Published in final edited form as:
Environ Res. 2014 July ; 132: 244–250. doi:10.1016/j.envres.2014.04.009.

Polybrominated Diphenyl Ether (PBDE) Exposure in Children: Possible Associations with Cardiovascular and Psychological Functions

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Abstract

Background—Polybrominated diphenyl ethers (PBDE) have been used widely in consumer products and are currently found at detectable levels in the blood of humans and animals across the globe. In stark contrast to this widespread exposure to PBDEs, there is relatively little research on potential adverse health effects of exposure of children to these chemicals.

Objectives—We performed this cross-sectional study to determine if blood PBDE levels (for 4 congeners) are associated with cardiovascular stress responses and psychological states in children.

Methods—Levels of 4 PBDE congeners (BDE-28, -47, -99, and -100) in whole blood were measured in children (N = 43). These levels were analyzed in relation to cardiovascular disease risk factors, including cardiovascular responses to acute stress and relevant psychological variables, namely, hostility and depression.

Results—Higher levels of blood PBDEs were associated with significantly greater sympathetic activation during acute psychological stress and greater anger, as evidenced by significant associations with 3 different measures of this psychological variable.

Conclusions—This study suggests an association between PBDE exposure and children's cardiovascular responses to stress as well as parental and self-reported anger in the child. These variables are particularly important as they may be of potential relevance to the future development of cardiovascular disease (CVD). Although intriguing, there is a need for further investigation and replication with a larger sample of children.

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Keywords

Polybrominated diphenyl ether; PBDE; children; sympathetic reactivity; hostility; stress

1. Introduction

Polybrominated diphenyl ethers (PBDEs) represent a specific class of brominated flame retardants. As such, PBDEs have been used in a wide variety of consumer and industrial products, including building materials, electronics, furnishings, and plastics. Similar to other persistent organic pollutants (POPs), PBDEs show a marked resistance to metabolic or environmental degradation and this, in combination with widespread use, has resulted in detectable levels of PBDEs in wildlife around the world (Trumble et al. 2012; Vanden Berghe et al. 2012; Shaw and Kannan 2009) as well as in humans with (Schecter et al. 2009) and without (Hohenblum et al. 2012) occupational exposure. In addition, levels of PBDEs appear to be higher in children than adults (Lunder et al. 2010), making this a particularly important population to study. The largest exposure pathway for children is through contact with and ingestion of house dust (US Environmental Protection Agency (EPA) 2010).

Some recent research suggests potential associations between prenatal and postnatal exposure to PBDEs and psychological functioning. For example, associations between deficits in attention and PBDE exposure were found in children enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort (Eskenazi et al. 2013). Similarly, postnatal exposure to BDE-47 was related to an increased risk of attention deficits (but not hyperactivity) associated with attention deficit and hyperactivity disorder (ADHD) as well as poor social competence symptoms (Gascon et al. 2011).

The potential for PBDE exposure to affect cardiovascular functioning has yet to be determined. However, PBDE neurotoxicity is beginning to be explored using animal models and these findings may suggest a “downstream” effect on the cardiovascular system. For example, protein analysis in the neonatal mouse brain showed PBDE-induced increases in the levels of calcium/calmodulin-dependent protein kinase II (CaMKII; Viberg and Eriksson 2011) and these levels were increased specifically in the hippocampus (Viberg et al. 2008). With respect to a link with cardiovascular functioning, CaMKII may mediate the heart’s “fight-or-flight” response, specifically the response to β-adrenergic stimulation (Mohler and Hund 2011). The evidence for this function can be found in research showing that reduced CaMKII (modeled with CaMKII knock-out mice or transgenic mice expressing a CaMKII inhibitory peptide) have normal heart function at baseline (Backs et al. 2009) but display a blunted increase in heart rate in response to isoproterenol treatment (a β-adrenergic agonist; Wu et al. 2009).

Although we measure both psychological and cardiovascular variables in the current study, these outcomes can be integrally connected. Most notably, increasing hostility and anger are associated with heightened cardiovascular responses to psychological stress (e.g., Matthews 1982). A number of models have been proposed to explain this association. For example, according to the “psychophysiological reactivity model” (Williams et al. 1985), those that

are hostile are more prone to heightened anger and consequently greater cardiovascular and neuroendocrine responses to stressors. Alternatively, individual differences in both cardiovascular reactivity and hostility may be caused by genetically determined differences in autonomic lability (Smith 1992). Within the current research context, PBDE exposure may relate to both psychological and cardiovascular variables as a consequence of effects on one variable (e.g., hostility that in turn affects cardiovascular responses to psychological stress) or effects on the underlying autonomic system (that in turn affects both hostility and cardiovascular responses to psychological stress).

In the present study, we conducted a cross-sectional investigation of potential cardiovascular and psychological associations with blood PBDE levels in children. Children are an important population to study given their greater PBDE exposure (Toms et al. 2008) and the potential for a child's environmental context to set a trajectory for significant effects in adolescence and adulthood (e.g., Moody-Ayers et al. 2007). Specifically, we considered potential PBDE associations with cardiovascular responses to acute psychological stress as well as with psychological variables (namely, temperament, hostility, depression, and aggression). Although there is limited prior research upon which to base predictions, our study considers the hypothesis that increasing blood PBDE levels will be associated with greater hostility and greater cardiovascular reactivity – particularly indicators of β-adrenergic stimulation characterized by increasing HR and decreasing pre-ejection period as well as lower vascular resistance.

2. Methods

2.1 Participants

Participants were recruited as part of an ongoing study designed to address the effects of low level lead (Pb) exposure on cardiovascular responses to acute stress (Gump et al. 2011). For that study (N = 100), we mailed 889 invitations to homes in Oswego County, New York, containing a child within our target age group (9–11) using a direct mailing list of households in Oswego County. This recruitment method elicits participation from a sample that closely resembles an eligible population and is cost effective (Hinshaw et al. 2007). The low response rate (11.2%) was expected given the nature of the study (namely, a venous blood draw for non-medical reasons in a population of children); however, this response rate does raise concerns regarding possible selection bias. Although we have no specific data on those not responding to our invitation, 2012 American Community Survey (ACS) data for this geographic area suggests that our sample has more minority participants with slightly lower income: as shown in Table 1, our sample included 84.8% White with an average family income of $35,000–45,000 while ACS data for this county shows 93.5% White for age groups 5–14, with median household income of $47,288. Further inclusion criteria included: 1) reporting no use on the day of testing of medication that might affect cardiovascular functioning (e.g., Ritalin), and 2) having no significant developmental disorders that might affect task performance (a component of our broader study). As a consequence of new hypotheses generated mid-way through this ongoing study, we began drawing an additional 2-ml of whole blood for the analysis of PBDE levels only for the final 45 children we tested. In addition, we were unable to obtain sufficient blood for the

additional analysis of PBDE levels for 2 of these children. This resulted in a final sample of 43 children (16 females, 27 males). This reduced sample differed significantly from the 57 children we were unable to analyze on only 1 of 26 covariates and outcomes we measured – namely, the sample for the present analyses had a significantly lower socioeconomic status (*p*s < .05). This difference cannot be readily explained and we believe it is likely a result of chance, given the number of comparisons.

2.2 Blood draw

Participants arrived at our blood draw center and first signed an assent form while their parents signed a separate consent form approved by the Institutional Review Board of SUNY Oswego. Whole blood specimens (2 mL) were collected into 2 different Vacutainer tubes for the analysis of PBDE and non-essential metals (using a tube that had been pre-certified by the analyzing laboratory for low-level measurements of Pb). Additional blood was collected for the analysis of antioxidant capacity. Our laboratory testing (see below) was scheduled to occur within 1 week of this blood draw.

2.3 Measurement of Blood PBDE Levels

PBDEs were analyzed following the method described elsewhere, with some modifications (Fitzgerald et al. 2012). Briefly, 1 g of blood was spiked with ^{13}C-labeled PBDEs (MBDE-MXFS, Wellington Laboratories, Merriam, KS) and sonicated with 88% formic acid (1:1 v/v ratio; 1 mL) for 15 minutes. HPLC grade water was added to the sample at a 1:1 ratio (2 mL) before the Rapid Trace (Caliper Life Science, Hopkinton, MA) solid phase extraction (SPE) and purification. The SPE column was packed with 1.3 g of C18-Sepra sorbent (Phenomenex, Torrance, CA). After loading the sample onto the column, nitrogen was passed for 40 minutes at 35 psi to remove moisture. Then, the sample was extracted with 12 mL of 30% dichromethane in hexane. The extract was cleaned by a SPE column packed with 0.2 g of silica gel and 1 g of 40% acidic silica gel, and was eluted using 12 mL of 15% dichloromethane in hexane. Lipid content was determined gravimetrically from an aliquot of blood that was extracted with dichloromethane and hexane (3:1 v/v).

2.31. Identification and Quantification—PBDEs congeners were determined by high-resolution gas chromatography (HRGC; Trace GC Ultra; Thermo Electron Corporation, Bremen, Germany) coupled with a high-resolution DFS mass spectrometer (Thermo Electron Corporation, Bremen, Germany) at a resolving power of 9000–10,000 (10% valley). Ion source temperature was kept at 285 °C. The GC column used was DB-5MS (30 m × 0.25 mm I.D. × 0.25 μm). The injector temperature was kept at 270 °C. The GC column oven temperature was programmed from 130 °C (1.5 min) and increased at a rate of 15 °/min to 216 ° (1 min), then at 5 °/min to 300 ° (4.1 min). All congeners determined by HRGC/MS were quantified using the isotope dilution method based on the response from the corresponding ^{13}C labeled congeners. Procedural blanks were analyzed and the reported concentrations in samples have been subtracted from blank values, when applicable. Recoveries of surrogate standards spiked into individual samples were 82±11% for PCB 30 and 94±10% for PCB204. Recoveries of ^{13}C labeled PBDE internal standards were 47–66%. PBDE congeners 28, 47, 85, 99, 100, 153 and 154 were analyzed in this study. The detection limits of target compounds ranged from 0.042 (BDE-47) to 0.003 ng/g on a wet weight

basis. Congeners 85, 153 and 154 were not detected (below the LOQ of 0.003 ng/g wet wt) in any samples and therefore, the data were not reported. For congeners 28, 47, 99, and 100, samples with levels below the LOQ were assigned a value ½ the LOQ for statistical analysis (cf. Schantz et al. 2001).

2.4 Experimental Procedure

On the day of cardiovascular reactivity testing, children arrived and first had their height and weight measured, followed by the application of electrodes for impedance cardiography and the electrocardiogram (ECG) and the blood pressure cuff was positioned on the nondominant arm. Each experimental session was comprised of the following: 1) an initial rest period (10 minutes), 2) a mirror tracing task (1.5 minutes for each trial, 2 trials), 3) an inter-task rest (8 minutes), 4) a Go/No Go task (2.5 minutes for each trial, 2 trials), 5) an inter-task rest (8 minutes), 6) a continuous performance task (75 seconds for each trial, 5 trials), and 7) a final recovery/rest period (10 minutes). The order for the three acute stress tasks was counterbalanced. Questionnaires were also administered during this visit.

2.5 Experimental Tasks

2.5.1 Mirror Tracing—The mirror image tracing task is a psychomotor task that traditionally requires subjects to trace the outline of a figure while viewing the figure in a mirror. A computerized version of this task was created by slightly modifying an existing E-Prime™ mirror image tracing program (Balslev et al. 2004). Participants are asked to trace an image of a star on the computer screen using a cursor directed by a mouse; however, the mouse control is inverted (cursor moves to the right when mouse moves to the left and vice versa) and a loud tone is sounded if the participant's cursor leaves the star. We administered 2 trials lasting 1.5 minutes each. The number of star segments completed was difficult to measure because the cursor was frequently outside of the star. Therefore, task performance was measured by the percent of time the cursor was outside the star.

2.5.2 Go/No Go Task—Using the E-Prime™ program, an auditory Go/No Go task was developed for this study and run on a Dell Pentium computer. We administered 2 trials lasting 2.5 minutes each with the goal being to respond as quickly as possible to the target tone but not to a non-target tone. Tones occurred on a variable interval schedule of 10 seconds and included 8 targets and 7 non-targets. Task performance was measured by hit rate (proportion of correct tones with response) and false alarm rate (proportion of incorrect tones with response). In addition, reaction time to hits was used as another measure of task performance.

2.5.3 Continuous Performance Task—E-Prime™ software is used to program five variants of the signal detection task that systematically manipulate demands on response inhibition. In short, each signal detection task employed a series ($N = 100$) of numerical stimuli (0–9) that were presented in rapid and random sequence (250 ms stimulus interval, 500 ms inter-stimulus interval). The target is the numeral 9. The proportion of targets to non-targets was varied across the five signal detection conditions (target proportions of 10, 30, 50, 70 or 90% at 200 trials per condition) and was given within a randomized block. To measure performance on this task, we calculated the signal detection parameters *d'*, a

measure of discriminability calculated from the difference between hit rate and false alarm rate, and β, a measure of bias calculated from the proportion of all stimuli with responses.

2.6 Physiological Data Collection

2.6.1 Physiological Recording Apparatus—Impedance cardiography and the electrocardiogram (ECG) were used for the measurement of stroke volume and heart rate. An Impedance Cardiograph (Model HIC-2000, Bio-Impedance Technology, Chapel Hill, NC) was used for the generation of the impedance waveforms using a tetrapolar band electrode configuration (Kubicek et al. 1970). The ECG signal was transduced using two disposable silver/silver chloride electrodes (Meditrace 533) placed on each side of the abdomen below the impedance electrode bands, as well as a ground electrode beside the navel. Calculations of the physiological measures from the impedance cardiography were performed as previously described (Sherwood et al. 1990) and included the assessment of pre-ejection period (PEP), stroke volume (SV), and cardiac output (CO). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were monitored using the Vasotrac device (APM 205A; Medwave, Danvers, MA). The pressure readings were entered into the COP program after the experimental session was over, and the program automatically computed total peripheral resistance (TPR) using the formula: TPR = [(((SBP – DBP)/3) + DBP)/CO]*80 where TPR is in dyne-sec/cm^5, CO is in liters/min, and SBP and DBP are in mmHg. Measures based on volumetric calculations (i.e., SV, CO, and TPR) are only analyzed as change scores (see recommendations in (Sherwood et al. 1990).

Nevrokard™ HRV program (Nevrokard Kiauta, k.d., Slovenia) was used for the analysis of heart rate variability (HRV). Inter-beat intervals (the times between successive heart beats) are generated and stored from ECG data generated at a sampling rate of 500 Hz, well within the sampling frequency recommended by the Task Force of the European Society of Cardiology that published guidelines for the collection and interpretation of HRV data (Cardiology 1996). Nevrokard HRV software conducts a spectral analysis of this inter-beat interval data and calculates the HF component, among other heart rate variability measures. The HF component of HRV is considered an indirect measure of parasympathetic activation (Cardiology 1996). We had insufficient signal quality for 2 participants. Therefore, HF-HRV data were available for 41 participants.

2.6.2 Blood pressure and impedance-derived variables—Blood pressure measurement was recorded every 30-seconds during the last 3-minutes of the initial rest period and during the entire acute stress tasks. Similarly, data for heart rate and impedance-derived variables were collected using a 15 second inter-sample interval and 14 second ensemble average duration (allowing 1 second for storing data) was collected during the last 3 minutes of the initial rest and during the entire acute stress tasks. For the calculation of HF-HRV, inter-beat interval data was collected continuously for the last 3-minutes of the initial rest and continuously during each acute stress task.

2.7 Psychological Measures

2.7.1 Temperament—As a measure of temperament, parents were administered the 25-item Strengths and Difficulties Questionnaire (SDQ; (Goodman 1997). The SDQ contains

five different subscales measuring: emotional symptoms, conduct problems, hyperactivity-inattention, peer relationship problems and prosocial behavior. A total difficulties score (range 0–40) is obtained by summing these subscales. The SDQ subscales are valid with respect to the corresponding child psychiatric diagnostic categories (Achenbach et al. 2008; Becker et al. 2004).

2.7.2 Aggression—As a measure of aggression, we administered the 29-item scale developed by Buss and Perry (Buss and Perry 1992) to the children. This measure includes four subscales: physical aggression (9 items), verbal aggression (5 items), anger (7 items), and hostility (8 items). These subscales typically have good internal consistency (Cronbach's alphas ranged from .72 to .85 in validation sample) and good test-retest reliability (correlations ranged from .72 to .80; Buss and Perry 1992).

2.7.3 Hostility—As a measure of hostility, a 26-item version of the Cook-Medley Ho Scale (Cook & Medley, 1954) was administered to children. The 26-item version is highly correlated with the full scale (r = .95) and has good test-retest reliability and internal consistency in children (Woodall & Matthews, 1993). This measure generates a total score as well as 3 subscales: cynicism (13 items), angry affect (5 items), and aggressive responding (8 items).

2.7.4 Depressive Symptoms—Depressive symptoms in the child were measured using the Child Depression Inventory (CDI; Kovacs 1982). The CDI is a 27-item measure with well-documented psychometric properties and is administered to the child. Internal consistency typically ranges from .84 to .94 (Kovacs 1982). Test-retest reliability over 1, 3, 4, and 6 weeks ranges from .38 to .87 (Kovacs 1982; Smucker et al. 1986). In addition to a total score, this measure also provides scores for 5 subscales: negative affect (6 items), interpersonal problems (4 items), perceived ineffectiveness (4 items), anhedonia (8 items), and negative self-esteem (5 items).

2.8 Potential Confounds

Potential confounders were chosen using an *a prior* selection of a limited set of variables shown in prior literature to relate to the outcome (Ewout and Harrell 2009). This approach avoids over-fitting a model that occurs when "cherry picking" covariates from a larger set of potential confounds (Babyak 2004). The following covariates were used in multivariate models: BMI percentile standing (age and gender adjusted using a SAS program developed by the Centers for Disease Control and Prevention; (CDC 2008), socioeconomic status (SES) score (using an average of parents' education, occupation, and income after being converted to z-scores), and total blood lipid levels. Because of the effects of Pb exposure on the cardiovascular system that we have previously documented (Salonen et al. 2000), this metal was also included as a covariate in all analyses. Details regarding the measurement of Pb are provided in a prior publication (Gump et al. 2011). In order to avoid the inclusion of too many covariates (and the corresponding loss of power), we did not include controls for age and race as these variables had very little variability in our sample (which was 9–11 years of age and 84.8 % White) and we did not include task performance (based on results reported below demonstrating no significant associations with PBDE levels).

2.9 Data Analysis

2.9.1 Analytic Models—The distribution of blood PBDE levels was not normally distributed and was therefore log-transformed before analysis. Using SAS PROC REG, each outcome was regressed on PBDE blood levels. Therefore, all analyses were linear regression models with covariates entered first, followed by PBDE levels.

2.9.2 Cardiovascular responses to acute stress—Change scores for systolic blood pressure, diastolic blood pressure, and heart rate were computed by subtracting baseline levels of a variable from the task means. For impedance-derived variables involving volume measures (cardiac output, stroke volume, and total peripheral resistance), percent change from baseline to task was used because of questions about the accuracy of absolute levels of these variables (Miller and Hovrath 1978; Sherwood et al. 1986). For all analyses of responses to acute stress, cardiovascular change scores were standardized within the three acute stress tasks and then averaged across tasks (cf. Matthews et al. 2003). We took this approach because averaging across tasks improves the reliability of cardiovascular reactivity assessment (Kamarck and Lovallo 2003), and averaging responses across these same tasks (with the addition of two other tasks) has been shown to predict future blood pressure in children (Matthews et al. 2003).

3. Results

3.1 Sample Characteristics

Table 1 shows characteristics of the children and their mothers and fathers in this sample. By design, children in our sample were 9, 10, or 11 years old (M = 10.13) and prepubertal (Gump et al. 2011). Table 2 reports the PBDE levels in the whole blood of the children. These levels are approximately 2–8 times lower than other population studies of PBDE for children residing in the United States (Bradman et al. 2012; Lunder et al. 2010; Windham et al. 2010), perhaps reflected regional differences in PBDE levels in children (cf. Windham et al. 2010) as well as the matrix analyzed in this study (whole blood in this study versus serum in other studies). As shown in Table 3, levels of different PBDE congeners in the blood for this population were highly intercorrelated.

3.2 PBDEs and Task Performance

Before considering the potential associations between PBDEs and cardiovascular responses to our acute stress tasks, we considered whether PBDEs were associated with task performance and might thereby have affected cardiovascular responses (i.e., the task may have been more difficult and frustrating as a function of PBDE levels and thereby increase cardiovascular responses). After controlling for the standard covariates outlined above, performance on the mirror tracing task was not significantly associated with specific PBDE congeners nor total PBDE levels (all p values > 0.05). Similarly, PBDE congeners and total PBDE were not significantly associated with reaction times, false alarm rates, or hit rates during the Go/No Go task (all p values > 0.05). Finally, neither PBDE congeners nor total PBDE were associated with d' or β performance indices during the continuous performance task (all p values > 0.05). Because PBDE levels were unrelated to task performance, we did not include these measures as covariates for the analyses reported below.

3.3 PBDEs and Cardiovascular Functioning

We first analyzed associations between PBDE congeners (4) and *baseline* levels of SBP, DBP, HR, PEP, and HRV, controlling for the standard set of covariates. As might be expected by chance alone, only 1 association was significant in the 20 that were considered (results not shown). However, the analysis of cardiovascular *changes* during acute stress tasks revealed a number of significant associations with some PBDE congeners indicative of heightened β-adrenergic stimulation during these stressors. As shown in Table 4, BDE-28 was associated with significantly greater HR, lower PEP, and lower TPR (p values < .05). For purposes of illustrating these associations, regressions were repeated using averages for unstandardized outcomes (notably, associations remained significant using this alternative approach). Based on the standardized β for these analyses, each 1 SD increase in BDE-28 was associated with a 1.68 beats/min greater increase in HR, 1.38 second shorter PEP, and 4.0% lower TPR response to acute stress. In addition, BDE-47 was associated with significantly lower DBP and BDE-100 was associated with significantly lower DBP and shorter PEPs during acute stress (p values < .05). Again, based on the standardized β for analyses using unstandardized outcomes, each 1 SD increase in BDE-47 was associated with a DBP response that was 2.00 mmHg lower and each 1 SD increase in BDE-100 was associated with a DBP response that was 1.89 mmHg lower and a PEP response that was 1.68 seconds shorter.

3.4 PBDEs and Psychological Functioning

There were a number of significant associations between blood PBDE congener levels and measures of hostility and anger. Parental reports of conduct problems in their children were significantly associated with greater BDE-28, -47, and -99 (p values < .05). In addition to these associations, two questionnaires administered to children revealed significant associations that were strongest for subscales assessing anger (see Table 3). For example, the Angry Affect subscale in the Cook-Medley Ho Scale was significantly associated with blood levels of BDE-28 (p < .05, see Figure 1). The effect size for this association was quite large (β = .49), with BDE-28 accounting for nearly 25% of the variation in Angry Affect scores. Although it creates some range restriction and limits the power of our analyses, removing the top 3 PBDE exposed children did not change these results (new β = .56, p < .01). Depressive symptoms (based on child reports) were not significantly associated with PBDE congener levels in blood.

4. Discussion

PBDEs are ubiquitous environmental contaminants. In fact, 4 of the 7 PBDE congeners (BDE-28, -47, -99, and -100) measured for the present study were found at detectable levels in over 75% of the children in our sample. The present study also provides preliminary evidence of an association between cardiovascular responses to acute stress and some PBDE congeners. The particular hemodynamic pattern associated with elevated BDE-28 (higher HR, shortened PEP, and lower TPR) fits the pattern that would be expected with heightened β-adrenergic stimulation and consequent increases in tissue perfusion in response to stress or threat. Although the reduced DBP in response to stress that was associated with BDE-47 and -100 might suggest a reduced risk for subsequent elevations in blood pressure (Matthews et

al. 1993), the apparent increase in sympathetic reactivity as indexed by increasing HR (with BDE-28) and decreased PEP (with BDE-28 and -100) may indicate a chemically induced "hyperkinetic state" (Amerena and Julius 1995). Such a hyperkinetic state is presumed to precede vascular remodeling, a transition to hypertension as a consequence of this remodeling, and corresponding sustained vascular resistance (Julius 1994; Julius and Gudbrandsson 1992).

In addition to these associations between PBDE and cardiovascular responses to stress, a number of positive associations between PBDE and hostility were observed. These associations were consistent across different measures and from different sources (both parent and child). These associations also seemed to be strongest for the anger component of hostility/aggression: "conduct problems" for parental reports of temperament, "angry affect" for child's report on the Cook-Medley measure of hostility, and "anger" on the child's Buss-Perry measure of aggression. Finally, although these associations varied slightly across PBDE congeners, it did not appear that any specific congener was most strongly related to anger. In addition to the direct importance of PBDE exposure being associated with greater anger in children, numerous studies have demonstrated a significant positive association between anger and risk of CVD (Haukkala et al. 2010; Barefoot et al. 1983; Matthews et al. 2004).

It is difficult to place the current findings within the context of prior PBDE literature because of the lack of similar research. The study of associations between environmental toxicants and cardiovascular responses to psychological stress remains unique to our laboratory (e.g., Gump et al. 2011) and this represents the first paper to consider these outcomes in the context of PBDE levels. In addition, the only other study of PBDE in children that might be relevant to our finding of increased anger was a finding of reduced social competence (Gascon et al. 2011) associated with PBDE exposure and subsequent analysis of this measure of social competence suggesting that it may reflect hostility (Flint et al. 1980). If the current findings are replicated with a larger sample, it will be important to then consider if alterations in cardiovascular functioning and anger might be an antecedent or consequence of the neurodevelopmental outcomes that have been linked to PBDE levels in other studies.

There are notable limitations with the present study. Foremost, we employed a cross-sectional study design making it difficult to establish causality. For example, it is possible that children's anger produced behaviors that increased exposure to PBDEs. Or perhaps hemodynamic responses to stress affect PBDE toxicokinetics and clearance from the blood. Similarly, although we controlled for some potential confounds, there may have been other unmeasured confounds (e.g., maternal anger) that account for the present associations and these should be considered in future (larger) studies of PBDE exposure effects. In addition, exposure to other toxicants may be confounded with PBDE levels. However, levels of one toxicant (Pb) with demonstrated associations with anger (Needleman et al. 2000; Needleman et al. 1996) were controlled for in all our analyses. We did not have a sufficient volume of blood to measure additional toxicant exposures nor an adequate sample size to allow inclusion of additional covariates. This small sample size is a second limitation of the present study. However, the evidence for significant associations despite this small sample

size demonstrates potentially large effect sizes. At the very least, the study suggests a need for replication with a large sample. Third, we conducted numerous tests of associations and therefore inflated the potential for Type I error. However, the consistency in findings for anger (across reporting sources and across measures) enables greater confidence in the validity of our findings. Finally, although we included a number of potentially confounding variables in all statistical analyses, uncontrolled confounding variables remain a possibility.

4.1 Conclusions

The present study investigates blood levels of various PBDEs in children and associations with cardiovascular and psychological variables. The results demonstrated significant associations between a "hyperkinetic [cardiac] state" and blood levels of BDE-28 and -100. In addition, anger (but not depression) was specifically associated with all the PBDE congeners we analyzed. With respect to a possible mechanism, this pattern of associations is consistent with research demonstrating PBDE-induced increases in α-CaMKII and corresponding findings that α-CaMKII knockout mice display a blunted increase in heart rate in response to a chemical "stressor" ((Wu et al. 2009) and reduced aggression using resident-intruder paradigms (Chen et al., 1994). These results are novel and were found in a small sample; however, the consistency in findings across measures increases our confidence in the findings and suggests a need for further investigation and replication with a larger sample of children. In addition, based on the particular associations we observed (hyperkinetic state and greater anger) long-term effects of PBDE exposure on cardiovascular disease risk should be explored.

Acknowledgments

We are grateful for the assistance of Drs. Patrick J. Parsons and Christopher D. Palmer (Wadsworth Center and University at Albany) for the measurement of nonessential metals (Pb and Hg) in our samples. In addition, we are grateful to Amy Dumas, Keri Favreau, Arlen Halstead, Julia Stead, Christie Turenchak, and Jordan Greeno for their assistance in data collection and for the assistance of Ed Hogan (Laboratory Manager), Ed Hale (Chemistry Supervisor), and Barb Samson (phlebotomist) with the Oswego Hospital Laboratory.

Funding and Human Subjects Review

Grant ES015619 from the National Institutes of Health as well as funding from SUNY Oswego and Syracuse University supported this work. SUNY Oswego's Institutional Review Board (IRB) approved this research and all participants provided assent and corresponding parents provided consent.

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Highlights

- Levels of four PBDE congeners were measured in children's whole blood.
- The higher the PBDE levels the greater the stress induced sympathetic activation.
- The higher the PBDE levels the greater the child’s hostility and anger.

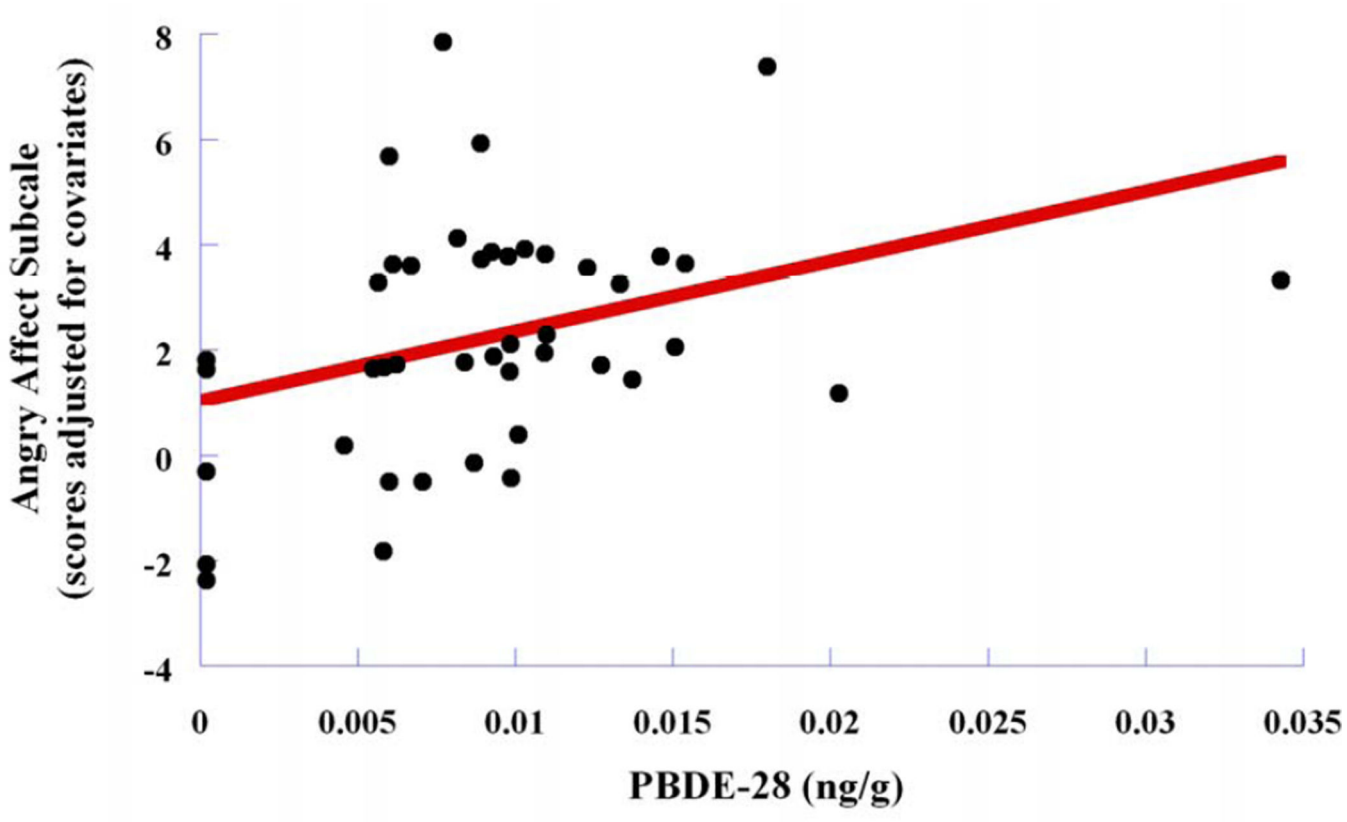

Figure 1.
PBDE-28 concentrations in blood in relation to angry affect subscale scores from the Cook-Medley Hostility (Ho) Inventory.

Table 1

Characteristics (Mean and SD or %) of Participants (N = 43)

Measure	Mean (SD)/%
Child age (yrs)	10.00 (1.13)
Child's height (inches)	55.07 (2.63)
Child's weight (in lbs)	88.38 (21.14)
Child's BMI (kg/m^2)	20.31 (3.76)
Gender (0=male; 1=female)	36.14 % female
Race (0=White; 1=Other)	84.81 % White
Socioeconomic Status (SES) [2]	
Education [3]	5.22 (1.23)
Occupation (score)	5.46 (1.67)
Income [4]	7.37 (2.25)
Lipids in blood (%)	0.13 (0.07)
Blood Pb (mg/dL	1.02 (0.45)

[1] BMI was standardized by age and gender for use in statistical analyses.

[2] As indicated in the methods section, the 3 measures of socioeconomic status (education, occupation, and income) were converted to z-scores and combined to yield a single measure of SES.

[3] On this education scale, a score of 5 corresponds to "some college". As outlined in the methods section, education was averaged across parents.

[4] On this income scale, a score of 7 corresponds to "35,000 – 45,000". As outlined in the methods section, this income was subsequently adjusted for the number of persons living in the household.

Table 2

PBDE content (ng/g) in whole blood samples (Mean, Standard Deviation, Median, Minimum, Maximum, % of samples with levels above LOQ) of participants (N = 43).

			Minimum			Lipid Adjusted (ng/g lipid)
	Mean (SD)	Median	(LOQ)	Maximum	% above LOQ	Mean (SD); Range
BDE-28	0.009 (0.006)	0.009	0.004	0.034	88.37	1.07 (3.23); 0.002–22.86
BDE-47	0.124 (0.083)	0.105	0.042	0.378	86.05	8.53 (5.68); 0.021–22.22
BDE-99	0.033 (0.042)	0.026	0.002	0.269	76.74	2.30 (2.70); 0.002–17.94
BDE-100	0.012 (0.114)	0.012	0.003	0.066	83.72	0.86 (0.78); 0.001–4.43

Table 3

Pearson correlation coefficients (r) among different PBDE congeners in blood samples (N = 43).

	BDE-28	BDE-47	BDE-99	BDE-100
BDE-28	1.00	--	--	--
BDE-47	0.52 **	1.00	--	--
BDE-99	0.24 $^{\tau}$	0.64 **	1.00	--
BDE-100	0.31 *	0.80 **	0.86 **	1.00

$^{\tau}$ p < 0.10;

* p < 0.05;

** p < .001

Table 4

Associations (standardized βs) of Blood PBDE Levels with Children's Cardiovascular Stress Responses and Psychological State (controlling for covariates).

	PBDE Congeners			
Measures	**−28**	**−47**	**−99**	**−100**
Cardiovascular Responses to Acute Stress				
Systolic blood pressure (mmHg; SBP)	−0.26	−0.23	−0.09	−0.26
Diastolic blood pressure (mmHg; DBP)	−0.26	**−0.39** *	−0.21	**−0.36** *
Heart rate (beats/minute; HR)	**0.39** **	0.08	0.15	0.17
Pre-ejection period (msec; PEP)	**−0.32** *	−0.21	−0.18	**−0.39** *
Stroke volume (% change; SV)	0.01	0.06	0.08	−0.12
Cardiac output (% change; CO)	0.25	0.10	0.16	0.01
Total peripheral resistance (% change; TPR)	**−0.35** *	−0.20	−0.12	−0.19
High Frequency Heart Rate Variability (HRV)	0.03	0.14	0.08	0.09
Psychological States				
Temperament (Parent Report)				
Total Score	**0.35** *	**0.37** *	0.24	**0.36** *
Conduct Problems	**0.30** *	**0.31** *	**0.32** *	0.25
Hyperactivity	0.23	0.29 #	0.18	0.23
Emotional Symptoms	0.27 #	0.12	−0.02	0.22
Prosocial Activities	−0.11	−0.01	0.04	−0.06
Problems with Peer Relationships	0.22	0.32 #	0.18	0.34 #
Hostility (Cook-Medley)				
Total Score	**0.45** **	**0.37** *	**0.39** *	0.30 #
Cynicism	0.25	0.14	0.15	0.14
Angry Affect	**0.49** **	**0.45** **	**0.43** *	0.35 #
Aggressiveness Responding	0.28 #	0.24	0.30 τ	0.18
Aggression Questionnaire (Buss-Perry)				
Total Score	**0.34** *	**0.38** *	**0.41** *	0.31
Physical Aggression	0.24	0.23	0.20	0.32 #
Verbal Aggression	0.06	0.17	0.27	0.02
Anger	**0.34** *	**0.39** *	**0.42** *	0.24
Hostility	**0.31** *	0.30 #	0.27 #	0.31 #
Depressive Symptoms (CDI)				
Total Score	0.16	0.32 #	0.26	0.27
Negative Affect	0.08	0.19	0.16	0.05
Interpersonal Problems	0.14	0.27	0.23	0.18
Ineffectiveness	0.10	0.30 #	0.28 #	0.22
Anhedonia	0.02	0.15	0.15	0.24

	PBDE Congeners			
Measures	**−28**	**−47**	**−99**	**−100**
Negative Self-esteem	0.29 #	0.24	0.11	0.29

Ns: SBP, DBP, HRV= 42; PEP, SV, CO = 43;

# p < .10;

* p < .05;

** p < .01

NOTE: All models included covariate control for SES, BMI, gender, lipids, and lead (Pb); Statistically significant associations are shown in bold.