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# Prenatal exposure to polybrominated diphenyl ethers and predisposition to frustration at 7 months: Results from the MIREC study

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A B S T R A C T

*Background:* Prenatal exposure to polybrominated diphenyl ethers (PBDEs) has been associated with cognitive deficits and behavioral problems in children. To date, no study has examined this exposure in association with neurobehavioral development in infants younger than 12 months assessed with observational tasks.

*Objectives:* This study examined the relation between prenatal PBDE concentrations and predisposition to frustration, assessed by the arm restraint task (ART), in Canadian infants.

*Methods:* In a prospective longitudinal study conducted in Canada, exposure to nine PBDE congeners was measured in maternal plasma during the first trimester of pregnancy. The ART was used to measure predisposition to frustration in infancy (N = 333; mean age = 6.9 months), as assessed by negative vocalizations (crying and screaming) and physical reactivity (discomfort movements).

*Results:* Maternal plasma PBDE-47 concentrations collected during pregnancy were associated with negative vocalizations using the ART (adjusted Relative Risk [aRR] = 1.04, 95% CI: 1.00, 1.09). Prenatal PBDE-99 concentrations during pregnancy were also related to a shift to the left in the tail of the distribution of onset of negative vocalizations as measured by a decrease of 38 s (95% CI: −78.1, 1.3) in the 75th quantile of the distribution for infants whose mothers had detectable levels of PBDE-99 compared to infants of mothers with undetectable levels. Similarly, infants whose mothers had detectable levels of PBDE-100 showed an increase of 24.1 s (95% CI: 4.1, 44.1) in the 75th quantile of the distribution of proportion of time in negative vocalizations compared with infants of mothers with undetectable levels. Finally, the association between PBDE-47 and PBDE-153, and physical reactivity was significantly modified by sex ($p < 0.1$), with opposite patterns in girls and boys.

*Conclusions:* Prenatal exposure to PBDEs was associated with increased incidence of crying and screaming with delayed onset of discomfort movement, which may indicate a predisposition to frustration and lack of habituation in infants younger than 12 months from the general population.

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## 1. Background

Polybrominated diphenyl ethers (PBDEs) are toxic chemicals that were widely used as flame retardants in electronic equipment, plastics and textiles (Darnerud et al., 2001; Pijnenburg et al., 1995). Most PBDEs, which are persistent and bioaccumulate in the environment (*e.g.*, soil, sediments, air, water), are routinely found in humans (Gobas and Morrison, 2000), with half-lives ranging from 1 to 7 years, depending on the congener (Trudel et al., 2011). Although PBDEs were voluntarily phased out in North America starting in 2004, and their manufacture was prevented and their use restricted in Canada in 2008 (Government of Canada, 2017), higher serum concentrations are found in North Americans than in other populations (European and Asian) (Frederiksen et al., 2009, Fromme et al., 2016, Rawn et al., 2014). In North Americans, the most prevalent congeners found are PBDE-47, -99, -100, and -153 (Fisher et al., 2016; Gill et al., 2004; Oulhote et al., 2016; She et al., 2002). The main routes for human exposure to PBDEs are ingestion of some foods, and ingestion and inhalation of house dust (Frederiksen et al., 2009; Fromme et al., 2009; Gobas and Morrison, 2000). PBDEs readily cross the placenta (Mazdai et al., 2003) and are found in umbilical cord blood (Fisher et al., 2016; Kawashiro et al., 2008).

An increasing number of experimental and epidemiological studies have reported adverse behavioral effects of prenatal exposure to PBDEs. In rodents, experiments on motor behaviors, fear, and learning in novel situations revealed that gestational PBDEs exposure was associated with less activity and lower performance on learning and habituation tasks (Eriksson et al., 2001; Gee and Moser, 2008; Viberg et al., 2006). In humans, prospective cohort studies have documented associations of prenatal PBDEs exposure with toddler and child neurobehavioral development (Chen et al., 2014; Eskenazi et al., 2013; Gascon et al., 2011; Roze et al., 2009). In the Netherlands, results from the Groningen Infant Compare study (GIC) including 62 children aged between 5 and 6 years, showed both positive and negative significant associations between higher PBDE concentrations and poorer fine manipulative abilities, and worse attention (Roze et al., 2009), whereas the INfancia y Medio Ambiente (INMA) study in Spain reported significant associations between postnatal, but not prenatal, PBDE-47 concentrations and an increased risk of symptoms on the attention deficit subscale of ADHD symptoms, and poorer social competence symptoms at 4 years (Gascon et al., 2011). In the U.S., the Health Outcomes and Measures of the Environment Study (HOME) and Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) studies reported significant associations with hyperactivity at 60 months (Chen et al., 2014) and attention deficit hyperactivity disorder at 84 months (Eskenazi et al., 2013).

Collectively, the results in human and animal studies indicate that the prenatal period is sensitive to PBDE exposure, and support plausible biological mechanisms to explain the associations observed with behavioral problems. However, the associations of prenatal PBDE exposure on behaviors during infancy have not been studied, even though infant behavior can be predictive of childhood behavioral problems including poor emotion regulation and aggressive behavior (Fox and Calkins, 2003; Hay et al., 2010; Propper and Moore, 2006). The arm restraint task (ART) is a standardized task that appears to be the preferred assessment strategy to assess infant's temperamental reactivity and response to frustration in the first year of life. The ART has been used repeatedly in various studies of the responsiveness of infants to frustration (Braungart-Rieker and Stifter, 1996; Stifter and Fox, 1990), and constitutes a useful tool to study individual differences in frustration reactivity and regulation in infants as young as 2 months of age (Moscardino and Axia, 2006). Laboratory observations of children using tools, such as the ART, allow investigators to control and manipulate the environment and measure the reaction time, intensity and duration of the child's reactive behavior. This is a task analogous to those used in experimental studies involving animals. Although the ability of the ART to predict later behavioral function has not been formally evaluated and no sensitivity or specificity measures are available, infant's emotional reactivity and ability to regulate emotional responses are considered to be important predictors of later adaptive social-emotional and psychological functioning (Fox and Calkins, 2003; Propper and Moore, 2006). In particular, heightened reactivity to frustrating events in infancy has been associated with noncompliance (Stifter et al., 1999), aggressive behavior (Crockenberg et al., 2008), and poor emotion regulation (Calkins et al., 2002). Additional studies have shown that children's excessive anger and negative affectivity during a frustration task in infancy might interfere with the later development of inhibitory control in early childhood and be predictive of later behavioral difficulties (He et al., 2010; Fox et al., 2001).

In the present study, we sought to investigate the potential association between prenatal exposure to PBDEs and predisposition to frustration at around 7 months, as measured by the ART in a sample of Canadian infants from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort (Arbuckle et al., 2013).

## 2. Methods

### 2.1. Participants and procedures

Participants were mothers and infants enrolled in the MIREC pregnancy cohort study. MIREC is a cohort of 2001 women recruited during the 1st trimester of pregnancy (6–13 weeks) over a 3-year enrolment period in 10 cities (11 study sites) across Canada. Inclusion criteria were: having the ability to give consent; being pregnant for 13 weeks or less; speaking English or French; being at least 18 years old; and receiving prenatal care at one of the study sites (Arbuckle et al., 2013). The exclusion criteria for the first trimester of pregnancy were congenital malformations in the fetus, history of drug use, a history of major chronic disease, threatened abortion, and maternal medical complications such as epilepsy and cancer. Blood samples were collected during the first trimester of pregnancy to quantify prenatal PBDE exposure. The MIREC participants from seven of the eleven original sites were invited to participate in the MIREC-Infant Development (MIREC-ID) follow-up conducted at birth and around 6 months of age. The MIREC-ID cohort recruited 525 women from the original MIREC cohort. The exclusion criteria for newborns were multiple birth, major congenital malformations and neurological disorders, and seizures at delivery. The visit at 6 to 7 months included a semi-structured interview with the mother, completion of self-reported questionnaires, and a child-testing session. Written consents were obtained from the mothers for the MIREC and MIREC-ID phases. Study procedures were approved by ethics committees at Health Canada, CHU Sainte-Justine Research Center, Quebec CHU-Laval University Hospital, and each study site's Ethics Review Board.

### 2.2. Chemical analyses

Laboratory analyses for PBDEs in first trimester maternal plasma were performed at the Centre de toxicologie du Québec of the Institut national de santé publique du Québec and previously reported for the full MIREC cohort (Fisher et al., 2016). Organohalogenated compounds, including PBDE 15, PBDE 17, PBDE 25, PBDE 28, PBDE 33, PBDE 47, PBDE 99, PBDE 100, and PBDE 153 were measured in first trimester maternal plasma samples (Fisher et al., 2016) using an Agilent 6890 Network or 7890A gas chromatograph (GC) coupled to an Agilent 5973 Network or 5975C mass spectrometer (MS) (Agilent Technologies; Mississauga, Ontario, Canada). The limits of detection (LOD) were 0.03 μg/L for PBDE 15, PBDE 17, PBDE 25, PBDE 28, PBDE 33, PBDE 47; and 0.02 μg/L for PBDE 99, PBDE 100, and PBDE 153. Only PBDE 47, PBDE 99, PBDE 100, and PBDE 153 were retained for the analyses because they were detected in at least 10% of plasma samples. We also measured total serum lipid concentrations to adjust PBDE serum levels.

**Table 1**
Distribution of plasma PBDE concentrations in the study population (n = 333).

| PBDE | LOD | % > LOD | GM[a] (GSE) | 25th percentile | 50th percentile | 75th percentile | 95th percentile | Max |
|---|---|---|---|---|---|---|---|---|
| Volume based PBDE concentrations (μg/L) | | | | | | | | |
| PBDE-15 | 0.03 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-17 | 0.03 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-25 | 0.03 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-28 | 0.03 | 1.5% | n/a | < LOD | < LOD | < LOD | < LOD | 0.097 |
| PBDE-33 | 0.03 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-47 | 0.03 | 64% | 0.044 (0.003) | < LOD | 0.04 | 0.08 | 0.25 | 4.0 |
| PBDE-99 | 0.02 | 19% | 0.005 (0.0004) | < LOD | < LOD | < LOD | 0.05 | 0.93 |
| PBDE-100 | 0.02 | 22% | 0.006 (0.0005) | < LOD | < LOD | < LOD | 0.085 | 1.8 |
| PBDE-153 | 0.02 | 43% | 0.014 (0.001) | < LOD | < LOD | 0.039 | 0.22 | 2.9 |
| Lipid based PBDE concentrations (ng/g lipids) | | | | | | | | |
| PBDE-15 | 5 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-17 | 5 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-25 | 5 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-28 | 5 | 1.5% | n/a | < LOD | < LOD | < LOD | < LOD | 16.1 |
| PBDE-33 | 5 | 0 | n/a | < LOD | < LOD | < LOD | < LOD | < LOD |
| PBDE-47 | 5 | 64% | 7.32 (0.43) | < LOD | 7.13 | 12.98 | 44.23 | 727.3 |
| PBDE-99 | 3.3 | 19% | 0.91 (0.07) | < LOD | < LOD | < LOD | 9.00 | 169.09 |
| PBDE-100 | 3.3 | 22% | 0.99 (0.08) | < LOD | < LOD | < LOD | 13.90 | 327.27 |
| PBDE-153 | 3.3 | 43% | 2.40 (0.21) | < LOD | < LOD | 6.42 | 36.36 | 527.27 |

GM: geometric mean, GSE: geometric standard error, LOD: limit of detection.
[a] Values below LOD were imputed using regression on order statistics to calculate the GM and percentiles for the individual PBDE congeners.

Total cholesterol (TC), free cholesterol (FC), triglycerides (TG) and phospholipids (PL) levels were measured in the samples by enzymatic methods combined with colorimetry (in g/L) at the laboratory of Centre Hospitalier de l'Université Laval and were used to calculate the total lipid level using the following Formula: $1.677 * (TC - FC) + FC + TG + PL$ (Patterson et al., 1991).

### 2.3. Predisposition to frustration in infancy

The ART is a validated and standardized task to objectively assess infant's reactivity and regulatory behavior when experiencing a situation eliciting frustration (Braungart-Rieker and Stifter, 1996; Moscardino and Axia, 2006). Research assistants were asked to place the infants in seats located on a table at eye level and across from their mothers, and to gently restrain the infants by holding their arms down to their sides. Each assistant was kneeling at the height of the infant, and instructed to hide their face by looking to the floor and to refrain from all interactions. After 2 min of arm restraint or 20 s of hard crying, the assistant was cued to release the infant's arms and could give comfort if necessary. The following instructions were provided to the parent: sit near the child without visual contact, avoid stimulations and interactions, and have a neutral facial expression. The parent could ask to stop the task at any time. No toy or pacifier was allowed. The ART has often been adapted according to the age of the children; at six months, the task is shorter than for older children. The task was recorded on video for later analysis.

The ART was administered to 383 parent/child dyads at the 6-month site visit; however, 38 videos were not coded due to technical problems during recording, missing infant identification numbers, or infants who were too upset and unable to calm down at the start of the task. Therefore, only 345 ARTs were video recorded. Video coding was done with *The Observer* software (version 5.0). Coders were blinded to the PBDE status of the children. As part of the training of two research assistants to code the videos, the assistants viewed the same video sequences (n = 84) and independently coded negative vocalizations and physical reactivity during the task: 1) presence of negative vocalizations (cries and screams; dichotomous); 2) onset of negative vocalizations (continuous in seconds); 3) proportion of time in negative vocalizations (continuous); 4) presence of physical reactivity (discomfort body movements, including: moving arms a little and stretching legs, to struggling with the whole body); 5) onset of physical reactivity (continuous in seconds); and 6) frequency of physical reactivity classified into 3 categories: no, low, or high frequency physical reactivity. Frequency of physical reactivity was defined as the child's movement to get free form arm restraint, and was coded as absent when none was observed, low frequency when observed for less than half of the duration of the situation, and high frequency when observed for half the situation or more. Inter-rater agreement of at least 70% for each ART variable was required prior to coding; any exceedance of the 70% criterion was resolved by the two assistants reviewing the videos together. To maintain inter-rater agreement, one out of ten videos was randomly selected to be coded by both assistants; of the 345 videos, 34% were coded by both assistants.

### 2.4. Covariates and potential confounders and effect modifiers

We considered a number of covariates as potential confounders based on *a priori* knowledge of the associations between neurotoxicants and behavioral outcomes: sex; weight at birth (grams); age at visit (months); video coder; maternal and sociodemographic characteristics such as parity (nulliparous/primiparous/multiparous), maternal age (years), education (number of years), pre-pregnancy maternal body mass index (BMI, continuous), and income (six categories, with $20,000 CAD increments between categories, entered as an ordinal variable); other prenatal exposures, known to be associated with behavioral outcomes, such as maternal smoking and alcohol consumption during pregnancy (never/ever). Covariates included in the models were inferred using a Directed Acyclic Graph. Child age and sex were included in all models. Because PBDEs accumulate in lipids, we included total lipid concentrations in all models. The final models included: lipid concentrations, video coder, child's sex and age, maternal age, education, marital status, parity, country of birth (Canada *vs* elsewhere), and smoking during pregnancy.

### 2.5. Statistical analysis

We transformed PBDE concentrations (log base 2) to reduce the influence of outliers. Associations between PBDEs and ART were assessed only for the four congeners with detection frequencies > 10% (PBDE-47, 99, 100, and 153; see Table 1). We ran separate models for each PBDE congener. PBDE-47, 99, 100, and 153 were introduced as binary variables (≤LOD/ > LOD) because of their low detection

frequencies. To compute descriptive statistics (*i.e.*, geometric mean [GM]) for the 4 congeners, we imputed values < LOD with regression on order statistics (Helsel, 2005), a semi-parametric method that performs a regression on data > LOD, assuming log-normal centiles to predict concentrations ≤LOD.

For dichotomous outcomes: for the presence of negative vocalizations and of physical reactivity, we used a modified Poisson regression model with robust variance estimates to infer the adjusted relative risk (aRR) and confidence intervals (CI) because the outcomes were common (≥10%) (Zou, 2004). For these two outcomes, and in secondary analyses, we divided the PBDE congeners into 3 categories according to the LOD and the median of values above the LOD (≤LOD, > LOD to median, > median). For the outcomes that exhibited a skewed distribution: for onset of negative vocalizations, proportion of time in negative vocalizations, and onset of physical reactivity, we used a quantile regression (Koenker and Basset, 1978) for expected 25th, 50th (median), and 75th percentiles of the outcome to study PBDEs potential effects on specific areas of the outcomes distribution. In classical linear regression models, the change in the conditional mean of the outcome is associated with a change in the exposure; however, with quantile regression models, changes in the conditional quantiles are associated with the exposure. Quantile regression provides greater flexibility than other regression methods to identify differing relationships at different parts of the distribution of the dependent variable and, more importantly, it is distribution-free since it does not specify any distribution for the residuals. The 95% CI for quantile regressions were constructed using bootstrapped (N = 500) standard errors of the estimates (Gould, 1992). Finally, we used multinomial logistic regressions for analyses pertaining to the frequency of physical reactivity.

In additional analyses, we explored possible sex-related differences in the association between PBDE concentrations and ART outcomes by introducing a term for sex X PBDE.

We performed a few sensitivity analyses. First, we included in the models previously reported environmental risk factors for behavioral problems: first trimester pregnancy concentrations of polychlorinated biphenyls (plasma PCB 153, μg/L), mercury (blood Hg, nmol/L), and lead (blood Pb, μg/L), all log-transformed. Second, we also included in the models postnatal maternal depressive symptoms (Center for Epidemiological Studies Depression Scale, CES-D-10) (Radloff, 1977); and a maternal self-report measure of parental perceptions and behavioral tendencies toward her infant, as assessed by the Parent's Cognition and Conduct Toward the Infant Scale (PACOTIS) (Boivin et al., 2005). The PACOTIS includes dimensions that presumably reflect the quality of parents' involvement vis-a-vis their infant. Two dimensions, parental self-efficacy and perceived parental impact, focus on parents' beliefs about their role as a parent, while the three other dimensions, parental hostile-reactive behaviors, parental overprotection and parental warmth, reflecting behavioral tendencies. Finally, we ran our analyses excluding infants with birth weight below 2500 g (N = 13).

We set the threshold for statistical significance at $p < 0.05$ for the main analyses and $p < 0.10$ for interactions (two-tailed tests). All statistical analyses were performed using STATA version 12 (StataCorp, 2011) and R version 3.3 (R Core Team, 2016). We present the results for all the exposures and outcomes, and interpret the findings based on the consistency of the observed patterns, along with the magnitude and precision of effect estimates rather than solely relying on statistical significance.

## 3. Results

### 3.1. Sample characteristics

Participants included in this investigation were comparable to the participants enrolled in the MIREC cohort (Table S1). A total of 333 participants for whom we had information about prenatal concentrations of PBDEs and ART were included in the analyses (Tables 1 and 2).

**Table 2**
Descriptive statistics of the study population (n = 333).

| Variables | N | Mean ± SD | Min-max | % |
|---|---|---|---|---|
| Child characteristics | | | | |
| Sex (% girls) | 333 | | | 47 |
| Age at testing (months) | 333 | 6.9 ± 0.9 | 4.9–10.1 | |
| Weight at birth (g) | 332 | 3480.0 ± 518.9 | 1892.0–5070.0 | |
| Mother and family characteristics | | | | |
| Age at testing (years) | 314 | 33.5 ± 4.7 | 21.0–45.0 | |
| Parity (% nulliparous) | 332 | | | 44.6 |
| Breastfeeding (weeks) (% yes) | 312 | 21.7 ± 8.3 | 0.0–34.6 | 96.2 |
| Education (years) | 312 | 17.4 ± 3.1 | 6.0–27.0 | |
| Income (% under $20,000) | 326 | | | 4.9 |
| Marital status (% married or in couple) | 333 | | | 95.5 |
| Prenatal exposure to neurotoxicants | | | | |
| Maternal report of cigarette use (% ever) | 330 | | | 6.1 |
| Maternal report of alcohol consumption (% ever) | 333 | | | 46.7 |
| Plasma PCB 153 (μg/L) (% detected) | 333 | 0.5 ± 0.6 | 0.1–7.1 | 96.4 |
| Blood Hg (nmol/L) (% detected) | 332 | 4.7 ± 4.5 | 0.6–39.0 | 90.4 |
| Blood Pb (μmol/L) | 332 | 0.03 ± 0.02 | 0.008–0.11 | 100 |
| Arm restraint task[a] | | | | |
| Negative vocalizations (% yes) | 333 | | | 76.3 |
| Onset of negative vocalizations (s) | 333 | 46.7 ± 47.3 | 0.1–124.0 | |
| Proportion of time in negative vocalizations (%) | 333 | 21.7 ± 28.9 | 0.0–99.8 | |
| Physical reactivity (% yes) | 317 | | | 88.6 |
| Onset of physical reactivity (s) | 317 | 27.3 ± 36.6 | 0.4–124.0 | |
| Frequency of physical reactivity | 317 | | | |
| Absence | 36 | | | 11.4 |
| Low frequency | 238 | | | 75.1 |
| High frequency | 43 | | | 13.5 |

[a] Arm restraint task (Calkins et al., 2002).

The study sample was largely composed of college-educated mothers, with family income higher than $80,000 CAD for 58% of the sample. Infants were on average 7 months old at testing, about 4% of them weighed < 2500 g at birth, and almost all were breastfed (mean = 22 weeks). Seventeen percent of mothers reached the threshold for clinical levels of depression (score ≥ 10) on the CES-D-10 scale. Only 6% of women reported smoking tobacco during pregnancy. Forty-seven percent of women reported drinking alcohol at least once while pregnant.

About 75% of infants manifested frustration through negative vocalizations during the ART; 89% were physically reactive during the task, indicating that the task elicited frustration for the majority of tested infants (see Table 2). Behavioral manifestations of physical reactivity ranged from moving arms a little and stretching legs to struggling with the whole body. Onset of negative vocalizations exhibited a U-shaped distribution with a median of 22.5 seconds (s) (Interquartile range [IQR]: 6.53–107.7 s), whereas the proportion of time in negative vocalization exhibited a skewed distribution to the right with a median of 7.2% (IQR: 0.2–35.2%) (Fig. 1). Onset of physical reactivity also exhibited a U-shaped distribution with a median of 11.3 s (IQR: 4.4–29.1 s). Finally, of the 88% of children who were physically reactive, 75% were low-frequency and 14% were high-frequency.

PBDE congeners 47, 99, 100, and 153 were detected in 64%, 19%, 22%, and 43% of plasma samples, respectively. The geometric mean (GM) for plasma concentrations of PBDE congeners varied from 0.005 to 0.044 μg/L (Table 1). On a lipid basis, GMs of PBDE congeners were

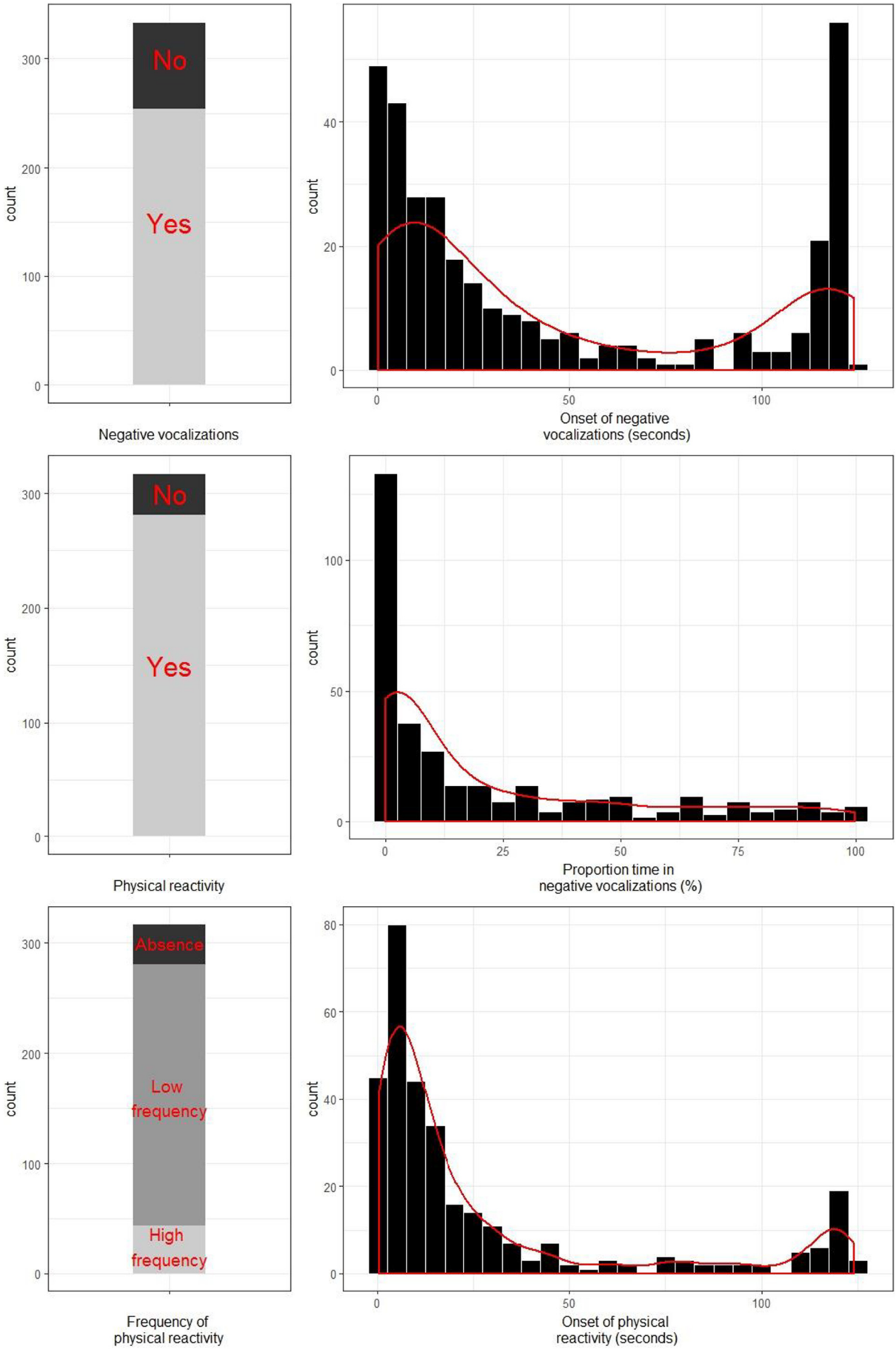


**Fig. 1.** Distribution of the arm restraint task outcomes (n = 333).

**Table 3**
Estimates (95% confidence interval) for the associations between first trimester plasma PBDE concentrations and arm restraint task outcomes.

| Arm restraint task | PBDE 47 | PBDE 99 | PBDE 100 | PBDE 153 |
|---|---|---|---|---|
| Presence of negative vocalizations[a] | 1.16 (0.99, 1.35)* | 1.21 (1.05, 1.40)** | 1.15 (0.99, 1.32)* | 1.10 (0.96, 1.26) |
| ≤Median *vs* < LOD | 1.11 (0.93, 1.32) | 1.23 (1.03, 1.48)** | 1.19 (1.00, 1.42)** | 1.09 (0.92, 1.29) |
| > Median *vs* < LOD | 1.23 (1.04, 1.46)** | 1.17 (0.96, 1.41) | 1.09 (0.88, 1.34) | 1.14 (0.97, 1.34) |
| p-Trend | 0.01 | 0.06 | 0.34 | 0.13 |
| Onset of negative vocalizations[b] | | | | |
| 25th percentile | −1.00 (−6.36, 4.35) | 0.43 (−5.68, 6.54) | −1.63 (−7.31, 4.04) | 0.44 (−5.00, 5.88) |
| 50th percentile | 6.07 (−10.56, 22.70) | −6.91 (−24.66, 10.84) | −8.25 (−25.87, 9.37) | 2.09 (−14.02, 18.19) |
| 75th percentile | −16.93 (−43.00, 9.15) | −37.82 (−74.64, −1.00)** | −20.36 (−59.58, 18.85) | −15.58 (−40.44, 9.27) |
| Proportion time in negative vocalizations[b] | | | | |
| 25th percentile | 0.22 (−0.37, 0.82) | 0.48 (−2.26, 3.21) | 0.26 (−1.37, 1.89) | 0.25 (−0.56, 1.06) |
| 50th percentile | −0.43 (−6.84, 5.97) | 9.70 (−4.98, 24.37) | 9.48 (−7.05, 26.02) | 7.34 (0.89, 13.79)** |
| 75th percentile | −7.44 (−27.61, 12.72) | 12.42 (−8.23, 33.06) | 23.19 (3.34, 43.05)** | 12.40 (−4.37, 29.16) |
| Presence of physical reactivity (incidence)[a] | 1.06 (0.96, 1.17) | 1.01 (0.90, 1.13) | 0.99 (0.88, 1.11) | 0.99 (0.90, 1.08) |
| ≤Median *vs* < LOD | 1.06 (0.95, 1.18) | 1.12 (1.00, 1.25)* | 1.06 (0.94, 1.18) | 1.02 (0.92, 1.13) |
| > Median *vs* < LOD | 1.05 (0.94, 1.17) | 1.01 (0.88, 1.16) | 0.93 (0.77, 1.11) | 0.97 (0.86, 1.10) |
| p-Trend | 0.44 | 0.66 | 0.46 | 0.61 |
| Onset of physical reactivity[b] | | | | |
| 25th percentile | −0.48 (−2.59, 1.63) | −0.15 (−4.27, 3.96) | 0.09 (−4.10, 4.28) | 0.84 (−2.34, 3.17) |
| 50th percentile | −0.43 (−5.12, 4.26) | 0.86 (−6.31, 8.02) | 6.18 (−1.97, 14.34) | 3.22 (−2.34, 8.79) |
| 75th percentile | 0.54 (−26.46, 27.53) | 2.14 (−17.85, 24.13) | 8.41 (−13.94, 30.75) | 4.98 (−15.04, 25.04) |
| Frequency of physical reactivity[a] | | | | |
| Absence | 0.59 (0.27, 1.30) | 0.90 (0.33, 2.46) | 1.07 (0.41, 2.80) | 1.17 (0.52, 2.63) |
| Low frequency, low or high intensity | Reference | Reference | Reference | Reference |
| High frequency, low or high intensity | 0.80 (0.37, 1.75) | 0.93 (0.37, 2.33) | 0.84 (0.32, 2.23) | 0.83 (0.37, 1.84) |

All models were adjusted for: lipid concentrations, video coder, infant's sex and age, maternal age, education, marital status, parity, country of birth, and smoking during pregnancy.

[a] The RR is calculated comparing children with prenatal PBDE concentration ≤/ > LOD for PBDE47, −99, −100, and − 153; and also comparing children with PBDE concentrations ≤ median and > median to children with PBDE concentrations < LOD.

[b] The estimate corresponds to the change in the specific quantile comparing children with prenatal PBDE concentration ≤/ > LOD for PBDE47, −99, −100, and −153.

** $p < 0.05$.

* $p < 0.10$.

7.3, 0.9, 1.0, and 2.4 ng/g lipids. In bivariate analyses, PBDE concentrations differed significantly according to maternal age and country of birth (Supplementary material; Table S1).

### 3.2. Associations between maternal plasma PBDE concentrations and ART

Infants with higher maternal PBDE levels were more likely to manifest frustration through negative vocalizations during the ART (Table 3). For instance, infants born to mothers with detectable plasma PBDE 99 levels were significantly more likely to manifest frustration through negative vocalizations during the ART than infants born to mothers with undetectable levels (aRR = 1.21, 95% CI: 1.05, 1.40). Congeners PBDE 47, 100 and 153 exhibited the same trend with comparable estimates, although not significantly. In regard to the onset of negative vocalizations, the associations appeared to be heterogeneous across different quantiles, and the difference was much smaller in the 25th quantile of the distribution and considerably larger in the upper quantiles of the distribution (75th quantile). For instance, infants born to mothers with detectable plasma PBDE 99 levels had a 38-second (95% CI: −74.6, −1.0) decrease on the 75th quantile of onset of negative vocalizations compared with infants of mothers who had undetectable levels. Other PBDE congeners exhibited the same pattern. We also observed heterogeneous estimates across different quantiles of the proportion of time in negative vocalizations in relation to PBDE concentrations (Table 3). Infants born to mothers with detectable plasma PBDE 100 levels had 23-seconds (95% CI: 3.3, 43.0) increase on the 75th quantile of proportion of time in negative vocalizations compared with infants of mothers who had undetectable levels.

To appreciate the magnitude of these shifts, we illustrated the observed changes in the distributions of onset of negative vocalizations and proportion of time in negative vocalizations between children who had detectable maternal PBDE99 levels and children with undetectable levels (Fig. 2). Fig. 2a shows how exposure to detectable levels of PBDE99 results in a shifting to the left of the right tail of the distribution of onset of negative vocalizations, increasing in particular the probabilities of lower onset of negative vocalizations. Fig. 2b shows the opposite pattern where exposure to detectable levels of PBDE99 results in a shifting to the right of the tail of the distribution of proportion of time in negative vocalizations.

We observed no significant association between PBDEs concentrations and the presence of physical reactivity, onset of physical reactivity, or with the frequency of physical reactivity. However, we observed a significant effect modification by sex ($p < 0.10$) for the presence of physical reactivity for PBDE 47 and PBDE 153 (Table S3). For instance, boys born to mothers with detectable plasma PBDE 47 levels had a 16% higher prevalence of physical reactivity (aRRs = 1.16; 95% CI: 1.00, 1.35) compared with boys born to mothers with undetectable plasma PBDE 47 levels. This association was in the opposite direction in girls (aRR = 0.97, 95% CI: 0.84, 1.11). The same pattern was observed for PBDE 153 (aRR = 1.06 [95% CI: 0.95, 1.18] in boys and 0.91 [95% CI: 0.79, 1.05] in girls). Furthermore, boys and girls exhibited an opposite pattern for the associations between PBDE levels and frequency of physical reactivity for PBDE congeners, although the interaction reached the level of significance only for PBDE 47 and 153 (Table S3).

Girls showed a more extreme response to higher PBDE concentrations as informed by higher odds of having no physical reactivity or having a high frequency of physical reactivity compared to the reference of low frequency of physical reactivity. In contrast, boys showed lower odds of exhibiting one of the extreme responses (Fig. 3a). For instance, girls of mothers with detectable PBDE 47 levels had higher odds of having no physical reactivity in comparison to the reference category of having a low-frequency physical reactivity (aRR = 1.44, 95% CI: 0.45, 4.61), while exposure to detectable maternal PBDE 47 levels was associated with lower odds in boys (aRR: 0.25, 95% CI: 0.08, 0.77). Similarly, boys and girls exhibited opposite patterns for the onset

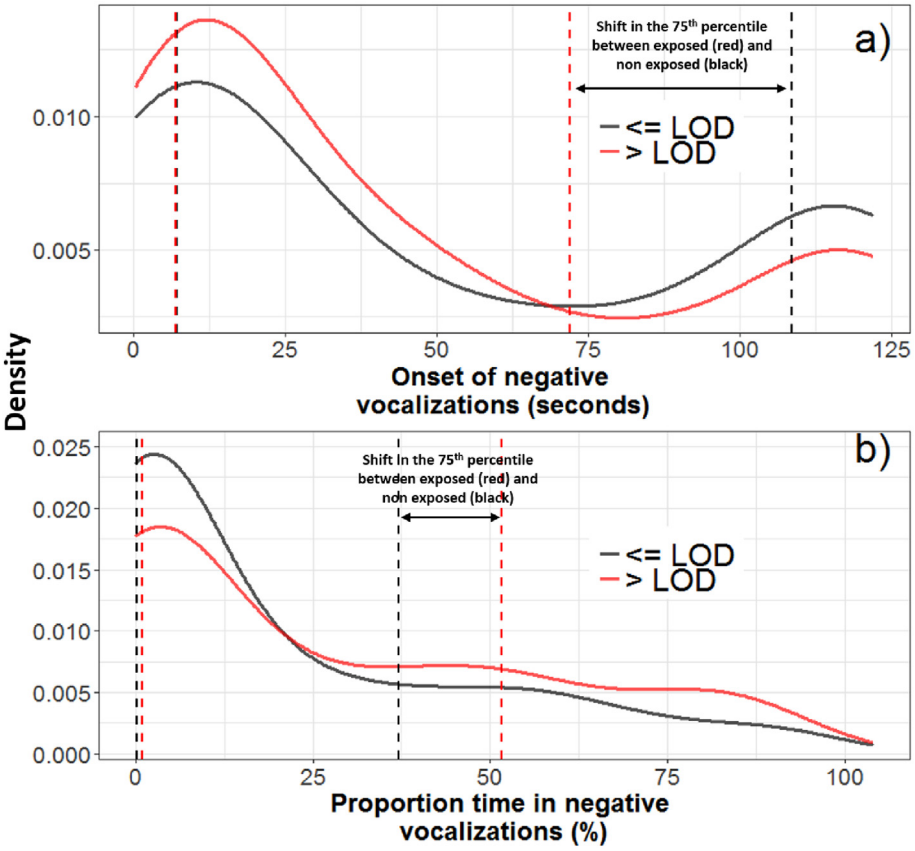


**Fig. 2.** Predicted distribution of the a) onset of negative vocalizations and b) proportion time in negative vocalizations. The black line represents the density plot distribution of ART outcomes for infants of mothers with PBDE 99 ≤ LOD (non-exposed) and the red line represents the distribution for infants of mothers with PBDE 99 > LOD (exposed). The dashed lines show the quantiles 25 and 75 of the distribution of the outcomes for exposed (red) and non-exposed (black) infants. As an illustration, a) shows the shift to the left by ~38 s in the 75th quantile of the distribution of onset of negative vocalizations for between exposed and non-exposed infants. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

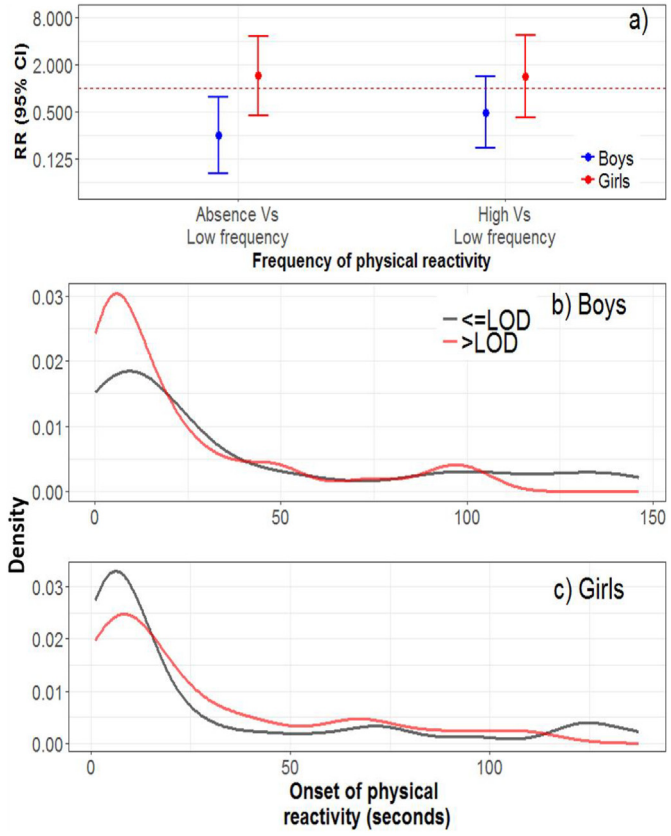


**Fig. 3.** a) Frequency of physical reactivity in relation to exposure to PBDE47 (> LOD *vs* ≤LOD) and predicted distribution of onset of physical reactivity in b) boys and c) girls.

of physical reactivity, and this effect modification was significant for PBDE 47 and 153 at the 25th percentile and for PBDE 153 at the 75th percentile (Fig. 3b and c).

Including maternal blood concentrations of PCB 153, Pb, and Hg in the models did not significantly change the estimates (< 10% change). Similarly, including maternal depression and PACOTIS scores did not change the estimates. Finally, removing 13 infants with birth weights < 2500 g did not appreciably alter the results of the analyses (data not shown for sensitivity analyses).

## 4. Discussion

The aim of this study was to assess the association between *in utero* exposure to PBDEs and predisposition to frustration in infancy, as expressed by vocal and physical manifestations of discomfort during an arm restraint task. Infants in this study who had higher *in utero* PBDE exposure – as measured by maternal plasma PBDE levels – had a higher incidence of crying and screaming during the task eliciting frustration and earlier onset of negative vocalizations. Finally, we observed a pattern of higher proportion of time in negative vocalizations for infants whose mothers had higher PBDE concentrations.

Regarding physical reactivity, we observed sex-specific associations between PBDE levels in maternal plasma and frequency of physical reactivity, with opposite patterns for boys *versus* girls. Interestingly, girls showed a more extreme response to higher PBDE concentrations, with higher odds of having no physical reactivity or having a high frequency of physical reactivity compared to the reference of low frequency; whereas boys showed the opposite pattern, with lower odds of exhibiting one of the extreme responses.

Our results are difficult to compare with other birth cohort studies because none of them tested infants or used similar standardized tasks with older children. Concentrations of PBDE congeners in this subsample were similar to those reported for the whole sample of pregnant

women from the MIREC study (Fisher et al., 2016) and from the Canadian Health Measures Survey (Oulhote et al., 2016). PBDE concentrations were, however, notably lower than those found in earlier studies of pregnant women (Woodruff et al., 2011) and females (CDC, 2014) from the U.S. National Health and Nutrition Examination Survey (NHANES). Finally, PBDE concentrations in this study were also comparable to those reported from the CHAMACOS (Erkin-Cakmak et al., 2015) and the INMA studies in Spain (Lopez-Espinosa et al., 2015), although PBDE-47 concentrations were higher, whereas PBDEs 99 and 153 concentrations were lower in our cohort compared to the INMA cohort.

Experimental animal studies showed global aberrations in spontaneous behavior as well as reduced or a lack of habituation to novel environments in mice exposed to multiple PBDE congeners (Eriksson et al., 2001; Viberg et al., 2006; Buratovic et al., 2014). Altogether, animal studies observed hypo-reactivity in mice that suggests poorer habituation in a novel situation. Our results, especially in regard to the pattern of earlier onset of negative vocalizations and delayed reaction to frustration in terms of physical reactivity, point to similar conclusions, although hypo-reactivity of physical reactivity was apparent only in girls (Fig. 3b). Our results with seven-month-old infants exposed to PBDEs who appeared to have a pattern of later onset of physical reactivity (struggling, squirming or wriggling when arms are constrained by a stranger) could manifest a poorer adaptation to a threatening or stressful situation, suggesting a pattern of hypo-reactivity. A pattern of hypo-reactivity may be associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic branch of the Autonomic Nervous System in children (Chrousos and Gold, 1992; Snoek et al., 2002). Infants display mobilization of the cortisol and salivary alpha amylase in response to the ART (Martinez-Torteya et al., 2017); recent data suggest that PBDEs can disrupt the endocrine and autonomic systems as well as the HPA axis through increased release of adrenal catecholamine and HPA overactivation (Gutierrez et al., 2015). These results, together with findings from animal studies, suggest a new direction of research in the understanding of the mechanisms of action of prenatal PBDEs exposure on children's behavior.

Results from the two components of the ART, *i.e.*, negative vocalizations and physical reactivity, appeared to have different associations with prenatal PBDE exposure. Negative vocalizations and physical reactivity (or avoidance behavior) in infants during a frustrating situation reflect two distinct dimensions, reactivity and regulation, respectively (Rothbart and Derryberry, 1981). Although these differential associations might appear contradictory, since more negative vocalizations may be interpreted as a sign of good adaptation to novelty, reactivity and regulation (especially avoidance behavior) are highly negatively correlated in infancy, and the two factors become more independent over time (Braungart-Rieker and Stifter, 1996). Infants who exhibit high reactivity tend to show low regulation and *vice versa*, suggesting a possible similar underlying response system where an infant may substitute his primarily regulatory behavior by communicative negative vocalizations. Our results, especially those relating to physical reactivity, suggest that prenatal exposure to different PBDE congeners may result in different developmental outcomes. Reasons for these differences could lie in the mechanisms of action of the different PBDE congeners in the organism. Congener-specific differences in metabolism, determined by the structure and bromine substitution of the PBDE congener, may play a role in these differential associations. At least a part of the negative associations between PBDEs and neurodevelopment was attributed to the effects of these chemicals on thyroid hormones during critical phases of development (Costa and Giordano, 2007). Human and animal studies found evidence of disruption of thyroid functions (Chevrier et al., 2010; Hartoft-Nielsen et al., 2011; Vuong et al., 2015) associated with PBDE exposure. Congener-specific differences have also been reported with respect to the potential to disrupt thyroid function. For instance, different PBDE congeners and particularly their hydroxylated metabolites differ in terms of their binding affinity for the thyroid hormone-transport proteins (Meerts et al., 2000).

This is the first study to document the associations between environmental contaminants and observed expressions of frustration using a quasi-experimental stressful situation originally designed to document infancy precursors of later behavior problems. Strengths of our study include its prospective design and sample size (largest to date), and the use of an objective task that does not rely on parental report while providing comparison data with animal studies. Additionally, we were able to adjust for several potentially important confounders, including socioeconomic characteristics of the family and important risk factors for neurodevelopment including several other environmental neurotoxicants. Finally, we were able to document the potential modifying influence of sex, though the real nature of these effects is still unclear. The main limitation of this study pertains to the high proportion of maternal plasma samples with non-detected PBDE levels. This may be due to the higher limits of detection of the analytical methods in the current study compared with other studies that have lower detection limits for PBDEs (4.2, 5, 1.4, and 2.2 ng/g lipids respectively for PBDE47, −99, −100, and −153 in NHANES). It may also be due to lower use of these PBDE congeners in consumer products in Canada. Another important limitation of this study is that the ART has not been fully investigated for its ability to predict later behavioral problems in childhood or adolescence. To our knowledge, sensitivity and specificity of the ART to predict later behavioral difficulties has not been investigated previously. However, a few longitudinal studies reported associations between ART outcomes scores and later behavioral problems including aggressive behavior and poor emotion regulation (Calkins et al., 2002; Crockenberg et al., 2008). Future examination of neuropsychological outcomes of children included in the MIREC cohort will provide further insights on the predictive ability of the ART. We also examined numerous statistical models that increase the possibility of a chance finding; however, our interpretation is based on converging and consistent patterns rather than solely relying on statistical significance. We used quantile regressions for the outcomes that exhibited skewed and non-Gaussian distributions. As our results demonstrate, quantile regressions may provide useful information about the associations at various points of the distribution of the outcome, rather than relying on a single coefficient for the mean, especially when the exposures of interest may exert their effect at the tails of the distribution, or when the effects vary for individuals from different parts of the distribution. Of particular interest, quantile regressions allow for the use of all the information from the outcome distribution in comparison to approaches that rely on outcome categorization, resulting in a substantial loss of information (Beyerlin, 2014).

PBDEs were assessed from the maternal blood concentrations during the first trimester of pregnancy to document prenatal exposure to PBDEs. This parameter appears to be a good indicator, since concentrations found in maternal and cord serum or plasma are moderately to highly correlated ($r$ = 0.55 to 0.99) (Bi et al., 2006; Frederiksen et al., 2010; Fisher et al., 2016), and both can be used to document prenatal exposure. Finally, the lack of data on postnatal exposure to PBDEs during the first months precludes the assessment of the contribution of very early post-natal exposures to these findings.

## 5. Conclusion

This is the first study to show that Infant regulation and reactivity to a frustrating task is associated with gestational exposure to PBDEs. Our results, obtained with an observational assessment of infant behavioral development, add to the current literature by suggesting that associations with observed behaviors are independent of parental report, and can be detected in a low-to-moderate exposure cohort of mostly middle-upper class individuals from the Canadian population. Follow-up of the MIREC cohort at a later age will enable us to determine if reactivity observed during a stressful situation that is associated with *in utero*

PBDE exposure will manifest as behavioral problems into childhood.

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## Conflict of interest statement

The authors declare that there are no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.06.010.

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