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Original Contribution

Prenatal Exposure to Polybrominated Diphenyl Ether Flame Retardants and Neonatal Thyroid-Stimulating Hormone Levels in the CHAMACOS Study

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Studies published in the last 3 decades have demonstrated global human exposure to polybrominated diphenyl ether (PBDE) flame retardants. A growing body of literature suggests that PBDEs may disrupt thyroid hormone homeostasis. Although thyroid hormones play an essential role in brain development, few studies have investigated relations between prenatal exposure to PBDEs and neonatal thyroid hormone levels, and none have measured thyroid-stimulating hormone (TSH) levels in neonates. The authors measured 10 PBDE congeners in serum collected between October 1999 and October 2000 from 289 pregnant women living in California's Salinas Valley and abstracted TSH levels from their children's medical records. Individual PBDE congeners showed null or weak nonsignificant inverse relations with neonatal TSH. Total serum PBDE was not associated with neonatal TSH ($\beta = 0.00$, 95% confidence interval: -0.06, 0.06). Except for brominated diphenyl ether 153, a higher serum PBDE level was related to elevated odds of high TSH ($\geq$80th percentile), but associations were not statistically significant. Associations were not modified by infant sex, age at TSH measurement, maternal serum polychlorinated biphenyl concentration, or mode of delivery. Results were robust to sensitivity analysis. The authors found no conclusive evidence that prenatal exposure to PBDEs at levels similar to those of the general US population is related to neonatal TSH.

endocrine disruptors; flame retardants; halogenated diphenyl ethers; prenatal exposure delayed effects; thyroid hormones; thyrotropin

Abbreviations: BDE, brominated diphenyl ether; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; SD, standard deviation; TSH, thyroid-stimulating hormone.

Polybrominated diphenyl ethers (PBDEs) are synthetic flame retardants used in a variety of consumer products, including furniture, carpets, textiles, and electronics. Studies have demonstrated global human exposure to PBDEs. In the United States, virtually all residents have detectable serum levels of PBDEs (1). Of the 3 commercially available mixtures, two (penta-brominated diphenyl ether (BDE) and octa-BDE) were phased out in Europe and the United States in 2004. However, exposure is probably ongoing, as PBDEs may continue to leach out of products manufactured before this time.

Recent epidemiologic studies have suggested that PBDEs may disrupt the endocrine system and affect reproductive and endocrine-regulated health outcomes in humans. For instance, serum PBDE concentrations have been associated with decreased testosterone levels in men (2), higher odds of cryptorchidism in neonates (3), lower birth weight (4), reduced fecundability in women (5), and lower scores on measures of intelligence and attention in toddlers and school-aged children (6, 7). A growing body of literature also suggests that PBDEs may disrupt the hypothalamic-pituitary-thyroid axis in adults (8–10). Thyroid hormones play an essential role in fetal and neonatal brain development (11), but studies investigating relations between PBDE exposure and thyroid hormone levels during these critical developmental periods are scarce.

We previously reported that serum concentrations of BDE-28, -47, -99, -100, and -153 and total PBDEs ($\sum$PBDEs) were negatively associated with thyroid-stimulating hormone (TSH) levels but not free or total thyroxine levels around the 27th week of gestation in 270 pregnant women participating in the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) Study (12). Those results, suggestive of a *hyper*thyroidic effect of PBDE exposure, agreed with most previous human studies of nonpregnant adult populations (8–10) but contrasted with experimental studies conducted in rodents, which have suggested that pre- and postnatal exposure reduces serum triiodothyronine and/or thyroxine levels, consistent with a *hypo*thyroxinemic effect (13–15).

Results from studies based on measured thyroid hormone levels in umbilical cord blood have been inconsistent. For instance, Kim et al. (16) found no significant correlation between concentrations of BDE-28, -47, -99, -100, -153, -154, and -183 or their sum ($\sum$PBDEs) and TSH or total thyroxine ($n = 108$) in the umbilical cord serum of South Korean women undergoing cesarean section. Similarly, Mazdai et al. (17) found no association between $\sum$PBDEs in cord serum and thyroxine or triiodothyronine in 9 Indiana women. On the other hand, Herbstman et al. (18) found that higher concentrations of BDE-153, but not BDE-47 or -100, were related to increased odds of low cord free thyroxine (<20th percentile) ($n = 289$). However, it is unclear whether thyroxine concentration in umbilical cord serum represents maternal or fetal thyroid function, since 30%–60% of cord thyroxine may be of maternal origin (19, 20).

To our knowledge, only 1 study has measured thyroid hormone levels in human neonates. Herbstman et al. (18) found no statistically significant relation between total thyroxine measured in 289 blood spots collected on average 2 days and 18 days after birth and cord serum concentrations of BDE-47, -100, or -153. Increased odds of low total thyroxine (<20th percentile) at 18 days of age but not 2 days of age were associated only with cord BDE-153 levels in a subsample of 92 children born by spontaneous unassisted vaginal delivery (18). Neonatal TSH was not measured.

Thus, the purpose of the present study was to determine whether maternal serum PBDE concentrations during pregnancy were related to neonatal TSH levels in the CHAMACOS population.

MATERIALS AND METHODS

Participants

Data and banked samples collected as part of the CHAMACOS Study were used for this analysis. The study population and methods have previously been described in detail (21). Briefly, pregnant women who received prenatal care at one of 6 clinics in California's Salinas Valley and were planning to deliver at Natividad Medical Center, the local county hospital, were screened for enrollment between October 1999 and October 2000. Women who were aged ≥18 years, spoke English or Spanish, were eligible for state-sponsored health care, and had completed less than 20 weeks of gestation were invited to participate in the study. Of the 601 women who agreed to participate, 536 were followed through delivery of a liveborn child. We excluded twin births ($n = 5$), women with insufficient serum for PBDE analysis ($n = 90$), and neonates with missing data on TSH levels ($n = 111$) or age at the time of blood collection for TSH measurement ($n = 16$). Data were also not reported for 25 samples that failed to meet quality assurance criteria for PBDE measurement, leaving a final population of 289 mother-child pairs. According to medical record and questionnaire data, none of these women used medications that would be expected to influence thyroid hormones during pregnancy. Women included in the analyses tended to be younger and more educated than those excluded.

All women gave written informed consent for themselves and their children prior to study participation. Research activities were approved by the University of California, Berkeley, Committee for the Protection of Human Subjects.

Data collection

Health and sociodemographic information. Trained study staff interviewed participants at enrollment (mean = 14 weeks' gestation (standard deviation (SD), 5)), at the beginning of the third trimester (mean = 27 weeks' gestation (SD, 3)), and at delivery using structured questionnaires. Information on demographic factors, country of birth, language spoken at home, duration of residence in the United States, parity, prepregnancy body mass index (weight (kg)/height $(m)^2$), and health-related behaviors was collected. A registered nurse abstracted medical records to obtain data on infant birth weight; duration of gestation; mode of delivery; maternal health status, thyroid-related diseases, and medication use; and neonatal TSH level (see below).

PBDE analysis. Blood samples were collected around the beginning of the third trimester of pregnancy ($n = 209$; mean = 27 weeks' gestation (SD, 3)) and at delivery ($n = 80$; mean = 40 weeks' gestation (SD, 2)). Samples were immediately processed at Natividad Medical Center and stored at −80°C at the University of California, Berkeley, School of Public Health Biorepository. PBDE levels were measured in serum by the Centers for Disease Control and Prevention using gas chromatography–isotope dilution high-resolution mass spectrometry (22). Organochlorines, including polychlorinated biphenyls (PCBs), hexachlorobenzene, dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenyldichloroethylene (DDE), were measured using the same method. Blank and spiked samples were included in each run for quality control purposes. Limits of detection ranged between 0.2 ng/g lipids and 2.6 ng/g lipids for BDE-47 and between 0.2 ng/g lipids and 0.7 ng/g lipids for all other PBDE congeners. Serum triglyceride and total cholesterol levels were determined in serum using enzymatic assays (Roche Chemicals, Indianapolis, Indiana) to estimate total lipid concentration (23). Note that strong correlations were previously reported between lipid-adjusted PBDE levels measured in maternal serum and umbilical cord serum ($r = 0.8$–0.9), suggesting that maternal PBDE levels are an appropriate estimate of fetal exposure (24).

For values below the limits of detection, we estimated PBDE concentrations on the basis of instrument response. When no signal was detected, values were imputed based on a lognormal probability distribution whose parameters were

Table 1. Serum Concentrations of Total Polybrominated Diphenyl Ethers in Pregnant Women and Neonatal Thyroid-Stimulating Hormone Levels, According to Demographic Characteristics, CHAMACOS Study ($n = 289$), Salinas Valley, California, 1999–2000

	No. of Participants	%[a]	Geometric Mean (GSD)	
			Total PBDEs, ng/g lipids	Thyroid-Stimulating Hormone, mIU/L
Infant characteristics				
Sex				
Female	147	51	30.4 (2.5)	6.0 (1.8)
Male	142	49	26.9 (2.4)	5.5 (1.8)
Birth weight, g				
<2,500	10	3	36.7 (2.9)	5.1 (2.1)
2,500–3,500	149	52	29.3 (2.9)	5.6 (1.8)
>3,500	130	45	27.2 (2.0)	5.9 (1.7)
Duration of gestation, weeks				
<37	19	7	34.9 (3.1)	4.1 (2.4)*
37–42	270	93	28.2 (2.4)	5.9 (1.7)
Maternal characteristics				
Age, years				
18–24	155	54	27.4 (2.7)*	5.6 (1.7)
25–29	83	29	24.5 (2.0)	6.2 (1.8)
30–34	33	11	45.3 (2.3)	5.1 (1.7)
35–45	18	6	35.9 (2.3)	5.7 (2.0)
Race/ethnicity				
Caucasian	3	1	177.1 (5.5)**	6.1 (1.2)
Latina	279	97	27.9 (2.4)	5.7 (1.8)
Other	7	2	35.0 (2.4)	6.7 (1.3)
Marital status				
Not married	61	21	34.5 (2.9)	5.8 (1.7)
Married/living as married	228	79	27.1 (2.4)	5.7 (1.8)
Education				
6th grade or less	116	40	25.4 (2.3)	5.7 (1.8)
7th–12th grade (without diploma)	102	35	28.5 (2.5)	5.5 (1.8)
High school diploma or more	71	25	34.6 (2.8)	6.1 (1.6)
Country of birth				
United States	46	16	48.6 (2.6)**	6.5 (1.6)
Mexico	237	82	25.9 (2.4)	5.6 (1.8)
Other	6	2	22.7 (2.1)	5.8 (1.2)

Table continues

determined by maximum likelihood estimation (25, 26). Data analysis was limited to congeners detected (based on instruments' signals) in more than 75% of samples (BDE-47, -85, -99, -100, and -153). Only these congeners were used to calculate $\sum$PBDEs.

Thyroid hormone analysis. TSH is routinely measured in infant blood by the Genetics Disease Branch of the California Department of Health Services as part of the state's Neonatal Screening Program. Dried blood spots collected by hospital staff were analyzed by solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELPHIA; PerkinElmer, Wellesley, Massachusetts). Coefficients of variation were 6.8%–7.8% (6.8%–7.2% within the reference range). TSH levels and neonates' ages (in hours) at the time of blood collection were abstracted from medical records by a registered nurse. Samples were collected 24 hours (SD, 14; median, 21 (interquartile range, 18–26)) after birth, on average.

Data analysis

We first used generalized additive models with 3-df cubic splines to evaluate the shape of exposure-response curves while controlling for covariates. Relations appeared linear, and none of the digression from linearity tests was statistically

Table 1. Continued

	No. of Participants	%[a]	Geometric Mean (GSD)	
			Total PBDEs, ng/g lipids	Thyroid-Stimulating Hormone, mIU/L
Language spoken at home				
Mostly Spanish	251	87	26.9 (2.4)**	5.7 (1.8)
Both Spanish and English	19	7	30.0 (1.8)	5.3 (1.5)
Mostly English	15	5	81.5 (3.2)	6.9 (1.4)
Other	4	1	19.4 (2.2)	5.5 (1.3)
Duration of residence in the United States, years				
≤5	153	53	22.3 (2.5)**	5.7 (1.8)
6–10	60	21	33.2 (2.0)	5.7 (1.9)
≥11	76	26	41.6 (2.4)	5.9 (1.7)
Parity				
Primiparous	113	39	23.9 (2.5)*	5.9 (1.8)
Multiparous	176	61	32.1 (2.4)	5.6 (1.8)
Smoking during pregnancy				
Yes	13	4	32.4 (2.5)	6.4 (1.5)
No	276	96	28.4 (2.5)	5.7 (1.8)
Alcohol consumption during pregnancy, drinks/week				
≥1	3	1	41.5 (2.2)	5.1 (1.6)
<1	286	99	26.1 (2.5)	5.7 (1.8)
Caffeine intake during pregnancy				
Yes	136	47	34.2 (2.8)*	5.9 (1.7)
No	153	53	24.3 (2.1)	5.6 (1.9)
Mode of delivery				
Spontaneous unassisted delivery	76	26	28.2 (2.7)	5.6 (1.7)
Induced or assisted delivery	137	47	29.6 (2.4)	5.9 (1.7)
Cesarean section	76	26	27.0 (2.4)	5.5 (1.9)
Family income				
At or below federal poverty line	175	61	27.3 (2.2)	5.6 (1.8)
Above poverty line–200% of poverty line	104	36	31.3 (2.9)	6.0 (1.8)
>200% of poverty line	10	3	24.7 (2.5)	5.1 (2.2)

Abbreviations: CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; GSD, geometric standard deviation; PBDE, polybrominated diphenyl ether.

* $P < 0.01$; ** $P < 0.001$ (2-sided P value calculated using analysis of variance).

[a] Percentages may not add to 100% because of rounding.

significant at $P < 0.15$. Categorizing PBDEs in quartiles also did not show evidence of a nonmonotonic relation. We thus expressed exposures continuously in multiple linear regression models.

Other covariates (expressed as shown in Table 1 or as indicated in parentheses) considered for inclusion in the models comprised maternal age (years; continuous), race, country of birth, marital status, education (years; continuous), parity, and duration of residence in the United States (years; continuous); duration of gestation (weeks; continuous); serum concentrations of total PCBs, hexachlorobenzene, DDT, and DDE; mode of delivery; family income; and infant sex and birth weight (grams; continuous). Variables associated with the outcome ($P < 0.20$) in bivariate analyses were included in all models. Final models included duration of gestation and infant birth weight, sex, and age at heel stick. TSH levels surge at birth and drop substantially within the first days of life (11), resulting in a strong association between neonatal TSH and age at the time of heel stick (27). Therefore, we applied cubic splines to this variable in order to minimize residual confounding. For covariates that had less than 2% of values missing, the missing values were imputed at random based on observed probability distributions; missing data on alcohol and illegal drug use during pregnancy (≥2% missing values) were imputed in multiple logistic regression models, using known correlates of these variables.

In addition, we investigated in separate models whether maternal serum PCB concentrations (expressed continuously and dichotomized at the 50th, 75th, and 90th percentiles), sex, child's age at heel stick (dichotomized at 24 hours), and mode of delivery modified associations as suggested by previous reports (18, 28). Mode of delivery was expressed as a dichotomous variable, identifying women who gave birth via spontaneous unassisted vaginal delivery as compared with other types of delivery.

Finally, we performed stratified analysis for the subset of mother-child pairs with PBDE measurements determined at delivery based on the hypothesis that maternal PBDEs at this time point may be more closely related to neonatal TSH. The above analyses were repeated using multiple logistic regression with TSH expressed as a dichotomous variable (using the 80th percentile as the cutoff) to compare our results with those of prior reports (18). TSH and PBDE values were $\log_{10}$-transformed for all analyses. Thus, percent change in TSH associated with every 10-fold increase in serum PBDE may be computed by transforming beta coefficients generated by linear regression using the following formula: $(10^{\beta} - 1) \times 100$. Two-sided P values smaller than 0.05 and 0.15 were considered statistically significant for main effects and interactions, respectively.

We also performed sensitivity analysis to evaluate the robustness of our results. First, we reran the analyses after excluding observations with high leverage and outliers identified by means of the extreme studentized deviates many-outlier procedure at $\alpha = 0.01$ (29). In addition, we constructed separate models with PBDE concentrations expressed on a serum lipid basis (ng/g lipids) and on a serum weight basis (pg/g serum) while adjusting for triglycerides and total cholesterol (expressed continuously). We also repeated the analyses by expressing $\sum$PBDEs on a weight and molar basis and by summarizing $\sum$PBDEs using the first factor of a principal component analysis. Finally, we attempted to adjust for selection bias due to exclusion from the analyses by conducting regressions with weights equal to the inverse probability of inclusion in the final models (30). Weights were determined using multiple logistic regression, and independent variables were identified on the basis of a deletion-substitution-addition algorithm that selects variables based on cross-validation (31). Findings were similar for all of the models described above. We thus present results from unweighted regression analyses, with $\log_{10}$-transformed exposures expressed on a serum lipid basis, ΣPBDEs and individual congeners expressed on a weight basis, and potential outliers included.

All analyses were performed using STATA/IC, version 10.1 (StataCorp LP, College Station, Texas), or R statistical software, version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population characteristics

The study population comprised primarily young (mean age = 25.1 years (SD, 5.0)), low-income (61% at or below the federal poverty line) Latina (97%) women, most of whom had been born in Mexico (82%) and had not completed high school (75%) (see Table 1). Few women smoked (4%) or drank alcohol (1%) during pregnancy, while 47% consumed caffeine. More than 1 in 5 women (21%) were obese (body mass index ≥30) before pregnancy, and about 1 in 4 (26%) gave birth by spontaneous unassisted vaginal delivery. Approximately half (49%) of the children were male, 3% were of low birth weight (<2,500 g), and 7% were premature (<37 weeks' gestation).

Prenatal exposure to PBDEs

As reported in most previous studies (1, 3–6, 9, 10, 12, 17, 18), BDE-47 was the dominant congener in this population (Table 2). BDE-47, -99, -100, and -153 were detected in more than 96% of samples; at least 1 PBDE congener was detected in every sample. Correlations among PBDE congeners ranged between 0.7 and 0.9 ($P < 0.001$).

We observed higher $\sum$PBDE serum concentrations in women who were Caucasian, had been born in the United States, spoke mostly English at home, were multiparous, were aged 30–34 years, and consumed caffeine during pregnancy (Table 1). Furthermore, maternal prepregnancy body mass index, education, and years of residence in the United States were positively related to PBDE exposure.

Neonatal TSH

The geometric mean value for neonatal TSH was 5.7 mIU/L (geometric SD, 1.8); 1 neonate had a TSH level above the reference range (25 mIU/L). Of the variables considered, only duration of gestation was related to TSH levels.

Associations between maternal PBDE serum concentration and neonatal TSH

Table 3 shows the results from unadjusted and adjusted linear and logistic regression models for the full study sample ($n = 289$). We observed no statistically significant associations between maternal serum PBDE concentrations and neonatal TSH levels. Unadjusted linear models consistently showed weak, nonsignificant, negative relations ranging between a 2.3% decrease (95% confidence interval (CI): −18.7, 14.8) and a 6.7% decrease (95% CI: −20.6, 9.6) in TSH levels for every 10-fold increase in PBDE congeners (computed from Table 3). Adjustment for covariates drove some measures of association closer to the null. A 10-fold increase in $\sum$PBDEs, for instance, was associated with a 4.5% (95% CI: −12.9, 14.8) reduction in neonatal TSH in the crude analysis, but including covariates in the model yielded a null relation (95% CI: −12.9, 12.2). Summarizing $\sum$PBDEs using the first factor of a principal component analysis (accounting for 79.9% of the variance) also resulted in a nonsignificant association ($\beta = -0.002$, 95% CI: −0.013, 0.008). In contrast to results obtained by linear regression, PBDE serum levels were generally related to increased odds of high (≥80th percentile) TSH levels, but none of the associations were statistically significant. We obtained similar results when analyses were restricted to the 80 participants whose exposure was determined in samples collected at delivery (Table 4) or at the end

Table 2. Concentrations of Polybrominated Diphenyl Ethers in Serum Samples Collected From Pregnant Women, CHAMACOS Study, Salinas Valley, California, 1999–2000

PBDE	No. of Participants	LOD, ng/g lipids	Detection Frequency, %	Geometric Mean[a], ng/g lipids	95% Confidence Interval	Minimum, ng/g lipids	25th Percentile, ng/g lipids	Median, ng/g lipids	75th Percentile, ng/g lipids	Maximum, ng/g lipids
Total PBDEs[b]	289	0.2–2.6	100.0	28.0	25.0, 31.5	1.3	15.4	25.4	42.8	1,113.8
Individual PBDE congener										
BDE-17	288	0.2–0.7	1.0			<LOD	<LOD	<LOD	<LOD	1.4
BDE-28	288	0.2–0.7	57.6	0.6	0.5, 0.7	<LOD	<LOD	0.6	1.5	29.7
BDE-47	288	0.2–2.6	99.7	15.3	13.7, 17.1	<LOD	8.5	15.2	25.6	677.0
BDE-66	288	0.2–0.7	18.8			<LOD	<LOD	<LOD	<LOD	8.0
BDE-85	289	0.2–0.7	51.0	0.4	0.3, 0.4	<LOD	<LOD	0.3	0.6	17.4
BDE-99	289	0.2–0.7	99.0	4.2	3.7, 4.7	<LOD	2.3	3.8	6.5	261.0
BDE-100	289	0.2–0.7	97.6	2.7	2.4, 3.0	<LOD	1.5	2.6	4.5	103.0
BDE-153	289	0.2–0.7	96.9	2.3	2.1, 2.6	<LOD	1.4	2.2	3.8	62.6
BDE-154	288	0.2–0.7	49.0			<LOD	<LOD	<LOD	0.6	18.0
BDE-183	289	0.2–0.7	30.2			<LOD	<LOD	<LOD	0.3	5.9

Abbreviations: BDE, brominated diphenyl ether; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; LOD, limit of detection; PBDE, polybrominated diphenyl ether.

[a] Not computed for congeners with detection frequencies less than 50%.

[b] Sum of congeners with detection frequencies greater than 75% (BDE-47, -85, -99, -100, and -153). Note that values for the sum of all measured PBDE congeners were virtually identical.

of the third trimester (results not shown). Web Figure 1 (http://aje.oxfordjournal.org/) shows that none of the interactions considered were statistically significant.

DISCUSSION

We found no associations between the concentration of PBDEs in maternal serum and neonatal TSH levels after examining the data continuously and categorically, performing sensitivity analyses, and exploring possible effect modification. In contrast, we previously reported a negative relation between maternal serum PBDEs and TSH during pregnancy (12) and found that maternal exposure to structurally similar PCBs was related to higher neonatal TSH levels (27) and lower maternal free thyroxine levels during pregnancy (32) in the CHAMACOS population.

Table 3. Unadjusted and Adjusted Associations Between Maternal Serum Concentrations of Polybrominated Diphenyl Ether and Neonatal Blood Levels of Thyroid-Stimulating Hormone in Mother-Child Pairs (Full Study Sample), CHAMACOS Study, Salinas Valley, California, 1999–2000[a]

	Log_{10} TSH Level				≥80th Percentile of TSH vs. <80th Percentile of TSH			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted[b]	
	β	95% CI	β	95% CI	OR	95% CI	OR	95% CI
Total PBDEs[c]	−0.02	−0.09, 0.05	0.00	−0.06, 0.06	1.15	0.56, 2.36	1.18	0.56, 2.46
Individual PBDE congener								
BDE-47	−0.02	−0.09, 0.05	0.00	−0.05, 0.06	1.29	0.65, 2.55	1.37	0.68, 2.76
BDE-85	−0.03	−0.10, 0.04	−0.03	−0.09, 0.03	1.23	0.61, 2.50	1.21	0.59, 2.49
BDE-99	−0.03	−0.10, 0.04	−0.01	−0.07, 0.04	1.13	0.58, 2.22	1.15	0.58, 2.28
BDE-100	−0.02	−0.09, 0.05	−0.02	−0.07, 0.04	1.04	0.52, 2.10	1.04	0.51, 2.10
BDE-153	−0.01	−0.09, 0.06	−0.01	−0.07, 0.05	0.77	0.37, 1.63	0.75	0.36, 1.56

Abbreviations: BDE, brominated diphenyl ether; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; OR, odds ratio; PBDE, polybrominated diphenyl ether; TSH, thyroid-stimulating hormone.

[a] PBDE serum concentrations were expressed in ng/g lipids, and TSH level was expressed in mIU/L. Variables were log_{10}-transformed.

[b] Adjusted for infant age at time of heel stick for TSH measurement, birth weight, sex, and duration of gestation.

[c] Sum of congeners with detection frequencies greater than 75% (BDE-47, -85, -99, -100, and -153).

Table 4. Unadjusted and Adjusted Associations Between Maternal Serum Concentrations of Polybrominated Diphenyl Ether and Neonatal Blood Levels of Thyroid-Stimulating Hormone in Mother-Child Pairs (Restricted Sample[a]), CHAMACOS Study, Salinas Valley, California, 1999–2000[b]

	Log_{10} TSH Level				≥80th Percentile of TSH vs. <80th Percentile of TSH			
	Unadjusted		Adjusted[c]		Unadjusted		Adjusted[c]	
	β	95% CI	β	95% CI	OR	95% CI	OR	95% CI
Total PBDEs[d]	−0.01	−0.18, 0.15	−0.01	−0.14, 0.11	0.87	0.15, 5.14	0.69	0.10, 4.67
Individual PBDE congener								
BDE-47	−0.01	−0.15, 0.13	−0.01	−0.12, 0.11	1.05	0.22, 5.05	0.92	0.17, 4.93
BDE-85	0.02	−0.15, 0.19	−0.01	−0.14, 0.13	0.87	0.14, 5.54	0.86	0.12, 6.18
BDE-99	−0.03	−0.17, 0.12	0.00	−0.11, 0.11	1.18	0.25, 5.46	1.17	0.23, 6.09
BDE-100	−0.01	−0.18, 0.16	−0.03	−0.17, 0.10	0.74	0.12, 4.63	0.57	0.08, 4.11
BDE-153	−0.01	−0.18, 0.15	−0.04	−0.17, 0.09	0.45	0.07, 2.80	0.31	0.05, 2.17

Abbreviations: BDE, brominated diphenyl ether; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; OR, odds ratio; PBDE, polybrominated diphenyl ether; TSH, thyroid-stimulating hormone.

[a] Sample was restricted to women whose serum PBDE levels were measured at delivery ($n = 80$).

[b] PBDE serum concentrations were expressed in ng/g lipids, and TSH level was expressed in mIU/L. Variables were log_{10}-transformed.

[c] Adjusted for infant age at time of heel stick for TSH measurement, birth weight, sex, and duration of gestation.

[d] Sum of congeners with detection frequencies greater than 75% (BDE-47, -85, -99, -100, and -153).

To our knowledge, this is the first study to investigate associations between prenatal exposure to PBDEs and neonatal thyroid function based on TSH levels. In another study, Herbstman et al. (18) measured total thyroxine levels in samples collected at 2 and 18 days of age and, consistently with our findings, found no association with umbilical cord serum levels of BDE-47, -100, or -153. Cord levels of BDE-153 were associated with increased odds of low (<20th percentile) total thyroxine at 18 days of age in a subset of children born by spontaneous unassisted vaginal delivery ($n = 92$) (18); however, in our study population, we found no effect modification by mode of delivery. Our results are also consistent with those of Kim et al. (16) and Herbstman et al. (18), who found no association between cord PBDE concentration and TSH measured in cord serum.

Experimental studies have generally found that postnatal exposure to PBDEs altered thyroxine levels but not TSH levels in rodents (33, 34). However, in contrast to our results, the only experimental study to have investigated effects of prenatal PBDE exposure on TSH in offspring found elevated TSH levels in pups following exposure of pregnant rats to BDE-209 (14). Differences in the congeners examined and exposure levels, as well as physiologic differences between rodent models and humans, may explain the discrepancy with our results. For instance, several hydroxylated PBDEs have been shown to displace thyroxine from the binding protein transthyretin, which may result in increased thyroxine metabolism and elevated TSH (35). Transthyretin, however, binds a much smaller percentage of circulating thyroxine in humans (10%–15%) than in rodents (approximately 75%) (36). In addition, it is unclear whether hydroxylated PBDEs bind thyroxine-binding globulin, the major thyroxine-binding protein in humans, but Cheek et al. (37) reported that structurally similar hydroxylated PCBs had a very low binding affinity to thyroxine-binding globulin. Taken together, these results suggest that rodents may be more susceptible to PBDE-induced thyroid hormone disruption than humans.

This study had limitations common to most previous studies. First, we had no data on maternal iodine intake, which is known to affect thyroid hormone homeostasis (38). However, given that exposure to PBDEs may occur primarily through contaminated home environments rather than diet (39), iodine intake would not be expected to be related to PBDE exposure and thus may not have confounded our results. We also had no data on serum levels of hydroxylated PBDEs, whose chemical structures more closely resemble those of thyroxine and triiodothyronine than parent compounds. Some hydroxylated PBDEs have been reported to strongly bind to transthyretin in vitro (35) and to compete with triiodothyronine binding to human thyroid receptors α and β (40). Parent compounds did not appear to have these effects, suggesting that hydroxylated PBDEs may be more potent thyroid hormone disrupters. Finally, California's Neonatal Screening Program does not measure free or total thyroxine levels in neonates. We thus had no data on these parameters.

Strengths of this study included the availability of data on a large number of covariates, including demographic factors, age at heel stick, and biomarkers of exposure to a number of environmental chemicals that may affect thyroid function, such as lead, PCBs, and organochlorine pesticides (41). Furthermore, we used state-of-the-art methods to measure PBDE levels and investigated possible interaction by sex, mode of delivery, age at heel stick, and PCB exposure. Finally, we employed a number of methods to confirm the robustness of our results, including inverse probability weighting to adjust for selection bias due to exclusion from

analyses, the summation of PBDEs on a weight and molar basis, and expression of PBDEs on a lipid and serum basis.

In summary, we found no association between prenatal exposure to any of the PBDE congeners considered or their sum and neonatal TSH levels in a Mexican-American population living in California. Although these results suggest that prenatal exposure to PBDEs may not affect neonatal TSH levels, in vitro studies suggest that hydroxylated PBDEs may be more likely to disrupt thyroid hormone homeostasis. We are aware of no animal or human studies that have examined this question. We thus recommend that future studies investigate whether prenatal exposure to hydroxylated PBDEs is associated with thyroid hormone levels in neonates.

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