Polybrominated Diphenyl Ethers in Maternal and Fetal Blood Samples

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Polybrominated diphenyl ethers (PBDEs) are widely used as flame retardants in consumer goods, such as plastics, electronics, textiles, and construction material. PBDEs have been found in human milk, fat, and blood samples. Rodent studies indicate that PBDEs may be detrimental to neurodevelopment, possibly by lowering thyroid hormone concentrations in blood. In the present study, we determined concentrations of PBDEs and thyroid hormones in human fetal and maternal serum. Patients presenting in labor to Indiana University and Wishard Memorial County hospitals in Indianapolis, who were older than 18 years, were recruited to participate. Twelve paired samples of maternal and cord blood were obtained and analyzed using gas chromatographic mass spectrometry; thyroid hormone concentrations were determined by radioimmunoassay. Six congeners of PBDE were measured in maternal and fetal serum samples. The concentrations of total PBDEs found in maternal sera ranged from 15 to 580 ng/g lipid, and the concentrations found in fetal samples ranged from 14 to 460 ng/g lipid. Individual fetal blood concentrations did not differ from the corresponding maternal concentrations, indicating that measurement of maternal PBDE blood levels is useful in predicting fetal exposure; similarly, other reports have shown a high correlation between PBDE in mother's milk and fetal exposure. In accord with reports on other biologic samples, the tetrabrominated PBDE congener BDE-47 accounted for 53–64% of total PBDEs in the serum. The concentrations of PBDEs found in maternal and fetal serum samples were 20–106-fold higher than the levels reported previously in a similar population of Swedish mothers and infants. In this small sample, there was no apparent correlation between serum PBDEs and thyroid hormone concentrations. Our study shows that human fetuses in the United States may be exposed to relatively high levels of PBDEs. Further investigation is required to determine if these levels are specific to central Indiana and to assess the toxic potential of these exposure levels. *Key words:* brominated diphenyl ethers, cord blood, human, pregnancy, serum. *Environ Health Perspect* 111:1249–1252 (2003). doi:10.1289/ehp.6146 available via *http://dx.doi.org/* [Online 10 March 2003]

Several substances are added to plastics, electronics, textiles, and construction material to protect against fire. Brominated flame retardants (BFRs) are the cheapest flame retardant and account for 39% of worldwide flame retardant production (Darnerud et al. 2001; de Wit 2002; Rahman et al. 2001). Polybrominated diphenyl ethers (PBDEs), a subgroup of BFRs, were produced at a worldwide annual rate of 40,000 metric tons in 1999 (Rahman et al. 2001). There are three technical products of PBDEs, each with a different range of bromine substitution (Darnerud et al. 2001). These molecules are similar in structure to polychlorinated biphenyls (PCBs) and are specified using the same numbering scheme (Ballschmitter and Zell 1980). Their structural similarity to PCBs, known to have neurotoxic and carcinogenic action, begs the question of potential biologic hazards associated with PBDEs.

With the advent of governmental regulations banning their use, the levels of PCBs have been slowly decreasing in our environment (Dallaire et al. 2002); on the other hand, the levels of PBDEs are rapidly increasing (Noren and Meironyte 2000). PBDEs have been found in fish from the Great Lakes and rivers in the United States (Dodder et al. 2002; Hale et al. 2001; Luross et al. 2002; Manchester-Neesvig et al. 2001). PBDEs have also been reported in chickens, seafood, seals, and other aquatic mammals and in human milk, fat, liver, and serum samples (Booij et al. 2002; Christensen et al. 2002; Darnerud et al. 2001; Huwe et al. 2002; Jakobsson et al. 2002; Ohta et al. 2002; She et al. 2002; Sjodin et al. 2001). Examination of Swedish human milk samples from 1972 to 1997 showed an alarming, exponential increase in PBDE levels, with a doubling rate of about 5 years (Noren and Meironyte 2000). Similarly, blood concentrations in pooled samples from Norway show a 9-fold increase in PBDEs between 1977 and 1999 (Thomsen et al. 2002). Given these findings, the Swedish government voted to ban some lower brominated formulations of PBDEs by July 2003 (Betts 2002). It has recently been reported that PBDE levels in milk samples from Swedish women have decreased since 1997 (Hooper and She 2002); whether this trend is due to the voluntary phase-out of penta-PBDE is not certain. Concentrations in North America also appear to be increasing. Levels of congeners found in the penta-PBDE formulation have been increasing in ringed seal from the Canadian Arctic (Ikonomou et al. 2002) and herring gull eggs from the Great Lakes (Norstrom et al. 2002) since 1981.

Human exposure to PBDEs comes mainly from ingestion of dietary products, such as fish and cow's milk (Darnerud et al. 2001). Airborne contamination has also been implicated, particularly in the electronics and computer industries (Jakobsson et al. 2002; Sjodin et al. 1999).

The aim of our study was to determine the human fetal and maternal serum concentrations of PBDEs in central Indiana. Although based on only a small sample set, our findings indicate that women in Indiana are exposed to levels even higher than those that warranted banning the use of PBDEs in products sold in Sweden. This preliminary report indicates that further, large-scale studies will be needed to assess exposure levels across a broader population, to identify the sources of exposure in the United States, and to examine possible neurodevelopment deficits associated with high levels of exposure during fetal development.

Materials and Methods

Clinical materials. Institutional review board approval was obtained for studies involving humans. Patients who were older than 18 years, presenting in labor to Indiana University and Wishard Memorial County hospitals in Indianapolis during August–December 2001, were asked to participate. Pregnancies were full term, and no other major medical problems were noted in the mothers. Patients were asked to fill out a survey to determine age, race, smoking habits, potential occupational exposures to PBDEs (e.g., working in computer or electronics manufacturing, repair, or dismantling plants), and any other chemical exposures. Body mass index (BMI; kg/m^2) was calculated from the mother's height, prepregnancy weight, and weight at the time of delivery. Maternal blood was obtained when the patient was admitted to the labor and delivery suite, and fetal blood was obtained from the umbilical cord vein by syringe after delivery. The weight and presence of any congenital defects were noted for each baby.

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This research was supported by an Indiana University Faculty Research Fund to R.A.H. and a grant from the National Institutes of Health (HD37025) to R.M.B.

The authors declare they have no conflict of interest.

Received 4 December 2002; accepted 10 March 2003.

PBDE analysis. **Serum extraction procedure.** The extraction of PBDEs from the serum was based on the method developed and validated by Hovander et al. (2002) but was modified to accommodate our larger sample sizes. Maternal serum (10 mL) or cord serum (5 mL) was transferred to a glass vial and spiked with the internal chlorodiphenyl ether (CDE) standards $^{13}C_{12}$–2,3,3′,4,4′,5-hexachlorodiphenyl ether (CDE-156) and $^{13}C_{12}$–2,2′,3,3′,4,4′,5,5′-octachlorodiphenyl ether (CDE-194). Hydrochloric acid (2 mL, 6 M) and then 2-propanol (12 mL) were added; the sample was vortexed after each addition. Hexane/methyl *t*-butyl ether (MTBE; 10 mL, 1:1, vol/vol) was added, and the sample was rotated for 20 min and then centrifuged. The organic layer was transferred to a new vial, and the serum was extracted with hexane/MTBE two more times, once with 10 mL and once with 5 mL. The three organic fractions were combined, and a 3-mL aliquot was removed for gravimetric determination of the lipid mass. The combined organic fraction was then exchanged into hexane and reduced in volume to approximately 5 mL using a rotary evaporator. The hexane, dichloromethane, and H_2SO_4 came from EM Science (Gibbstown, NJ); the MTBE and propanol came from Burdick & Jackson (Muskegon, MI); and the HCl came from Mallinckrodt (Hazelwood, MO). All of the organic solvents were of pesticide-analysis grade.

We removed the lipids by first adding H_2SO_4 (2 mL, concentrated) to the extract, centrifuging, and transferring the organic phase to a new vial. The sample was washed once with hexane, and the organic fractions were combined. The sample was then reduced in volume to 1 mL with a stream of nitrogen and loaded onto a 20-cm × 1.9-cm (inner diameter), 1% water-deactivated silica gel column (Grace Davison, Baltimore, MD). The silica gel had previously been cleaned using Soxhlet extraction with dichloromethane for 12 hr followed by activation at 120°C for 12 hr. Three 75-mL fractions were collected with the following solvents: hexane, 30% dichloromethane in hexane, and dichloromethane. The middle fraction was reduced in volume to 0.5 mL using a rotary evaporator followed by a nitrogen stream.

Alumina (ICN Biomedicals, Costa Mesa, CA) was cleaned and activated for 12 hr at 450°C. The alumina was dry loaded into a 0.5 cm (inner diameter) × 9.5 cm Pasteur pipette to a height of 6.5 cm and capped with 0.5 cm of anhydrous sodium sulfate. The column was wetted with hexane, and the sample was loaded onto the column. Two fractions of 8 mL each were collected: hexane followed by 40% dichloromethane in hexane. The PBDEs eluted in the second fraction, to which the PBDE congener BDE-118 was added as a recovery standard. The sample was reduced in volume to approximately 20 µL under a stream of nitrogen before injection into the gas chromatographic (GC) mass spectrometer.

Instrumental analysis and parameters. We analyzed the samples on an Agilent 6890 series GC coupled to an Agilent 5973 mass spectrometer with helium as the carrier gas (Agilent, Palo Alto, CA). The 2 µL injections were made in the pulse splitless mode, with a purge time of 2.0 min. The injection port was held at 285°C. The GC column was a 60 m × 250 µm (inner diameter) fused silica capillary tube coated with DB-5-MS (0.25 µm film thickness; J&W Scientific, Folsom, CA). A 60-m column was used to ensure separation of BDE-154 from polybrominated biphenyl 153 (PBB-153). The GC oven temperature program was as follows: isothermal at 110°C for 1.90 min, 15°C/min to 180°C, 1.85°C/min to 300°C, and held at 300°C for 45 min. The transfer line was held at 285°C. The mass spectrometer was operated in electron capture negative ionization (ECNI) mode using methane as the buffer gas. Selected ion monitoring (SIM) of the two bromide ions at *m/z* 79 and 81 was used to detect the PBDEs. The ions at *m/z* 351.9 and 349.9 were used to detect CDE-156, and ions at *m/z* 457.8 and 455.8 were used to detect CDE-194. In each case, the first ion was used for quantitation and the second for confirmation. The compounds were quantitated using quantitation standards with known amounts of all the target compounds, internal standards, and recovery standards. CDE-194 was used to quantitate the PBDEs; CDE-153 was used to confirm the match of the retention times of the compounds in the sample with those in the standard solution.

Quality control. Three quality control criteria were used to ensure the correct identification of the target compounds: *a*) The GC retention times matched those of the standard compounds; *b*) the signal-to-noise ratio was > 3; and *c*) the isotopic ratio between the quantitative ion and confirmation ion was within ±15% of the theoretical value. The average recovery of the internal standard was 65 ± 5%.

Two procedural blanks were run in parallel with every batch of six samples. The procedural blank consisted of an appropriate amount of hexane spiked with the internal standard. The blanks contained only BDE-47 and BDE-99, at average levels of 56 ± 11 pg and 31 ± 5 pg, respectively. If the average blank level for either congener was < 30% of the congener level in the serum sample, the average blank level was subtracted from the serum level. If the blank level for either congener was > 30%, that sample was excluded. This criterion was applied to each BDE congener so that the limits of detection of each congener varied from 0.01 to 0.19 ng. Six of the 30 samples analyzed had to be excluded because of high blanks.

Thyroid hormones. Serum thyroxine (T_4) and triiodothyronine (T_3) were measured in the Analyte Core Facility at Indiana University School of Medicine, Indianapolis. Radioimmunoassay kits for total and free T_4 and T_3 were purchased from Diagnostic Products Corp. (Los Angeles, CA) and used according to the manufacturer's protocols. Detection limits were 1 µg/dL and 0.02 µg/dL for total T_4 and total T_3, respectively; the detection limits for free T_4 and free T_3 were 1 ng/dL and 0.06 ng/dL, respectively.

Statistics. A paired *t*-test analysis was used to determine whether fetal and maternal PBDEs differed. In addition, correlations between maternal and fetal PBDEs and between PBDEs and BMI, birth weight, or thyroid hormones were tested using the Pearson coefficient of determination.

Results

Fifteen paired maternal and fetal samples were analyzed for PBDE; three pairs of these samples are not reported because they did not meet quality control specifications because of problems with blank analysis. Of the 12 patients reported, the average age was 26 years with a range of 18–37 years. The average BMI at presentation was 36 with a range of 27–56. None of the mothers reported any work-related potential for exposure to PBDEs, and all denied smoking exposure. Infant weights ranged from 3,050 to 4,040 g; no birth defects were documented. Six different congeners of PBDE were measured in the serum samples (Table 1). Of the six congeners detected, BDE-47 accounted for the majority (53–64%) of all PBDEs; BDE-99 was the next most abundant congener at 15–19% (Figure 1). The concentrations of total PBDEs found in maternal sera ranged from 15 to 580 ng/g lipid, and the concentrations found in fetal samples ranged from 14 to 460 ng/g lipid. The PBDE concentrations were highly correlated (r^2 = 0.986), exhibiting no statistical differences between maternal and fetal blood (Figure 2). All the PBDE congeners were detected in all the samples except BDE-154, which was not detected in two of the samples, and BDE-183, which was not detected in 20 of the 24 samples. The detection limits for BDE-154 and BDE-183 were 0.01 and 0.03 ng, respectively.

There was no apparent correlation between concentrations of PBDEs and any of the clinical parameters. Serum PBDE concentrations did not vary according to age or BMI, nor was there any relationship between infant birth weight and PBDE concentrations. Thyroid hormones were assayed in 9 of the 12 sample pairs. Figure 3 shows no apparent correlation between total PBDEs and T_4 concentrations

(total or free). Similarly, there was no correlation between PBDEs and either total or free T_3 (data not shown).

Discussion

This is the first report of PBDE blood levels in pregnant women and their fetuses from the United States. We found that total PBDEs varied over an approximate 40-fold range in the 12 pairs of samples analyzed. When compared with a similar population of Swedish mothers and newborns (Guvenius et al. 2003), serum PBDE levels in our study were 20- to 69-fold higher for maternal blood and 30- to 106-fold higher for fetal blood. Likewise, the range of BDE-47 levels we report in women from Indiana was approximately 20-fold that found in Norwegian blood samples from 1997–1999 (Thomsen et al. 2002). Moreover, the median blood levels found in our population indicate an exposure to PBDEs comparable with that of Swedish workers considered to have had direct, work-related exposures (Jakobsson et al. 2002; Sjodin et al. 1999). In contrast, samples collected from adult U.S. blood donors in 1988 had sum concentrations of PBDEs that were much lower (~0.12–0.65 ng/g lipid) (Sjodin et al. 2001) than the levels we found in the maternal samples. The reason for the disparity between our results and those of previous studies is not positively known; however, because PBDEs are not manufactured in Europe, as they are in the United States (Darnerud et al. 2001), exposure levels may be lower in Europe. In addition, concentrations of PBDEs in the North American environment have increased since 1988 (Ikonomou et al. 2002; Norstrom et al. 2002). It will require further investigation to determine whether the high human concentrations reported here represent a regional or a national trend. However, in a review of the currently available data, Ryan observed that concentrations of PBDEs in breast milk of North American women were 40–50 times greater than concentrations previously described in Swedish breast milk samples (Betts 2002). Similarly, a recent study of PBDEs in breast fat of women in San Francisco found concentrations averaging 86 ng/g lipid (She et al. 2002). Together with our study, these observations indicate that women in North America are exposed to much higher levels of PBDEs than are European women.

In general, the PBDE congener profile we found in human serum was similar to that detected in environmental samples, except that there is an apparent decrease in the proportion of BDE-99. In air, BDE-99 accounts for 35% of the total PBDEs (Strandberg et al. 2001), whereas in fish it was 27% (Dodder et al. 2002), and in humans it was 15–19% (present study). This range for BDE-99 is similar to the range found in other human studies (Hovander et al. 2002; Sjodin et al. 2001). The lower proportion of BDE-99 may indicate a differential metabolic degradation of BDE-99 as it goes through the food chain. In addition, BDE-183 was detected in only 4 of the 24 samples, even though it is the primary congener in the octa-BDE technical mixture (Darnerud et al. 2001). This may be the case because BDE-183, like BDE-209, has a lower bioavailability compared with the other lower brominated congeners or because its low vapor pressure does not facilitate its atmospheric transport as readily as the other congeners (Dodder et al. 2002; Strandberg et al. 2001). On the other hand, relatively high levels of BDE-183 have been observed in occupationally exposed workers (Sjodin et al. 1999; Thomsen et al. 2001). It would be interesting to identify the metabolites of the congeners present because they have the potential to behave as endocrine disruptors (Meerts et al. 2000, 2001).

It is apparent that, like PCBs and organochlorine pesticides (Covaci et al. 2002; DeKoning and Karmaus 2000; Sala et al. 2001; Waliszewski et al. 2000), PBDEs cross the placenta into the fetal circulation. Furthermore, our results indicate that all tetra- through hepta-substituted congeners have approximately the same potential to cross the placenta. The high correlation between maternal and fetal blood levels of PBDE indicates that measurement of maternal PBDE yields a strong indication of PBDE exposure of the fetus at the time of birth; whether this is true at earlier points in gestation will require additional studies. It is likely that lipophilic compounds such as PBDEs move into fetal circulation along with maternal lipids. Experimental analysis of maternal and fetal blood samples and lipid infusion studies indicate that there is an influx of lipids from maternal and placental sources into the fetal circulation (Berghaus et al. 1998; Elphick et al. 1978; Hendrickse et al. 1985). Furthermore, there is a dramatic mobilization of maternal fat stores during the third trimester of gestation (Pipe et al. 1979), a period critical to brain development (Porterfield 2000); the biologic significance and bioavailability of PBDEs in fetal circulation during this period of gestation have yet to be determined.

PCBs and dioxins are known neurotoxicants, as demonstrated in experimental animal studies and in humans through epidemiologic studies (Brouwer et al. 1995; Jacobson et al. 1990). PBDEs are structurally similar to PCBs, and studies have been performed to assess their neurotoxic potential. Neonatal and fetal exposure of mice to PBDEs showed a permanent effect on spontaneous behavior, learning, and memory (Eriksson et al. 2001, 2002). Thyroid hormones play an important role in brain development, and deficiencies in T_4 are known to cause mental delay in humans (Porterfield 2000;

Table 1. Concentrations (ng/g lipid) of BDE congeners in fetal and maternal serum (n = 12).

BDE congener	Fetal		Maternal	
	Median	Range	Median	Range
BDE-47	25	8.4–210	28	9.2–310
BDE-99	7.1	2.2–54	5.7	2.4–68
BDE-100	4.1	1.8–91	4.2	1.9–110
BDE-153	4.4	1.0–120	2.9	1.0–83
BDE-154	0.7	0.2–7.2	0.3	0.0–6.1
BDE-183	0	0.0–4.8	0	0.0–2.7
Total PBDEs	39	14–460	37	15–580

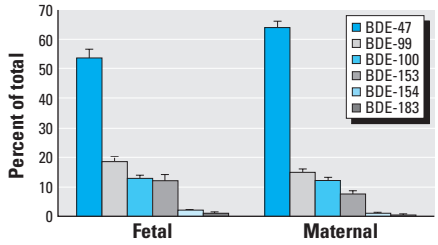

Figure 1. Congener profiles of PBDE in serum. The mean level of each congener detected was determined as a percentage of the total PBDEs present (mean ± SD, n = 12).

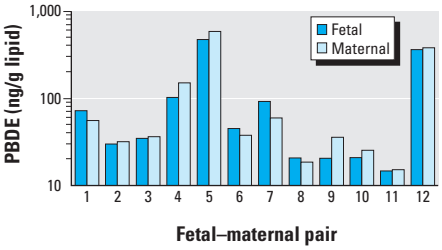

Figure 2. Total PBDE concentrations in maternal and fetal blood samples. The sum of all congeners detected in each sample is presented.

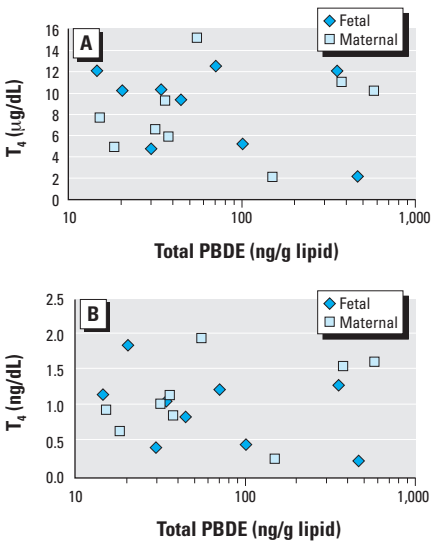

Figure 3. Thyroid hormone concentrations. The total (*A*) and free (*B*) T_4 concentrations were determined for nine of the paired samples and plotted against the corresponding level of total PBDEs in each sample.

Zoeller and Crofton 2000). Hallgren et al. (2001) demonstrated a dose-related reduction in both total T_4 and free T_4 concentrations in mice and rats exposed to PBDEs. It is likely that PBDEs or their metabolites displace thyroid hormones from the serum binding protein transthyretin, thereby allowing increased metabolism of the hormone (Hallgren and Darnerud 2002). In the present study, there was no apparent association between serum concentrations of PBDEs and thyroid hormones; however, the sample size may have been too small to detect such a relationship in a human population.

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