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Temporal Variability of Polybrominated Diphenyl Ether (PBDE) Serum Concentrations over One Year

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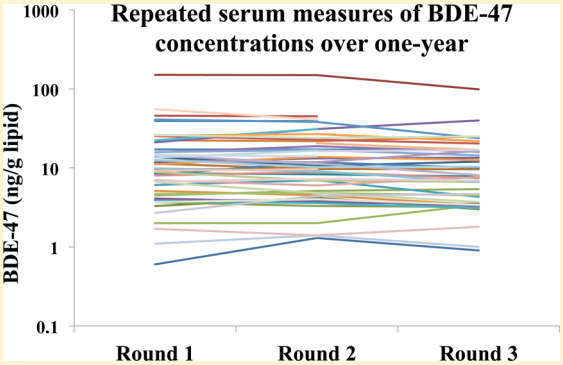
Supporting Information

ABSTRACT: Polybrominated diphenyl ethers (PBDEs) are flame retardant chemicals used in consumer products. They are common contaminants in human serum and associated with adverse health effects. Our objectives were to characterize PBDE serum concentrations in a New England cohort and assess temporal variability of this exposure biomarker over a one-year period. We collected three repeated measurements at six-month intervals from 52 office workers from the greater Boston (MA, United States) area from 2010 to 2011. The intraclass correlation coefficient for BDEs 28, 47, 99, 100, and 153 ranged from 0.87 to 0.99, indicating that a single serum measurement can reliably estimate exposure over a one-year period. This was true for both lipid adjusted and nonlipid adjusted concentrations. The kappa statistics, quantifying the level of agreement of categorical exposure classification, based on medians, tertiles, or quartiles ranged from 0.67 to 0.90. Some congeners showed nonsignificant increases from sampling round 1 (winter) to round 2 (summer) and significant decreases from round 2 to round 3 (winter). This study highlights the high reliability of a single serum PBDE measurement for use in human epidemiologic studies.



INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) are additive flame retardant chemicals used since the 1970s in commercial and household products. The technical formulation PentaBDE is composed of PBDE congeners containing three to six bromines, primarily BDE-28, BDE-47, BDE-99, BDE-100, and BDE-153. It was used in furniture containing polyurethane foam to meet fire standards such as California Technical Bulletin 117. BDE-153 also occurs in the OctaBDE technical formulation used in electronics. Of the worldwide production, 95% of the PentaBDE produced was consumed in North America,[1] where concentrations of several PentaBDE congeners in the environment and people are approximately an order of magnitude higher than those reported in Europe or Asia.[2−5]

Because of their persistence, lipophilicity, ability to bioaccumulate, and concerns regarding adverse effects on human health, production of PentaBDE and OctaBDE is now prohibited by the Stockholm Convention, an international treaty that governs persistent organic pollutants.[6] The main U.S. chemical manufacturers withdrew PentaBDE and OctaBDE from production in 2004.[7] Despite the current restrictions, human exposure is still occurring due to the release of these flame retardant chemicals from existing products and through contaminated foods.[8,9] In the United States, incidental ingestion of dust and diet are the dominant routes of human exposure.[10,11] Unlike the highly brominated BDE-183 and BDE-209 that have half-lives on the order of weeks to months,[12] the half-lives of the major PentaBDE congeners have not been directly measured in humans, but have been estimated to be on the order of years.[13] These half-life estimates are uncertain because the calculations assumed steady state conditions and compared body burdens with uncertain exposure estimates.

Toxicological studies have demonstrated that PBDEs, particularly of the PentaBDE formulations, adversely affect endocrine homeostasis[14] and neurodevelopment,[15] and have reproductive effects.[16] Recently, epidemiological studies conducted in the United States have linked PBDE exposure to

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adverse effects on neurodevelopment,[17−19] and altered thyroid and reproductive hormone levels.[20−22]

Exposure assessment is a critical element of environmental epidemiology. Exposure measurement error occurs when a study participant is assigned an exposure that is different from their true exposure over the biologically relevant time period. Such error, even if independent of outcome, can lead to biased effect estimates. It may even completely remove a true association between an exposure and outcome of interest.[23] With continuous exposures, epidemiologists typically use either a continuous exposure measure (e.g., serum concentration) or place participants into categories (e.g., low, medium, or high). Kappa statistics quantify the amount of agreement between an initial exposure categorization and an exposure categorization at a later point in time (e.g., did a participant in the high exposure category remain in the high exposure category later). Intraclass correlation coefficients (ICCs) evaluate continuous exposure measures. If the amount of variability over time within subjects is small compared to variability between subjects, the ICC will be close to 1 and the exposure metric is considered reliable. For example, a high ICC indicates that highly exposed people tend to remain high relative to other people. Both of these analyses require a cohort with repeated exposure measures. There are currently no studies of this kind that have evaluated the potential amount of PBDE exposure misclassification in epidemiological studies.

Our objectives were to characterize PBDE serum concentrations in a New England cohort and assess temporal variability of this exposure biomarker over a one-year period. Additionally, we assessed demographic characteristics and serum lipid concentrations as predictors of serum PBDE concentrations.

EXPERIMENTAL SECTION

Study Design and Population. We recruited a convenience sample of 52 adults living and working in the greater Boston (MA, United States) metropolitan area from winter 2010 to summer 2011 to participate in the Flame Retardant Exposure Study (FlaRE Study). Eligible subjects had to be healthy, nonsmoking adults over the age of 18, working in an office environment at least 20 h a week, and planning to reside in the greater Boston metropolitan area for the study duration. Participants were excluded for having a prior diagnosis of thyroid or male reproductive disease or if they were pregnant. The City of Boston requires that furniture in public spaces meet certain fire codes.[24]

We conducted three sampling rounds: Round 1 (1/13/10−4/15/10), Round 2 (6/3/10−9/15/10), and Round 3 (1/31/11−4/27/11). Serum samples were provided by 49 of 51 (96%) participants in Round 1, 50 of 52 (96%) participants in Round 2, and 42 of 52 (81%) participants in Round 3. One participant was added in Round 2. The missing blood samples were due to the following reasons: phlebotomist was unable to conduct venipuncture, participant declined, participant moved out of study area, or participant could no longer be contacted. All blood samples were nonfasting.

During each sampling visit, study personnel administered a questionnaire designed to collect basic demographic and health information. The Boston University Medical Center Institutional Review Board approved the study protocol and all subjects gave written informed consent prior to participation. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Blood Samples. A trained phlebotomist collected 30 mL of blood from each participant during each sampling round. Blood samples were processed on the day of collection and serum samples were stored at −80 °C in amber glass vials until analysis. To eliminate potential issues with interassay variability, serum samples collected from all three rounds were analyzed at one time following Round 3. Serum samples were analyzed for lipids (total triglycerides, total cholesterol) and 11 PBDE congeners (BDE-17, BDE-28, BDE-47, BDE-66, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-209) at the CDC using established methods.[25] Final analytic determination of the PBDE congeners was performed by gas chromatography isotope dilution high-resolution mass spectrometry using a MAT95XP (ThermoFinnigan MAT, Bremen, Germany) instrument. Samples were randomized and analyzed with quality control (QC) (n = 3) and blank samples (n = 3) in each batch of 24 unknowns. The coefficient of variation of included QC samples was less than 10%. All concentration data were reported as background subtracted, where correction was made based on the median amount present in blank samples. Limits of detection (LOD) were calculated as the highest of two methods: (i) 3 times the standard deviation of the method blank samples and (ii) as the lowest point in the calibration curve having a signal-to-noise ratio greater than 3 (primarily for analytes with low to no detectable method blank concentration).

Statistical Analysis. For measurements below the LOD, we substituted 1/2 LOD. PBDE congeners were log-normally distributed, as identified by histograms and Shapiro−Wilks tests, and thus log-transformed. We calculated round-specific geometric means (GM) and geometric standard deviations (GSD) for congeners detected in >50% of the samples. ΣPBDEs is defined here as the sum of BDE-28, BDE-47, BDE-99, BDE-100, and BDE-153. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). Statistical significance is reported at the 0.05 level.

We calculated kappa statistics to assess the amount of agreement between exposure categories in Round 1 and Round 3, the two winter time points. We used three exposure classification schemes: median (low, high), tertile (low, medium, high) and quartile (low, medium, high, very high). Kappa statistics range from 0 to 1, with 1 indicating perfect agreement between two observations. These analyses were restricted to participants who provided a blood sample in both sampling rounds (participants = 40, serum samples = 80). Contingency tables were constructed to display the level of agreement between each subject's initial and final exposure category. We report the weighted kappa, instead of the simple kappa, when assessing agreement for tertiles and quartiles.[26]

We used the following general linear model with a random intercept to estimate the between- and within-subject variance components associated with PBDE congener levels over the study period:

$$Y_{ij} = \beta_0 + b_i + \varepsilon_{ij} \quad (1)$$

where Y_{ij} represents the natural logarithm of the PBDE congener level of the ith participant on the jth round of sampling, β_0 is the fixed effect intercept, b_i is the random intercept of the ith individual, and ε_{ij} is the random error. To determine how serum lipids affect the variance components, we

added a predictor variable, $LIPID_{ij}$, the lipid level of the ith participant on the jth sampling round:

$$Y_{ij} = \beta_0 + \beta_1 \mathrm{LIPID} + b_i + \varepsilon_{ij} \quad (2)$$

We estimated the intraclass correlation coefficient (ICC) to assess reliability of serum PBDE congener concentrations using the following formula:

$$\mathrm{ICC} = \sigma_B^2/(\sigma_B^2 + \sigma_W^2) \quad (3)$$

where $\sigma^2{}_B$ is the between-subject variance and $\sigma^2{}_W$ is the within-subject variance.

We also determined whether (i) average biomarker levels increased or decreased by study round or (ii) if congener concentrations were associated with predictor variables obtained from questionnaires. Rather than standardizing PBDE measurements to lipids, we adjusted for lipid as a covariate in regression models,[27] allowing us to estimate the effect of this variable. To evaluate the fixed effects of time and covariates, we used the following model:

$$Y_{ij} = \beta_0 + \beta_1 \mathrm{TIME2} + \beta_2 \mathrm{TIME3} + \beta_3 \mathrm{AGE}_i + \beta_4 \mathrm{SEX}_i + \beta_5 \mathrm{BMI}_i + \beta_6 \mathrm{LIPID}_{ij} + b_i + \varepsilon_{ij} \quad (4)$$

where Y_{ij}, β_0, b_i, and ε_{ij} are defined as earlier. TIME2 and TIME3 are indicator variables: β_1 is the average difference of the log(PBDE) measurement from Round 1 to Round 2; β_2 is the average difference of the log(PBDE) measurement from Round 1 to Round 3. AGE is the age of the ith participant at the initial sampling round (categorized as ≥37 or <37 years old); SEX is the gender of the ith participant; BMI is the body mass index of the ith participant at the initial sampling round (categorized as ≥25 mg/kg^2 or <25 mg/kg^2). We exponentiated the beta estimates to obtain a percent change in PBDE congener concentration per unit change in predictor variable.

We did not have completely balanced data; however, we considered the reasons for missing serum data not related to PBDE level and classified these data as missing completely at random (MCAR). As general linear models are robust to MCAR and missing at random (MAR) patterns of missing data, inferences reported from our regression models are likely unbiased;[28] we therefore did not impute missing serum data. Sensitivity analyses were performed using only individuals with complete serum data.

RESULTS

The study population consisted of 27 males and 25 females. The median age was 37 years old, 88% were white, 98% had a college degree, and 64% had BMI < 25 kg/m^2 (Table 1). Twenty-three participants lived in the City of Boston and 30 lived in surrounding suburbs. Few participants moved residences during the study: three moved from Round 1 to Round 2, and two moved from Round 2 to Round 3. Baseline self-reported health status ranged from good to excellent (not shown). Forty-one participants provided a serum sample in all three sampling rounds, nine provided a sample in two rounds, and two provided a single serum sample. One serum sample was contaminated during field collection and removed from analysis, leaving 40 participants with three serum samples. After exclusions, we had 142 valid serum PBDE measurements from 52 participants.

Table 2 presents the round-specific geometric means (GM), geometric standard deviations (GSD), and ranges for PBDE congeners that were detected at >50%: BDE-28, BDE-47, BDE-99, BDE-100, and BDE-153. Both lipid-standardized and wet weight serum concentrations are shown. BDE-47 had the highest serum concentration followed by BDE-153; both were detected in 100% of serum samples. BDE-99, BDE-100, and BDE-28 had detection frequencies of 92%, 89%, and 68%, respectively. Detection rates for BDE-17, BDE-66, BDE-85, BDE-154, BDE-183, and BDE-209 ranged from 1% to 22% and were not further analyzed. Supporting Information (SI) Table 1 presents detection rates, LODs, and ranges for all analyzed congeners.

Table 1. Baseline Characteristics of 52 Adults from the FlaRE Cohort

characteristic	n (%)
age	
20–39 years	29 (56)
40–59 years	19 (36)
≥ 60 years	4 (8)
sex	
female	25 (48)
male	27 (52)
race/ethnicity	
white	46 (88)
other	6 (12)
education	
college graduate	51 (98)
< college graduate	1 (2)
BMI (kg/m^2)	
< 25	33 (63)
25–29.9	17 (33)
≥ 30	2 (4)

Reliability of Serum PBDE Measures over One Year. Table 3 presents the estimated ICCs for the serum PBDE congeners calculated using eqs 1 (unadjusted), 2 (adjusted for lipid), or 4 (adjusted for lipid and other covariates). Variance components are shown in SI Table 2. The ICC estimates were very high, particularly for ΣPBDEs, BDE-47, and BDE-153, ranging from 0.96 to 0.99. As a sensitivity analysis for missing data, we calculated ICCs using eq 1 for the subset of individuals that contributed three serum measurements (n = 40) and the results were similar (not shown). See SI Figure 1 for a graph of individual data for BDE-47 and SI Figure 2 for a simple correlation analysis for this congener.

Table 3 also presents the kappa statistics quantifying the agreement between exposure categorization in Round 1 and Round 3 (approximately one year apart). Kappa statistics between 0.61 and 0.80 are considered in substantial agreement and kappa statistics >0.80 are considered in almost perfect agreement.[26] For example, the kappa statistics for BDE-47, based on exposure categorization by median (e.g., low, high), tertile (e.g., low, medium, high), or quartile (e.g., low, medium, high, very high), were 0.80, 0.67, and 0.84, respectively. SI Figure 3 presents the contingency tables associated with the kappa statistics for BDE-47. ΣPBDEs had kappa statistics that ranged from 0.80 to 0.83. We also calculated kappa statistics for each congener comparing Round 1 and Round 2 (6 months apart) and the results were similar (SI Table 3).

Predictors of Serum PBDE Measures (Sampling Round, Lipids, Demographic Variables). Table 4 presents parameter estimates and p-values for regression models (eq 4) predicting PBDE levels as a function of sampling round, serum

Table 2. Selected Polybrominated Diphenyl Ethers, Lipids, and Their Geometric Means (GM), Geometric Standard Deviation (GSD), and Range by Sampling Round[a]

	round 1 (n = 49)			round 2 (n = 50)			round 3 (n = 43)		
analyte	GM (GSD)		range	GM (GSD)		range	GM (GSD)		range
serum (ng/g lipid)									
ΣPBDE	20.2	(2.2)	2.3–290	21.0	(2.5)	2.7–294	16.9	(2.3)	2.4–211
BDE-28	0.6	(2.3)	0.15–4.2	0.6	(2.2)	0.15–5.1	0.5	(2.2)	0.15–3.6
BDE-47	9.6	(2.8)	0.6–151	9.9	(2.7)	1.3–149.0	7.9	(2.6)	0.9–98.9
BDE-99	1.8	(2.9)	0.2–43.5	1.9	(3.0)	0.2–34.1	1.7	(2.5)	0.2–20.1
BDE-100	1.8	(3.4)	0.2–42.4	1.9	(3.3)	0.2–44.1	1.4	(3.0)	0.15–35.2
BDE-153	6.4	(3.2)	0.6–96.7	6.7	(3.1)	0.7–94.7	5.4	(3.1)	0.25–55.2
serum (pg/g wet weight)									
BDE-28	3.5	(2.4)	1.3–29.1	3.7	(2.4)	1.3–30.4	3.1	(2.3)	1.3–24.5
BDE-47	57	(2.9)	3.9–986	59	(2.8)	7.3–1000	48	(2.7)	5.5–707
BDE-99	11	(3.0)	1.3–285	11	(3.2)	1.3–229	10	(2.6)	1.3–144
BDE-100	11	(3.5)	1.3–278	11	(3.4)	1.3–297	8	(3.1)	1.3–252
BDE-153	38	(3.2)	3.9–695	40	(3.1)	4.5–584	36	(2.7)	5.3–395
serum lipids (mg/dL)									
cholesterol[b]	190	(33)	120–290	190	(33)	110–360	190	(45)	92–330
triglycerides[b]	130	(70)	50–340	130	(71)	42–340	140	(65)	45–290
total lipids[b]	620	(110)	450–860	620	(150)	370–1100	640	(140)	330–1000

[a]Participants = 52, serum samples = 142. Selected congeners were detected in serum no less than 65% of the samples. Additional congeners that were analyzed but detected infrequently (BDE-17, BDE-66, BDE-85, BDE-154, BDE-183, BDE-209) are presented in Supporting Information (SI) Table 1. [b]Means and standard deviation presented.

Table 3. Intraclass Correlation Coefficients (ICCs) and Kappa Statistics (κ) for Repeated Serum Markers for Selected PBDEs[a]

	estimate (95% CI)					
parameter	∑PBDE	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153
ICC_{NULL}[b]	0.96 (0.95 to 0.98)	0.87 (0.80 to 0.91)	0.96 (0.95 to 0.98)	0.91 (0.86 to 0.94)	0.92 (0.88 to 0.95)	0.98 (0.97 to 0.99)
ICC_{LIPID}[c]	0.97 (0.95 to 0.98)	0.89 (0.82 to 0.93)	0.97 (0.95 to 0.98)	0.91 (0.86 to 0.94)	0.93 (0.88 to 0.95)	0.99 (0.98 to 0.99)
ICC_{FULL}[d]	0.97 (0.95 to 0.98)	0.89 (0.82 to 0.93)	0.97 (0.95 to 0.98)	0.91 (0.86 to 0.94)	0.93 (0.88 to 0.96)	0.98 (0.97 to 0.99)
median classification						
κ	0.80 (0.61 to 0.99)	0.80 (0.62 to 0.99)	0.80 (0.61 to 0.99)	0.80 (0.61 to 0.99)	0.85 (0.69 to 1.0)	0.90 (0.77 to 1.0)
tertile classification						
$\kappa_{weighted}$	0.83 (0.71 to 0.96)	0.75 (0.60 to 0.90)	0.67 (0.50 to 0.84)	0.72 (0.57 to 0.88)	0.78 (0.64 to 0.92)	0.81 (0.66–0.96)
quartile classification						
$\kappa_{weighted}$	0.82 (0.71 to 0.93)	0.78 (0.66 to 0.90)	0.84 (0.73 to 0.95)	0.76 (0.64 to 0.88)	0.82 (0.71 to 0.93)	0.90 (0.81 to 0.98)

[a]participants = 52, serum samples = 142. [b]Equation (1): $Y_{ij} = \beta_0 + b_i + \varepsilon_{ij}$. [c]Equation (2): $Y_{ij} = \beta_0 + \beta_1 \mathrm{LIPID} + b_i + \varepsilon_{ij}$. [d]Equation (3): $Y_{ij} = \beta_0 + \beta_1 \mathrm{TIME2} + \beta_2 \mathrm{TIME3} + \beta_3 \mathrm{AGE}_i + \beta_4 \mathrm{SEX}_i + \beta_5 \mathrm{BMI}_i + \beta_6 \mathrm{LIPID}_{ij} + b_i + \varepsilon_{ij}$.

lipids, age, sex, and BMI. Exponentiating the beta coefficients, we find that BDE-47 and BDE-100 levels significantly decreased by 7.9% (p = 0.029) and 13.9% (p = 0.024), respectively, from Round 2 to Round 3. While there were no other significant temporal changes, all congeners except BDE-99 had negative slopes from Round 2 to Round 3 and positive trends from Round 1 to Round 2. We also ran regression analysis using PBDEs standardized to lipids and our results were similar to the presented model with lipid as a covariate (not shown). Using Akaike Information Criterion (AIC) as a guide, we found that evaluating time as a categorical variable (instead of continuous in months, e.g. j = month) provided the better fit, though results were similar in both models (not shown). We also analyzed these data using a model with continuous time adding a covariate for season (summer vs winter), and did not find any significant trends (not shown). Results were similar when analyzed using only individuals that contributed three serum measurements (not shown).

Serum lipids were highly significant predictors of all the PBDE congeners. For example, BDE-47 increased 0.15% (p < 0.0001) per one-unit increase of total lipids (mg/dL), while controlling for age, sex, time, and BMI. Because PBDEs are lipophilic, we would expect that as lipid levels increase we would see an increase in PBDE levels, which our results confirm.[29] For example, if total serum lipids increase one standard deviation above the mean in Round 1 (18%), our model predicts that ΣPBDEs should increase by about 19%. Additionally, we calculated ICCs for the lipid measurements using eqs 1 and 2 with the dependent variable Y_{ij} representing the lipid level of the ith participant on the jth sampling round. The ICCs were 0.80, 0.86, and 0.65 for total lipids, total cholesterol, and triglycerides, respectively (data not shown).

Although not statistically significant, sex and age were suggestive predictors for BDE-153. Such associations have been previously observed.[4,30,31] On average, men had 84% (p = 0.06) higher BDE-153 levels than women, after controlling for other covariates. Levels of BDE-153 were 41% lower (p = 0.09) in the older participants than the younger participants. Interestingly, for all other congeners, this trend appears to be reversed: levels of BDE-28, BDE-47, BDE-99, and BDE-100 were non-significantly higher on average in the older than the younger participants. BMI was not a significant predictor of any PBDE

Table 4. General Linear Models for Repeated Measures Assessing PentaBDE Serum Measurements from 2010−2011 by Demographic Characteristic (Fixed Effects)[a]

	ln(pg/g)											
	∑PBDE		BDE-28		BDE-47		BDE-99		BDE-100		BDE-153	
parameter	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
time (overall)		0.22		0.33		0.077		0.88		0.077		0.31
time 1	ref		ref		ref		ref		ref		ref	
time 2	0.029 (0.032)	0.37	0.048 (0.053)	0.37	0.017 (0.035)	0.61	0.020 (0.063)	0.75	0.076 (0.063)	0.23	0.044 (0.029)	0.13
time 3	−0.030 (0.034)	0.39	−0.034 (0.057)	0.55	−0.064 (0.037)	0.09	0.034 (0.068)	0.61	−0.077 (0.067)	0.26	0.028 (0.31)	0.37
time 2 vs 3	−0.059 (0.034)	0.08	−0.082 (0.056)	0.15	−0.082 (0.037)	0.03	0.014 (0.067)	0.83	−0.15 (0.067)	0.02	−0.017 (0.030)	0.59
lipid	0.0016 (0.0003)	<0.001	0.0016 (0.0004)	<0.001	0.0015 (0.0003)	<0.001	0.0014 (0.0005)	0.005	0.0021 (0.0005)	<0.001	0.0017 (0.0003)	<0.001
sex: female	ref		ref		ref		ref		ref		ref	
male	0.13 (0.27)	0.62	−0.16 (0.21)	0.45	−0.12 (0.27)	0.68	−0.07 (0.29)	0.81	0.0089 (0.34)	0.98	0.61 (0.32)	0.061
age: <37 yo	ref		ref		ref		ref		ref		ref	
≥37 yo	−0.069 (0.26)	0.79	0.39 (0.21)	0.07	0.25 (0.28)	0.37	0.34 (0.29)	0.23	0.15 (0.33)	0.65	−0.53 (0.31)	0.09
BMI: <25 kg/m^2	ref		ref		ref		ref		ref		ref	
≥25 kg/m^2	0.26 (0.28)	0.35	0.29 (0.22)	0.21	0.44 (0.29)	0.14	0.32 (0.30)	0.30	0.41 (0.35)	0.25	−0.081 (0.33)	0.81

[a]Participants = 52, serum samples = 142. Abbreviations: (pg/mL) picogram per milliliter serum; (ref) reference group; (SE) standard error; (yo) years old. Beta-coefficients are regression coefficients for log-transformed regression outcome data. Exp(β) yields the multiplicative increase in PBDE per unit change in predictor, e.g., exp(−0.082) = 0.921 = 7.9% decrease.

congener. We ran univariate models analyzing each fixed effect independently and found that the univariate and multivariate results were similar.

DISCUSSION

Reliability of Serum PBDE Measures over One Year. Many epidemiologic studies of PBDEs assess exposure using a single biological sample per person. We found ICCs of greater than 0.90 for BDE-47, BDE-99, BDE-100, BDE-153, and ΣPBDE. BDE-28 had a slightly lower ICC of ≥0.87. A high ICC indicates that differences in PBDE serum concentration between subjects are much greater than the variability within subjects over the study period.[32] As a result, individuals with high exposure levels tend to stay high compared to individuals with low exposures. The high ICCs we report signify that a single serum measurement of BDE-28, BDE-47, BDE-99, BDE-100, and BDE-153 is likely to provide a reliable biomarker of exposure over a one-year period.

Although an ICC is very useful for analyzing continuous measures, epidemiologists often categorize exposure data as well. We placed participants into exposure categories based on their PBDE serum concentration in Round 1 and Round 3. The kappa statistics were mostly ≥0.80, meaning excellent agreement between time points.[26] For example, the ΣPBDE exposure metric had a kappa statistic of 0.83 for categorization by tertiles, indicating almost all participants remained in their respective exposure category (e.g., low, medium, high) after a one-year period.

These data indicate minimal exposure measurement error for epidemiological studies that use a single serum sample to estimate U.S. adult exposure over a year. This information is important for the design and interpretation of epidemiologic studies of the health effects of PentaBDE congeners. Caution is needed in extrapolating to other populations (e.g., infants) or for much longer time periods. Additional research is needed on the time variability of BDE-183 and BDE-209.

Serum PBDE Concentrations. The serum concentrations of BDE-28, BDE-47, BDE-99, and BDE-100 in our study (collected in 2010−2011) were lower than those collected in 2009 from the pilot study to this investigation. Watkins et al. reported GM serum concentrations of BDE-28, BDE-47, BDE-99, and BDE-100 that were approximately 1.5−2 times greater than our Round 1 values collected one year later ($p < 0.01$).[33] For example, Watkins et al. reported GM (GSD) serum levels of BDE-47 of 14.2 (3.0) ng/g lipid, significantly different from our Round 1 BDE-47 serum levels of 9.6 (2.8) ng/g lipid ($p < 0.001$). This population was demographically and geographically similar to our study and utilized the same analytical laboratory. On the other hand, the levels of BDE-153 in our study were similar to those reported by Watkins et al., 5.0 ng/g lipid.[33] It is unclear whether the differences are due to chance variation, some unknown dissimilarity between the two populations, or time trends.

Predictors of Serum PBDE Measures. We observed nonsignificant increases in all PBDE congener concentrations from Round 1 (winter) to Round 2 (summer). In contrast, we found significant decreases of BDE-47 and BDE-100 from Round 2 (summer) to Round 3 (winter). BDE-47, the predominant congener in human serum, and BDE-100 decreased on average 7.9% and 13.9%, respectively, after controlling for age, sex, lipid, and BMI. BDE-28 and -153 also decreased while BDE-99 increased; these changes were not significant. These results occurred in the fully adjusted model

(Table 3) as well as the wet weight and lipid standardized PBDE models (Table 2).

The reason for these changes by round is unclear. There is typically a seasonal increase in mean serum cholesterol over the winter months compared to the summer,[34,35] but average serum lipid concentrations in our population did not differ by Round (Table 2). Because we only have one summer season, we have limited ability to determine if variations of serum concentration are due to factors that may change seasonally, e.g., activity patterns, diet, body weight. However, the alterations in PentaBDE serum concentrations we observed were not the result of a change in blood lipid levels. Changes in the volume of distribution—primarily adipose tissue for these lipophilic compounds—may affect concentrations in both adipose tissue and serum.[36] We could not evaluate this effect as we only had baseline BMI data.

A decrease of some congeners may be consistent with the hypothesis that exposure has declined since the discontinuation of PentaBDE and OctaBDE manufacturing in the mid-2000s. For example, if the half-life of a compound were two years and exposure ceased, one would predict a decrease of 16% over six months; presence of declining but nonzero exposure would reduce observed elimination rates. Furthermore, as stated earlier, the human half-lives of the major PentaBDE congeners are uncertain.

However, it is unclear if PBDE serum levels have declined in the United States since 2004. A recent study using data from the National Health and Examination Survey (NHANES)—designed to be a nationally representative sample of the U.S. civilian, noninstitutionalized population—reported that "PBDE levels overall were lower in 2007−08 than in NHANES 2003−04, however most comparisons were not significantly different."[37] It is difficult to compare our serum concentrations to those based on NHANES because of statistical, geographic, and demographic differences between these studies. The only previous study of Americans using repeated serum measures reported no significant changes in ΣPBDE or individual PentaBDE congeners from 2001 to 2003 to 2004−2005. However, the percent contribution of BDE-153 to ΣPBDE increased while the percent contribution of BDE-47 to ΣPBDE significantly decreased.[38,39] A study comparing two demographically similar populations sampled in 2008−2009 and 2011−2012 found that BDE-47, BDE-99, and BDE-100 decreased more than BDE-153.[40] Outside of the United States, a retrospective Swedish study comparing pooled breast milk samples reported decreasing concentration of BDE-47 beginning in the late 1990s, while BDE-153 appeared to level off.[3,41]

There are a few possible explanations for congener-specific temporal patterns in our study, if real. Potential decreases may be partly explained by differences in elimination rates. The median half-life of BDE-153 is indirectly estimated to be 7.4 years compared to 1.4, 1.8, and 3.0 years for BDE-47, BDE-100, and BDE-28, respectively.[12] However, the estimated half-life of BDE-99 is 0.8 years, but there were no significant decreases for this congener in our study. Unfortunately, we were unable to reliably estimate half-lives for PBDE congeners with our data.[42]

The different temporal patterns for congeners may also be partly due to differences in exposure sources. In the United States, both dust from the indoor environment and consumption of food were shown to be important pathways for adult exposure to PBDEs.[10] Exposure routes may vary by congener, however. Johnson et al. reported strong correlations between paired household dust and adult serum samples for BDEs 47, 99, and 100, but not for BDE-153.[43] In a study of young children, Stapleton et al. reported association among serum concentrations, hand-wipes, and dust for BDEs 47, 99, 100, and 153; only BDE-153 serum concentrations were strongly associated with duration of breastfeeding.[44] In a study using NHANES data, BDE-153 serum concentrations were more strongly associated with reported consumption of red meat and total daily fat intake than were serum levels of BDE-28, BDE-47, BDE-99, and BDE-100.[11]

A major strength of our study is the use of three serum samples from a longitudinal study of a relatively homogeneous population. With similar working conditions and demographic characteristics, the study population is likely to be similar with respect to unknown confounders. A limitation of our study is that our serum collection was not completely balanced; participants contributed one, two, or three serum samples. However, as we had a high retention rate (>80%), and study dropout was classified as MCAR, this limitation was unlikely to have biased our results. Our study sample size (52 participants, 142 serum samples) limited the amount of variables we could evaluate simultaneously in regression models and likely reduced our power to detect statistically significant associations. Participants self-reported height and weight at the beginning of the study, potentially introducing error into the estimate of BMI. With only one estimate of BMI, we cannot examine changes in weight (or adipose tissue) as a determinant of PBDE serum concentrations We used a convenience sample of office workers in the Boston area that were mostly white, not overweight, and highly educated, and we cannot be certain our results can be generalized to the U.S. population.

Our study demonstrates that a single PBDE serum measurement of BDE-28, BDE-47, BDE-99, BDE-100, and BDE-153 reliably estimates a participant's blood concentration over a one-year period. This result held for both lipid adjusted and nonlipid adjusted serum concentrations. Our analysis thus supports PBDE epidemiology studies that use single serum samples. We also observed decreases of serum concentrations of some PBDE congeners that were not explained by changes in serum lipid. Future studies should investigate changes in serum levels of PBDEs in the U.S. population and the possible implications of sampling season on PBDE serum concentrations.

■ ASSOCIATED CONTENT

Supporting Information

Three tables (T1, T2, and T3) and three figures (F1, F2, and F3) as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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