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Polybrominated diphenyl ethers (flame retardants) in mother-infant pairs in the Southeastern U.S.

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ABSTRACT

Polybrominated diphenyl ethers (PBDEs) are commonly used flame retardants in foams, building material, electronics, and textiles. These chemicals leach into the environment, where they persist, and are found today in virtually every population worldwide. Several studies in recent years have detected the presence of PBDEs in maternal and infant samples. However, few of these studies were conducted in the U.S., and few examined paired or matched mother blood-cord blood samples. We analyzed serum from 10 mother-infant pairs for the presence of PBDEs in a patient population in the Southeastern U.S. Out of 35 measured PBDE congeners, five (BDE-28, -47, -99, -100, and -153) were present, with detection frequencies of 65–100 %. The total PBDE concentrations in maternal and infant sera were highly correlated ($r^2 = 0.710$, $p = 0.0043$). The levels of BDE-47, -99, and -100 and of total PBDEs were higher in the infant cord sera when compared with those in maternal sera ($p < 0.017$), suggesting that fetuses and neonates might have higher circulating concentrations of these potentially neurotoxic and endocrine disrupting chemicals compared with their mothers. The primary focus henceforward should be whether there are any deleterious effects from exposure to these chemicals on human health.

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Introduction

Polybrominated diphenyl ethers (PBDEs) are commonly used flame retardants in foams, building materials, electronics, and textiles. These compounds are classified by the number of bromine atoms in the molecule, ranging from 1 (mono-) to 10 (deca-); overall there are 209 different congeners (Alaee et al. 2003). These chemicals are lipophilic, have a similar structure to thyroid hormones, are highly resistant to degradation, and are common contaminants of dust, various foods, such as fish, dairy products, and meats, and air, water, soil, and sediments (Darnerud et al. 2001; Frederiksen et al. 2009; Domingo, 2012). The widespread use of PBDEs in the past few decades (Sjodin et al. 2004) and their persistence in the environment (Sjodin et al. 2001; de Wit, 2002; Hites, 2004) and human tissues

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(Covaci et al. 2008) explain the presence observed in virtually every human population (Darnerud et al. 2001; Hites, 2004; Bi et al. 2006; Jaraczewska et al. 2006; Kawashiro et al. 2008; Meijer et al. 2008; Antignac et al. 2009; Kim et al. 2009; Vizcaino et al. 2011; Kim et al. 2012; Arbuckle et al. 2013; Chen et al. 2013).

PBDEs have been detected in fetal (Schecter et al. 2007), child and adult (Pacyniak et al. 2010) organ tissues, umbilical cord blood, human adipose tissue (Covaci et al. 2002; Petreas et al. 2011), and human breast milk (Carrizo et al. 2007). Several studies have linked these compounds to hormone disruption, especially thyroid hormones and estrogen (Meerts et al. 2001; Vuong et al. 2015), neurodevelopment toxicity (Eriksson & Fredriksson 1996; Viberg et al. 2002; Kuriyama et al. 2005; Costa & Giordano 2007; Dingemans et al. 2008; Roze et al. 2009; Herbstman et al. 2010), and lower birth weight and length (Chao et al. 2007). Because of these health concerns, PBDE commercial products are no longer manufactured in the United States, and have been banned by the European Union and Canada (Carrizo et al. 2007). Nonetheless, the compounds persist in the environment and in human tissues analyzed as recently as 2015, causing on-going exposure in humans.

Several studies have been performed in the last 14 years analyzing the presence of PBDEs in mothers and infants. These studies are important, especially if infant and childhood neurodevelopment is a concern. However, few of these studies were conducted in the U.S., and few examined paired or matched mother blood-cord blood samples. Here, we present the results of a recent study of mother-infant pairs in the Southeastern U.S., which analyzed maternal serum and umbilical cord blood from mother-infant pairs for the presence of PBDEs. We also provide a brief review of the more recent data on transplacental passage of PBDEs.

Materials and methods

All pregnant patients that entered labor and delivery at University of Tennessee Medical Center, Knoxville, were eligible. We enrolled 10 pregnant patients resulting in an analysis of 20 samples (10 mothers and 10 infants). Eligible patients were approached to participate in the study once they were admitted in active labor. If they agreed, an approved informed consent form was signed. The study was reviewed and approved by the institutional review board of the UT Graduate School of Medicine.

Once consented, an additional tube of blood was collected at the time the pregnant mother's admission blood work was obtained. At delivery, an additional tube of cord blood was also obtained, creating matched samples of mother and newborn. Samples were immediately processed and sera were frozen until analyzed for the presence of 35 common PBDE congeners (7, 10, 15, 17, 28, 30, 47, 49, 66, 85, 99, 100, 119, 126, 138–140, 153, 154, 156, 169, 180, 183, 184, 191, 196, 197, 201, and 203–209).

Information collected on the participating pregnant mothers included age, ethnicity, body mass index (BMI) at delivery, gestational age, type of delivery, and any major medical disorders (such as hypertension or diabetes). Neonatal data collection included birth weight, gender, Apgar score, and any neonatal complications.

Sample preparation and analysis

Sera samples (approximately 2–3 mL) were thawed overnight, weighed, transferred to a 50 mL screw-top tube, and spiked with known amount of surrogate recovery standards (BDE-77, BDE-166, and $^{13}C_{12}$-BDE-209). Each sample was denatured consecutively with 2 mL of hydrochloric acid (6 M) and 2 mL of 2-propanol. Samples were extracted with 10 mL of *n*-hexane : methyl *tert*-butyl ether (MTBE) (1:1 v/v) for three times. Extracts were combined and a small aliquot was taken for gravimetric lipid measurement. The remaining extract was rotary evaporated to approximately 1 mL with one solvent change of 25 mL of *n*-hexane and then fractionated on a 6 g of 2.5 % (by weight) water deactivated Florisil column. The column was eluted with 35 mL of *n*-hexane, then 35 mL of *n*-hexane : dichloromethane (1:1 vol) and the two fractions collected separately. Both fractions were rotary evaporated to approximately 1 mL and the second fraction was further solvent changed to *n*-hexane once. Each

fraction was transferred to a 4 mL amber glass vial and nitrogen blown down to 1 mL, spiked with BDE-118, BDE-181, and BB-209 as internal standards and further blown down to 0.1 mL for the analysis of PBDEs. PBDEs were eluted in both fractions.

Instrumental analysis

The analyses of 35 PBDE congeners (7, 10, 15, 17, 28, 30, 47, 49, 66, 85, 99, 100, 119, 126, 138–140, 153, 154, 156, 169, 180, 183, 184, 191, 196, 197, 201, and 203–209) were done on an Agilent 7890 series gas chromatograph (GC) coupled to an Agilent 5975C mass spectrometer (MS) operating in the electron capture negative ionization (ECNI) mode. Chromatographic separation was accomplished with an Rtx-1614 (15 m, 250 µm i.d., 0.1 µm film thickness) fused silica capillary GC column (Restek Corporation, Bellefonte, CA). High purity helium (99.999 %; Liquid Carbonic, Chicago) was used as the carrier gas and high purity methane (99.97 %, Praxair) was used as the reagent gas. Instrument detection limits ranged from 0.03 to 0.09 ng. Details on the instrumental analysis procedures have been previously reported (Ma et al. 2013). All samples were quantitated using the internal standard method.

Quality assurance and quality control

Samples were obtained and processed in 2013, following standard operating procedures and quality assurance and quality control measures. A procedural blank (total of three blanks) was run with every batch of samples. Average blank concentrations were 0.040, 0.025, 0.01, and 0.025 ng for BDE-47, -99, -100, and -153, respectively. BDE-28 was not detected in blanks. Concentrations below the average blank levels were treated as non-detects and replaced with empty cells in the data spreadsheet. The surrogate recoveries (average ± stt. error) were 110 ± 11, 75 ± 4, and 51 ± 5 % for BDE-77, BDE-166, and $^{13}C_{12}$-BDE-209, respectively. None of the concentrations were corrected for surrogate recoveries. All concentrations were adjusted for the lipid content of the sample. Lipid content (average ± st. error) for maternal sera was 0.99 ± 0.08 g (range of 0.49–1.5 g), while for cord sera it was 0.24 ± 0.06 g (range of 0.05–0.66 g).

Results

A total of 10 mother–infant pairs were recruited with 9 Caucasian and 1 Asian. The mean maternal age was 29.2 years with a range of 21–39. The mean BMI at delivery was 33.8 with a range of 24–51. There were four patients with a BMI of <30; 4 with a BMI of 30 to <40; and 2 with a BMI of ≥40. There was no clear correlation between PBDE level and BMI; concentrations are expressed on a lipid weight basis.

Out of 35 measured PBDE congeners, five were present with the detection frequencies of 65–100 % (Table 1) and only these congeners (BDE-28, -47, -99, -100, and -153) are discussed below. Of the five congeners, BDE-47 was the most abundant congener comprising 23–74 % of total PBDE concentrations, followed by BDE-99 (at 12–43 %). Both maternal and infant sera (from cord blood) had similar congener profiles, with the exception of BDE-99 which was relatively enriched in infant sera at 36 ± 8 % of total PBDE concentrations vs. 20 ± 2 % in maternal sera. The concentrations of total PBDEs in maternal sera ranged from 10 to 62 ng/g lipid weight (lw), whereas these concentrations in infant sera ranged from 17 to 120 ng/g lw (Figure 1). The total PBDE concentrations in maternal and infant sera were highly correlated ($r^2 = 0.710$, $p = 0.0043$ with the sample #2 excluded as an outlier). The levels of BDE-47, -99, -100 and of total PBDEs were higher in the infant cord sera when compared with the maternal sera concentrations ($p = 0.017$). In every mother–infant pair, the infant total PBDE concentration was higher than that in the maternal sample. We observed the same pattern when we examined individual PBDEs in our samples (Table 1). The average ratio of cord to maternal (CM) total PBDE concentrations was 2.1 ± 0.32, similar to the CM ratio for BDE-28, -47, and -100 at 2.5 ± 0.87, 2.2 ± 0.40, and 2.6 ± 064, respectively. This ratio was higher for BDE-99 concentrations at 3.7 ± 0.62, and lower for BDE-153 at 1.9 ± 0.78.

Table 1. Concentrations of polybrominated diphenyl ethers (PBDEs) in ten paired maternal serum and fetal cord blood samples (ng / g lipid weight).

Mother	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	Total PBDE*	Child	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	Total PBDE
1	2.61	9.41	5.23	2.61	2.61	22.5	1	2.93	41.0	11.7	n.d	n.d	55.6
2	0.710	5.68	2.13	1.42	n.d.	9.94	2	5.69	39.8	34.1	22.8	n.d	102
3	0.429	8.58	3.86	2.15	1.72	16.7	3	3.17	28.5	28.5	12.7	n.d	72.8
4	0.931	9.62	3.10	1.86	3.73	19.2	4	1.25	14.9	8.72	6.23	n.d	31.1
5	n.d.	2.62	3.49	1.31	3.93	11.4	5	n.d	n.d	19.2	n.d	n.d	19.2
6	0.338	8.44	4.39	1.69	7.09	21.9	6	n.d	11.3	18.8	3.76	9.39	43.2
7	0.857	9.85	3.43	3.85	10.3	28.3	7	1.42	15.6	14.2	2.83	7.08	41.1
8	5.30	26.5	7.94	8.83	13.2	61.8	8	4.99	54.8	19.9	19.9	19.9	120
9	1.11	14.4	4.44	3.33	2.22	25.5	9	3.74	31.8	11.2	9.34	9.34	65.4
10	0.504	8.56	3.02	2.52	2.01	16.6	10	0.787	8.65	4.72	3.15	n.d	17.3
Median	0.857	9.00	3.68	2.33	3.73	20.6	Median	3.05	28.49	16.47	7.78	9.37	49.4
Mean	1.42 ± 0.535	10.4 ± 2.03	4.10 ± 0.507	2.96 ± 0.701	5.20 ± 1.37	23.4 ± 4.64	Mean	3.00 ± 0.630	27.4 ± 5.29	17.1 ± 2.85	10.1 ± 2.74	11.4 ± 2.89	56.8 ± 10.8
Range	(n.d. –5.30)	(n.d. –26.5)	(n.d. –7.94)	(–n.d.- 8.83)	(–n.d.- 13.2)	(9.94–61.8)	Range	(0.787–5.69)	(8.65–54.8)	(4.72–34.1)	(2.82–22.8)	(7.08–19.9)	(17.3–120)

Note: (N.D. = not detected).
*Total PBDE concentrations are the sum of the concentrations of the five individual PBDE congeners included in this table.

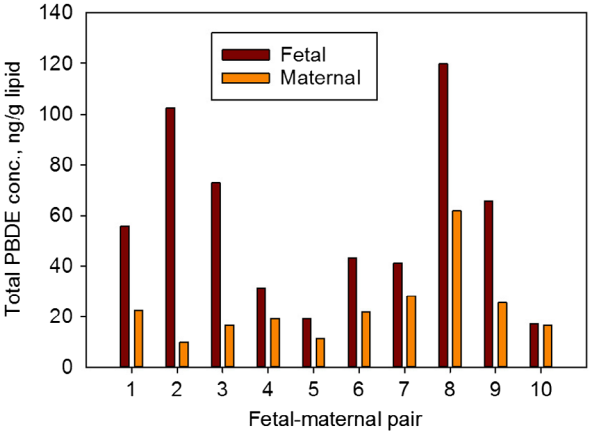

Figure 1. Total PBDE concentrations (the sum of BDE-28, 47, 99, 100, and 153, ng/g lipid weight) in matched maternal and fetal cord blood samples.

We provide a summary of the reports on this subject extending back 14 years (Table 2). As demonstrated, every study has found some PBDEs in both maternal samples and infant cord blood.

Comment

The results of our study are consistent with those of previous studies showing that PBDEs are found in maternal blood, cross the placenta and enter fetal circulation. Our results show that the levels of PBDEs in cord blood samples are higher than those in maternal samples collected at delivery. These increased levels of PBDEs in cord sera were evident in each maternal–infant sera pair, suggesting that fetuses and neonates might have higher circulating concentrations of these potentially neurotoxic and endocrine disrupting chemicals compared with their mothers.

The elevated PBDE concentrations found in infant sera in this study are consistent with the recent studies on PBDE distribution between infant and maternal blood (Chen et al. 2013; Choi et al. 2014). The congener profiles are similar between the maternal and infant samples, with BDE-47 accounting for about half of total PBDE concentrations. BDE-99 contribution to total PBDE concentrations was higher in cord blood than in maternal blood; and BDE-153 contribution was higher in maternal blood than that in cord blood. The latter observations were reported in several previous studies (Mazdai et al. 2003; Chen et al. 2013) and perhaps may be due to differences in the congeners ability to pass through the placenta.

Overall, given that the PBDE concentrations measured in maternal and infant sera were highly correlated, and the congener profiles were similar between maternal and fetal samples, it may be worth considering when planning an investigation to what extent measuring both may be redundant.

Despite the small sample size, our study is the first to include samples from mother–infant pairs living in the Southeastern United States. There are only three other such studies from North America, two from the Mid-western United States (Mazdai et al. 2003; Chen et al. 2013) and one from Canada (Foster et al. 2011). Our results are consistent with those reported in the U.S. samples, but lower than those found in the mothers and neonates in Canada (median at 50–100 ng/g lw, respectively). In all three studies, BDE-47 was the most abundant congener, similar to our findings. This might be explained by the fact that BDE-47 is the major component of the Penta-BDE commercial product that was widely used in North America until 2004. The latter might also explain generally lower PBDE concentration measured in European cohorts.

Table 2. Summary of the literature on PBDE concentrations in maternal and fetal cord blood (ng/g lipid weight).

Study	Location	Samples Tested	PBDEs Measured	Total PBDEs Median (range)
Current study	USA	10 maternal 10 cord blood (paired)	28, 47, 99, 100, 153	M[a]: 20.6 (9.94–61.8) C[b]: 49.4 (17.3–120)
(Chen et al. 2014)	South China	30 cord blood	17, 28, 47, 99, 138, 153, 154, 183, 197	9.73 (1.02–71.3)
(Choi et al. 2014)	South Korea	198 maternal serum 118 cord blood (paired)	28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 153, 154	M: 1.83 (0.93–3.81) C: 1.93 (0.55–3.56)
(Li et al. 2013)	China	29 maternal serum 29 cord blood (paired)	17, 28, 47, 49, 66, 206, 207, 208, 209	M: 29.3 C: 41.1
(Chen et al. 2013)	USA	20 maternal serum 20 cord blood (paired)	28, 47, 99, 100, 153, 154, 209	M: 28.5 (7.46–176) C: 41.5 (17.9–171)
(Kim et al. 2012)	South Korea	21 maternal serum 21 cord blood (paired)	28, 47, 99, 100, 153, 154, 183	M: 7.81 (1.8–17.7) C: 12.0 (2.28–30.9)
(Kim et al. 2011)	South Korea	90 cord blood	28, 47, 99, 100, 153, 154, 183	16.43[c] (2.78–94.64)
(Jakobsson et al. 2012)	Sweden	10 maternal serum 10 cord blood (paired)	28,47,99,153,154,197,209	M: 11.3 (3.30–32.4) C: 4.7 (1.2–26)
(Arbuckle et al. 2013)	Canada	Cord blood samples[d]	17, 28, 47, 66, 99, 100, 153, 154, 183	nd[e]
(Foster et al. 2011)	Canada	97 maternal serum 97 cord blood (paired)	17, 28, 47, 66, 99, 100, 153, 154, 183	M: 54.7 (6.84–1103) C: 113 (51.1–1450)
(Vizcaino et al. 2011)	Spain	174 maternal serum 174 cord blood (paired)	47, 99, 153, 154, 209	M: 9.6 (n.d-140) C: 9.6 (n.d-120)
(Lin et al. 2011)	Taiwan	54 cord blood	15, 28, 47, 99, 100, 153, 154, 183	3.49 (1.65–47.3)
(Wu et al. 2010)	China	153 cord blood	28, 47, 99, 100, 153, 154, 209	M: 13.8 (1.14–505) C: 5.23 (0.29–364)
(Frederiksen et al. 2010)	Denmark	51 maternal serum 40 cord blood	28, 47, 99, 100, 153, 154	M: 1.76 (0.64–51.9) C: 0.958 (0.213–54.5)
(Herbstman et al. 2010)	USA	210 cord blood	47, 85, 99, 100, 153, 154, 183	18.8
(Kang et al. 2010)	South Korea	20 maternal serum 20 cord blood (paired)	28,47,99,100,153,154,197 ,203.207,209	M: 7.8 (0.00–270) C: 13 (0.00–480)
(Kim et al. 2009)	South Korea	108 cord blood	28, 47, 99, 100, 153, 154, 183	8.23 (n.d.-29.4)
(Antignac et al. 2009)	France	91 maternal serum 90 cord blood (paired)	28, 47, 85, 99, 100, 118, 153, 154, 155, 183, 190, 196, 197, 201, 202, 203, 206, 207, 208, 209	M: 9.83 (0.474–81.5) C: 13.0(1.03–380)
(Kawashiro et al. 2008)	Japan	16 maternal serum 8 cord blood	15, 28, 47, 49, 66, 85, 99, 100, 153, 154, 197, 207, 209	M: 3.0 (1.8–17) C:0.65 (0.30–6.2)
(Meijer et al. 2008)	Netherlands	12 maternal serum 12 cord blood (paired)	47, 99, 100, 153, 154	3.3 (0.47–33.1)
(Herbstman et al. 2007)	USA	297 cord blood	28, 47, 85, 99, 100, 153, 154, 183	26.6 (n.d-672)
(Gomara et al. 2007)	Spain	113 maternal serum 92 cord blood	17, 28, 47, 66, 85, 99, 100, 153, 154, 183, , 191, 196, 197, 209	M: 12 (5.5–43); 9.7 (4.4–46) C: 17 (6.3–82); 15 (4.3–38)
(Carrizo et al. 2007)	Spain	92 cord blood	17, 28, 47, 99, 100, 183,	6.2 ± 7.2
(Bi et al. 2006)	South China	21 maternal serum 21 cord blood (paired)	28, 47, 99, 100, 153, 154, 183	M: 4.4 (1.6–17) C: 3.9 (1.5–12)
(Weiss et al. 2004)	Sweden	78 maternal and 12 cord blood samples	47, 99, 100, 153, 154	8.18 (0.9–26)
(Guvenius et al. 2003)	Sweden	15 maternal serum 15 cord blood (paired)	17, 28, 47, 66, 85, 99, 100, 153, 154, 183	M: 2.07(0.71–8.39) C: 1.69(0.46–4.28)
(Mazdai et al. 2003)	USA	12 maternal serum 12 cord blood (paired)	47, 99, 100, 153, 154, 183	M: 37 (15–580) C: 39 (14–460)

[a]M: maternal
[b]C: cord
[c]Mean
[d]Sample size was not available
[e]nd: not detected
[f]data from two different locations.

Experimental animal models have shown deleterious effects, such as developmental neurotoxicity, from pre-natal exposure to PBDEs (Costa & Giordano 2007; Costa et al. 2008). In humans, a few Asian studies have investigated neonatal PBDE levels in relation to stillbirth, low birth weight, and pre-term birth, with some showing increased risks among infants with higher cord blood (Wu et al. 2010) or breast milk (Chao et al. 2007). In a U.S. cohort study, Herbstman and colleagues (Herbstman et al. 2010) found that cord blood PBDE levels were inversely associated with tests of mental and physical development at 12, 48, and 72 months after birth. In a cohort of Dutch children, Roze and colleagues (Roze et al. 2009) found some weaker associations between higher levels of PBDE exposure with health outcomes, but their results overall did not support the U.S. findings. This is not surprising, however, because PBDE exposure levels in the U.S. cohort were several times higher, consistent with the appreciably higher environmental levels in North America compared with Europe and Asia (Foster et al. 2011). Ezkenazi and colleagues investigated the association between *in utero* and child PBDE exposure with neurobehavioral development among participants in a California birth cohort (Eskenazi et al. 2013) finding inverse associations between PBDE levels and IQ, particularly processing speed, verbal comprehension, and perceptual reasoning. PBDE levels were positively associated with hyperactivity.

There is now ample evidence for the placental transfer of PBDEs during pregnancy. However, epidemiologic studies of PBDE exposure and health outcomes in humans remain limited in number and scope (Linares et al. 2015). Future studies should include new or additional analyses of data from studies that are already measuring prenatal PBDE exposure in relation to health endpoints, and new flame retardant chemicals that replace those that have been phased out (Linares et al. 2015). Moreover, the current literature reveals several methodological limitations that may be addressable in future studies. For example, post-natal exposure of infants and children to PBDEs through breastfeeding, food, transdermal absorption, and dust (Guvenius et al. 2003; Carrizo et al. 2007; Herbstman et al. 2010) suggests the need for repeated measures of exposure during follow-up to reduce measurement error. To further improve validity, multivariate models may be used (in sufficiently large studies) to assess and control confounding from such factors as maternal age, pre-pregnant BMI, weight gain during pregnancy, maternal smoking, sex of child, race/ethnicity, rural or city residence, various socioeconomic factors, psychosocial stress, and gestational age (Herbstman et al. 2010; Lin et al. 2011) Future studies should also address possible interactions of PBDEs with PCBs and other chemicals in causing disease (Herbstman et al. 2010), as well as with individual genetic and epigenetic factors (Herbstman et al. 2007).

Conclusion

To our knowledge, this is the first study of PBDE levels in mother–infant pairs in the Southeastern U.S. As we expected, mother–infant PBDE levels were highly correlated, and PBDE levels were consistently higher in the infant of each mother infant pair, suggesting that fetuses and neonates may have higher circulating concentrations of these potentially neurotoxic and endocrine disrupting chemicals compared with their mothers. The primary focus henceforward should be whether there are any deleterious effects from exposure to these chemicals on human health. A definitive answer requires additional long-term follow-up studies of newborns that discern any differences in health based on PBDE levels that might be found at various times during pregnancy, at birth, and over the subsequent years of follow-up.

Disclosure statement

No potential conflict of interest was reported by the authors.

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