	12	47	20	9
Media	adipose	serum	serum	milk	milk	milk

[a] In this study, BDE-47 only was measured in serum; total PBDE levels were estimated by adjusting the BDE-47 values by the proportion (0.6) of the total that congener represented in similar media[3]. Measurements below the limit of detection were assumed to be one-half the limit of detection.

Estimation of daily intake of PBDEs among U.S. Women

PBDE concentrations along with estimates of terminal half-life of PBDEs in humans, were used to project the range of total daily intake among U.S. women (Table 3) through the following relationship: Intake (μg/d) = [(ln2)*(μg PBDE/kg_{lipid} measured)*(fraction adipose)*(body weight)] / [(half-life in days)*(fraction absorbed)].

The fraction of total PBDE dose absorbed was taken to be 0.9, based on 94% absorption of BDE-47 in rats[22] and 78% for BDE-99 in rats[23]. The body weight of women was assumed to 62 kg, of which 30 % is body fat. Terminal half-life estimates of PBDEs in humans differ for each congener and range from 2 years to 6 years, based on rodent-human comparisons of other persistent pollutants[7]. However, half-life estimates among workers were usually less than 2 years, with considerable variability noted[24]. Half-lives ranging from 1 to 4 years (for all congeners combined) were assumed for calculations of daily PBDE intake (Table 3).

Estimation of risks of developmental neurotoxicity or reproductive effects

Lipid-normalized concentrations in humans (C_{human}) were compared to lipid-normalized PBDE concentrations in rodent tissues (C_{rodent}) from doses that caused no adverse effect (NOEL) in rodent developmental studies (Table 4). In studies where the lowest dose caused developmental toxicity, the lowest observable effect level (LOEL) was compared. The ratio of (C_{rodent}/C_{human}) was taken as a measure of the "margin of exposure", or the level of safety of PBDEs levels currently attained in humans.

For rodent studies employing a single dose, PBDE concentrations (C_{rodent}) were estimated by assuming the absorbed dose parsed evenly throughout the body based on lipid content in the tissues, an assumption that creates some error as PBDE concentrations did not consistently correlate with tissue lipid content in rats given BDE-99 orally[23]. For multiple dosing, the lipid-normalized tissue concentrations were determined for each day of dosing by estimating daily contributions to body burden and first-order elimination of the prior-day concentration (e.g., a one compartment model).

Results and Discussion

PBDE levels in human serum, breastmilk, and fat followed similar lognormal distributions, which exhibited wide variability among individuals (Table 2). Interestingly, 5 % of the U.S. population have total PBDE levels of approximately 300 ng/g lipid. Empirically, 10 out of 170 (5.9 %) U.S. women sampled had lipid-normalized PBDE levels greater than 300 ng/g. Five percent of the U.S. population represents about 15 million individuals.

Table 2. PBDE levels (μg/kg lipid) in U.S. Women (C_{human})

Statistic	Serum	Milk	Adipose	All media
Mean	86.1	95.2	72.4	87.6
50th percentile	40.7	47.7	43.0	43.5
95th percentile	302	329	231	**304***
N	62	76	32	170

* value used in C_{rodent}/C_{human} comparisons in Table 4.

Estimates of mean daily intake of PBDEs by U.S. women (Table 3) ranged from 0.86 to 3.4 μg/d, depending on the half-life assumed. Estimates of daily intake for women at the upper-end of the body-burden distribution ranged from 2.9 to 12 μg/d. Inter-individual differences in rate of removal of PBDEs (e.g., variability in metabolism or diets that break the cycle of enterohepatic circulation[25]) may be major factors explaining the wide variability of PBDE levels observed.

Table 3. Estimates of Human Daily Intake (μg/d) of PBDEs in the U.S.

	Assumed Half-life:			
Body burden statistic	**1 year**	**2 years**	**3 years**	**4 years**
Mean	3.4	1.7	1.2	0.86
50th percentile	1.7	0.85	0.57	0.43
95th percentile	12	5.8	3.9	2.9

A low margin of exposure (defined as C_{rodent}/C_{human}) was observed for several studies (Table 4). These comparisons may overestimate risk since human concentrations were based on total PBDEs whereas the toxicity studies employed single congeners or the penta(technical) mixture, which may have more biological activity per unit dose. They may also be overestimates if research determines that applied dose (i.e., pulse dose) is a better predictor of risk than steady-state tissue concentrations. Clearly, better data are needed to compare PBDE tissue levels in humans and rodents.

Other data suggest that the risk estimates (Table 4) may be underestimates. These include observations that PBDEs and PCBs (which are also present in people) act additively to harm the developing brain[26]. Also, humans may be more sensitive than rodents to PBDEs and PCBs; no uncertainty factors were applied.

Table 4. Comparison of Human PBDE Levels to Studies of Developmental Effects

Ref.	Endpoint	Species	Age dosed	PBDE used	NOEL (LOEL) mg/kg	C_{rodent} ng/g	C_{rodent}/C_{human}
[9]	Behavior	Mouse	PN10	47	0.7	$3.4x10^3$	11
[10]	Behavior	Mouse	PN3or10	99	0.4	$1.6x10^3$	5
[11]	Behavior	Mouse	PN10	153	0.45	$1.7x10^3$	6
[12]	Behavior	Mouse	GD6–PN21	99	(0.6)	$6.0x10^4$	<200
[13]	Auditory	Rat	GD6–PN21	Penta	1.0	$9.9x10^{4\dagger}$	$330^\dagger$
[14]	T4	Rat	GD6–GD20	Penta	1.0	$5.2x10^{4*}$	170^*
[15]	Behavior	Rat	GD6–PN21	Penta	100	$9.9x10^6$	33,000
[17]	Male fertility	Rat	GD6	99	(0.06)	$2.3x10^2$	<1
[16]	Ovary cell	Rat	GD6	99	(0.06)	$2.3x10^2$	<1
[18]	Epididymis	Rat	GD10-18	99	(1.0)	$3.3x10^4$	<110

Abbreviations: NOEL, no observable effects level; LOEL, lowest observable effects level, GD, gestational day; PND, postnatal day; T4, thyroxine. *measured data = $2.74x10^4$ ng/g lipid, C_{rodent}/C_{human}=90.
† measured = $3.95x10^5$ ng/g lipid, C_{rodent}/C_{human}=1300 (Crofton, DiVito and Hale, personal communication).

Conclusions

Wide variability in PBDE levels was observed in U.S. women; 5 % of women have concentrations ≥ 300 ng/g lipid. If humans are as sensitive as animals to PBDE-induced developmental toxicity, the current margin of safety appears low for many individuals.

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