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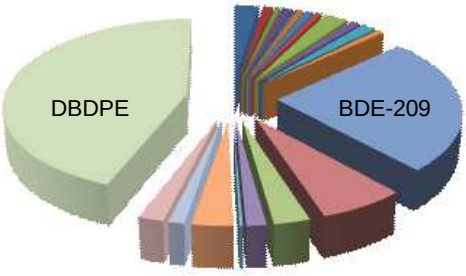
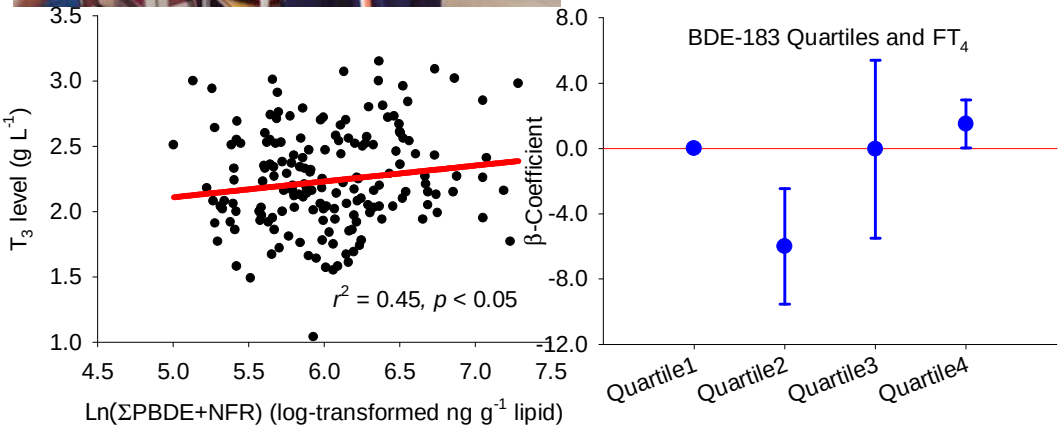


Relative Abundance



Association between serum polybrominated diphenyl ethers, new flame retardants and thyroid hormone levels for school students near a petrochemical complex, South China

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ABSTRACT

As surrogates of polybrominated diphenyl ethers (PBDEs), new flame retardants (NFRs) include a series of chlorinated and brominated flame retardants. Though the NFRs are thought to induce similar thyroid hormone (TH) disrupting effects as PBDEs, few studies have focused on them. Given the increasing levels of NFRs in the environment, more in depth investigation of the potential TH disrupting effects of NFRs is warranted. This research involved a health survey to collect data and examine the associations between PBDEs, NFRs

and TH. 174 school students lived near a petrochemical complex in South China participated in the survey, completing questionnaires and providing blood samples. Thirteen congeners of PBDEs, eight species of NFRs, TH and thyroid-stimulating hormone (TSH) were measured. The median levels of ΣPBDE (sum of thirteen congeners of PBDEs) and ΣNFR (sum of eight species of NFRs) for students were 140 and 240 ng g^{-1} lipid, respectively. Nonmonotonic relationships were observed between quartile levels of PBDEs, NFRs and corresponding TH. In contrast to ΣPBDE that was positively associated with triidothyrine (T_3) level, ΣNFR was not statistically associated with TH. ΣPBDE+NFR (sum of thirteen congeners of PBDEs and eight species of NFRs) was significantly associated with T_3 level.

Keywords: Polybrominated diphenyl ether; New flame retardant; Thyroid hormone

1. Introduction

Added as flame retardants to industrial and household electronic products, polybrominated diphenyl ethers (PBDEs) can leach into the environment during the manufacture, usage and disassembly of electronic products (De Wit, 2002; Eljarrat and Barceló, 2010). Environmental PBDEs can accumulate in organisms through house dust and other exposure pathways (Wang et al., 2013; Agency for Toxic Substances and Disease Registry, 2017). Due to their persistence, bioaccumulation and biotoxicity (McDonald, 2002; Birnbaum and Staskal, 2004), commercial mixtures of PBDEs (including Penta-BDE, Octa-BDE and Deca-BDE) have been gradually phased out in many countries (United Nations Environment Programme, 2009; United States Environmental Protection Agency, 2010; European Chemicals Agency, 2014). New chlorinated and brominated flame retardants have gradually been introduced to replace PBDE usage. For example, 2-ethylhexyl 2,3,4,5-tetrabromobenzoate (TBB) and Bis(2-ethylhexyl)-tetrabromophthalate (TBPH), 1,2-bis(trbromophenoxy)-ethane (BTBPE), 1,2-bis(2,3,4,5,6-pentabromophenyl)ethane (DBDPE) have been used to replace Penta-BDE, Octa-BDE and Deca-BDE, respectively (Arias, 2001; Covaci et al., 2011; Egebäck et al., 2012; Ma et al., 2012). Following the reduction in usage of PBDEs, the levels of new flame retardants (NFRs) in the environment have gradually increased in recent years (Zhu et al., 2007; Covaci et al., 2011; Liu et al., 2014; Zhang et al., 2015; Kuang et al., 2016; Li et al., 2016a; Li et al., 2016b). NFRs can also accumulate in organisms and have been widely detected in human serum and milk (Ren et al., 2009; Covaci et al., 2011; He et al., 2013; Brasseur et al., 2014; Zhou et al., 2014).

Due to their similar structure to thyroid hormone (TH), PBDEs can disrupt the homeostasis of TH. Significant associations between triidothyrine (T_3), thyroxine (T_4), thyroid-stimulating hormone (TSH) and PBDEs had been discovered in humans (Zota et al., 2011; Chao et al., 2014; Huang et al., 2014). These results suggest that PBDEs may negatively impact the

growth and development of the human body through their TH disrupting effects. Possessing similar molecule structures as PBDEs, NFRs may also exhibit TH disrupting effects and do harm to human health (Ezechiáš et al., 2012; Kim and Oh, 2014). However, since current levels of NFRs in human serum have been measured to be much lower than those of PBDEs (Brasseur et al., 2014; Rawn et al., 2014; Wang et al., 2014; Cequier et al., 2015), the TH disrupting effects of NFRs have rarely been examined. Though some NFRs are thought to have weaker TH disrupting effects than PBDEs (Colnot et al., 2014; Guyot et al., 2014), reliable conclusions cannot be drawn from the limited number of studies examining this topic to date. Given the increase in NFR levels in the environment (Covaci et al., 2011; Liu et al., 2014; Kuang et al., 2016; Li et al., 2016a), whether NFRs exposure can aggravate or abate the TH disrupting effects were largely known. Identifying the body burden of NFRs and their corresponding TH disrupting effects warrants further investigation.

Petrochemical industry was considered an important emission source of flame retardants (Reddy et al., 2002; Teuten et al., 2005), and large amounts of PBDEs continue to be released to the surrounding environment (Moon et al., 2007; Baek et al., 2008; Pan et al., 2011; Kim et al., 2012; Odabasi et al., 2015). In particular, NFRs levels were found to increase gradually in the environment near a huge petrochemical complex in South China (Shi et al., 2009; Zhang et al., 2009; Liu et al., 2014). As a result, the residents surrounding this petrochemical complex may be exposed to high levels of NFRs and PBDEs. School students (aged ten) were chosen as the target population as this age represents a time of rapid physical growth; and even marginal changes in TH levels may affect their normal growth (Kiciński et al., 2012; Jacobson et al., 2016).

To bridge the knowledge gap on above mentioned issues, students living near the above mentioned petrochemical complex in South China were chosen. A health survey, including questionnaires and blood sample collection, was conducted. The collected serums were

analyzed for thirteen congeners of PBDEs, eight species of NFRs, TH (including T_3, T_4, Free T_3, Free T_4) and TSH. The main objectives of the present study were to examine the potential TH disrupting effects of NFRs, and compare them with those of PBDEs. The results from the present study are expected to enhance the knowledge on TH homeostasis influenced by flame retardants and contribute to the evidence base to argue for improved management of the exposure to these chemicals and in the long term protect the health of children.

2. Materials and methods

2.1. Sample collection

174 Grade five students (average age, 10) were recruited from two schools near a petrochemical complex in South China. The survey was conducted from September 14 to 18, 2015. The questionnaires included questions relating to the student's age, sex, dwelling characteristics (passive smoking and self-reported air quality) and self reported incidence of respiratory illness in the past 12 months, as the literature indicates that these parameters may also influence TH levels in human serum (Gregerman and Solomon, 1967; Hashimoto et al., 1994; Brzezińska-Slebodzińska, 2001; Chevrier et al., 2010; De Cock et al., 2014; Allen et al., 2016) . Blood samples were collected from students at school by medical professionals; body height and weight were measured at the same time. Details about the questionnaires and sample collection are described in Supplemental Material. The sample collection process and questionnaire were approved by the Ethics and Human Subject Committee of Guangdong Provincial Center for Disease Control and Prevention.

2.2. Laboratory analysis

The serum PBDEs and NFRs were extracted by solid phase extraction, then determined with a gas chromatograph coupled with a mass spectrometer. Name, molecular formula,

character ions and reporting limits of PBDEs and NFRs are shown in Table S1. Serum T_3, T_4, Free T_3 (FT_3), Free T_4 (FT_4) and TSH were quantified by chemiluminescent immunoassay. Serum triglycerides and total cholesterol were analyzed by enzymatic measurements. Details about sample extraction, instrumental analysis, quality control and quality assurance are described in Supplemental Material.

2.3. Data analysis

The BMI index was calculated as weight divided by the body height squared. The serum lipid of each sample was calculated as follows (Thuresson et al., 2005):

$$\text{Total lipid} = (\text{Total cholesterol} + \text{Triglycerides}) \times 1.28 + 0.96 \quad (1)$$

The units of serum lipid were converted from molar concentration (mmol L^{-1}) to mass concentration (g L^{-1}).

The sum of 13 congeners of PBDE including BDE-28, -47, -85, -99, -100, -153, -154, -183, -196, -204, -206, -207 and -209 is labeled as ΣPBDE. The sum of 13 congeners of PBDE listed above excluding BDE-209 is labeled as Σ_{12}PBDE. This variable was derived in order to observe TH disrupting effects of PBDEs without BDE-209, which has the highest relevant abundance in environmental media in China (Eljarrat and Barceló, 2010). The sum of 8 species of NFR, including Tetrabromoethylcyclohexane (TBECH), Hexachlorocyclopentadienyldibromocyclooctane (HCDBCO), TBB, BTBPE, TBPH, DBDPE, Dechlorane Plus Syn (DPs) and Dechlorane Plus Anti (DPa) is labeled as ΣNFR. The sum of ΣPBDE and ΣNFR is labeled as ΣPBDE+NFR.

Bivariate analyses including Pearson's correlation coefficient (*r*), independent *t*-tests and paired *t*-tests were first conducted. Multiple linear regression analysis was then conducted to model relationships between the levels of PBDEs, NFRs and TH, with PBDEs and NFRs levels as independent variables and TH and TSH levels as dependent variables. Details of multiple

linear regression analysis are described in Supplemental Material. A dose-response model was calculated by linear regression for each individual component and TH using quartile concentrations, with quartile 1 as the reference group. Linear trends in the dose-response model were assessed by using the median value in each quartile as a continuous variable in the linear regression models.

In all statistical analyses, the criterion of significance was defined as $p < 0.05$. R software 3.2.0 (R Development Core Team, Vienna, Austria) was used for statistic analysis.

3. Results

3.1. Characteristics of study population

The characteristics of participating students are summarized in Table S2. The median value of BMI index was 16 (ranging from 12 to 32). The median levels for T_3, T_4, FT_3, FT_4 and TSH were 2.2 nmol L^{-1}, 124 nmol L^{-1}, 6.4 pmol L^{-1}, 16 pmol L^{-1} and 1.8 mIU L^{-1} (Table 1). No statistically significant difference was observed for BMI, TH, TSH and serum lipid between students from the two schools ($p > 0.05$, by independent *t*-test).

3.2. Occurrence of PBDEs and NFRs levels

Median and quartile levels of PBDEs and NFRs are provided in Table 1 and Table S3, respectively. The level of ΣPBDE (median: 140 ng g^{-1} lipid) was significantly lower than ΣNFR (median: 240 ng g^{-1} lipid) ($p < 0.05$ by paired *t*-test). The median level of ΣPBDE+NFR was 380 ng g^{-1} lipid, where ΣNFR accounted for 63% of the total. The top five most concentrated components in ΣPBDE+NFR were DBDPE (47%), BDE-209 (25%), TBECH (8.0%), HCDBCO (2.8%) and BDE-28 (2.7%) (Figure S1). In particular, three types of alternative NFRs (i.e., TBB+TBPH, BTBPE and DBDPE) were positively correlated with corresponding PBDEs (i.e., Penta-BDE (sum of BDE-47, -85, -99, -153 and -154), Octa-BDE

(sum of BDE-183, -196 and -204) and Deca-BDE (BDE-209)), respectively (Figure S2), suggesting they accumulated in human serum simultaneously. The fractions of [TBB+TBPH] / [TBB+TBPH+Penta-BDE], BTBPE / [BTBPE+Octa-BDE] and DBDPE / [DBDPE+Deca-BDE], representing the relative contributions of legacy and alternative brominated flame retardants, were 0.41 ± 0.16, 0.12 ± 0.12 and 0.64 ± 0.15, respectively. No statistically significant difference ($p > 0.05$, independent *t*-test) was observed for serum ΣPBDE, ΣNFR and ΣPBDE+NFR between students of two schools.

3.3. Relationships between PBDEs, NFRs, TH and TSH

The results of multiple linear regression models are shown in Table 2. Significant negative associations were observed between components of PBDEs, NFRs and TH, e.g., BDE-47, BDE-100, BDE-99, HCDBCO, TBB, BDE-183, TBPH, BDE-204 and FT_4; BDE-47, HCDBCO, BDE-183 and T_4; HCDBCO and T_3; HCDBCO and TSH. Significant positive associations were observed between BDE-209 and T_3. Significant positive associations between ΣPBDE, ΣPBDE+NFR and T_3, and a significant negative association between Σ_{12}PBDE and FT_4 were observed. However, no significant association was observed between ΣNFR and TH.

Dose-response models for quartile levels of PBDEs and NFRs are shown in Table S4. Significant linear trends occurred for some associations between quartile levels of PBDEs, NFRs and TH, TSH, e.g., a significantly negative association between BDE-183 and FT_4 in Quartile 2 and Quartile 4 (Table S4). However, β-coefficients from Quartile 1 to Quartile 4 did not increase in a monotonic manner, suggesting nonmonotonic relationships between levels of PBDEs, NFRs and corresponding TH, TSH levels, e.g., the quartile levels of BDE-183 and FT_4 appeared as an adverse N-shape (Figure S3 and Graphical Abstract).

4. Discussion

4.1. Magnitude of measured PBDEs and NFRs levels

The concentration of ΣPBDE (median: 140 ng g^{-1} lipid) in the present study was greater than levels of the general population in Asia, Europe and North America identified elsewhere (Table S5), e.g., adults in Shantou, China (5.2 and 10 ng g^{-1} lipid in two studies, respectively) (Qu et al., 2007; Wu et al., 2010), pregnant women in Denmark (7.7 ng g^{-1} lipid) (Vorkamp et al., 2014), and children, adults and older people in California (112, 39 and 46 ng g^{-1} lipid, respectively) (Wu et al., 2015). In contrast, the level of ΣPBDE in the present study was lower than levels measured in adults in an e-waste dismantling region in Shantou, China (190 ng g^{-1} lipid) (Xu et al., 2014) and a flame retardant manufacturing region in Laizhou Bay, China (240 ng g^{-1} lipid) (Wang et al., 2014). Thus, with the exception of occupationally exposed populations, the concentration of ΣPBDE in this study was greater than reports from most previous studies (Table S5). The high level of ΣPBDE in students may possibly associate with the petrochemical complex nearby, which can emit large amount of PBDEs to the surrounding environment (Moon et al., 2007; Kim et al., 2012; Liu et al., 2014).

The concentration of ΣDP (sum of DPs and DPa) (12 ng g^{-1} lipid) in this study was greater than levels of the general population in most previous studies (Table S5), e.g., adults in France (1.1 ng g^{-1} lipid) (Brasseur et al., 2014), Norway (1.3 ng g^{-1} lipid) (Cequier et al., 2015), Germany (2.0 ng g^{-1} lipid) (Fromme et al., 2015) and Laizhou Bay (3.6 ng g^{-1} lipid) (Wang et al., 2014). In contrast, the level of ΣDP in this study was lower than measures in adults in an e-waste dismantling region in Shantou, China (38 ng g^{-1} lipid) (Ren et al., 2009). The concentration of BTBPE (0.83 ng g^{-1} lipid) in this study was greater than level reported in Norway (0.19 ng g^{-1} lipid) (Cequier et al., 2015). The concentration of TBB (5.6 ng g^{-1} lipid) in this study was greater than level reported in Canada (1.6 ng g^{-1} lipid) (Zhou et al., 2014). On the other hand, the average ΣNFR in this study (240 ng g^{-1} lipid) was far higher than some

of other reported measurements (Table S5), e.g., 1.5 ng g^{-1} lipid in adults in Norway and 1.6 ng g^{-1} lipid levels in women in Canada (Zhou et al., 2014; Cequier et al., 2015). This may possibly be due to the high levels of DBDPE measured in this study (180 ng g^{-1} lipid), which were not detected in these previous studies. The high level of DBDPE in serum of students was in accordance with high levels of DBDPE in surrounding environment, e.g., air and sediments (Shi et al., 2009; Zhang et al., 2009; Liu et al., 2014). All of these indicated NFRs in students of the study region were higher than those reported in general populations in previous studies.

The relative abundance of ΣNFR (ΣNFR / ΣPBDE+NFR = 63%) was more than those of ΣPBDE (ΣPBDE / ΣPBDE+NFR = 37%); an opposite finding to previous studies (Ren et al., 2009; Brasseur et al., 2014; Wang et al., 2014; Cequier et al., 2015). The high relative abundance of NFRs in students indicated the increased exposure of NFRs in the petrochemical surrounding area.

4.2. PBDEs, NFRs and TH disrupting effects

Though disrupting effects of PBDEs on TH in this study (Table 2) were similar to some previous findings (Huang et al., 2014; Vuong et al., 2015; Makey et al., 2016), they were different from most of other reports. For example, positively association between T_4, FT_4 and PBDEs (Stapleton et al., 2011; Kim et al., 2013; Vuong et al., 2015); positively or negatively association between FT_3, TSH and PBDEs (Chevrier et al., 2010; Zota et al., 2011; Kiciński et al., 2012; Kim et al., 2013; Xu et al., 2014; Vuong et al., 2015; Jacobson et al., 2016); and no significant associations occurred (Kim et al., 2011; Xu et al., 2015).

There may be several reasons for these discrepancies. The most important reason is the nonmonotonic relationships between levels of PBDEs and TH in this study (Table S4) and many previous reports (Chevrier et al., 2010; Vuong et al., 2015; Jacobson et al., 2016). In

this study, some β-coefficients were different among quartiles (Table S4), and even appeared as an adverse N-shape, e.g., association between quartile levels of BDE-183 and FT_4 (Figure S3). These nonmonotonic relationships may relate to complex influences of PBDEs, i.e., PBDEs may disrupt transport, metabolism and function of TH (Eljarrat and Barceló, 2010). The first possible mechanism is the competitive binding of PBDEs and their metabolites with thyroxine transport proteins (including thyroxinebinding globulin and transthyretin), which can directly affect the levels of FT_3 and FT_4 in serum (Meerts et al., 2000; Hamers et al., 2006; Marchesini et al., 2008; Cao et al., 2010). Another mechanism is that PBDEs may deactivate the iodothyronine deiodinases (IDs: including three types, IDI, IDII and IDIII), and finally affect the metabolism and production of TH (Gereben et al., 2008; Butt et al., 2011; Roberts et al., 2015). The third mechanism is the direct binding of PBDEs to TH receptors (including thyroid hormone receptor α and β), which may not only affect the function of TH, but also change the levels of TH (Kitamura et al., 2008; Cai et al., 2011). These complex mechanisms may disturb the equilibrium of TH in serum simultaneously and lead to nonmonotonic relationships. Detailed disrupting mechanisms remain largely unknown and need to be better characterized in future studies.

Based on the nonmonotonic relationships, different levels of PBDEs among the studies may cause various TH disrupting effects. For example, the BDE-47 level in this study (4.4 (0.98–22) ng g^{-1} lipid) was much lower than those reported in Cincinnati (19 (1.5–1290) ng g^{-1} lipid), North Carolina (19 (nd–114) ng g^{-1} lipid) in North America (Stapleton et al., 2011; Vuong et al., 2015), which may possibly due to the nonmonotonic relationship between BDE-47 and FT_4 (Table S4) and low BDE-47 levels.

Another reason for discrepancies among various studies was differing populations studied. Most previous studies focused on pregnant women and adults (Stapleton et al., 2011; Zota et al., 2011; Kim et al., 2013,2015; Vuong et al., 2015), with only one of them involving children

(Jacobson et al., 2016). During the gestation period, the TH levels are increased while TSH level is decreased, making pregnant women different from others (Brent, 2012). Moreover, TH and TSH levels of children are different from those of adults, e.g., for Chinese people, T_3, T_4 and TSH levels are greater in children than in adults (Lin et al., 2013).

In this study, the TH disrupting effects of NFRs were not the same as those of PBDEs, i.e., NFRs compounds were only associated with T_4 and FT_4, while PBDEs compounds were also associated with T_3 (Table 2); HCDBCO were statistically significantly negatively associated with TSH levels, while PBDEs congeners were not.

Though DBDPE was most abundant component (47%) (Table 1 and Figure S1), it did not associate with TH and TSH. However, DBDPE has been reported as being positively associated with T_3 levels in rats (orally administrated 100 mg/kg/day of DBDPE in corn oil for 90 days) (Wang et al., 2010). Thus, exposure to high level of DBDPE may adversely affect TH in human. Since the TH disrupting effect of DBDPE in humans has rarely been studied, this should be further investigated.

The TH disrupting effects were not identical among ΣPBDE, Σ_{12}PBDE, ΣNFR and ΣPBDE+NFR (Table 2). Both ΣPBDE and ΣPBDE+NFR were positively associated with T_3, which was associated with the strong influence of BDE-209, i.e., BDE-209 was the only component that was associated with T_3 (β-coefficient 0.079), and was a relatively large contributor (66% in ΣPBDE and 25% in ΣPBDE+NFR). In contrast, ΣPBDE and ΣPBDE+NFR were not associated with other TH and TSH, possibly because other TH disrupting components had much lower relative abundance than that of BDE-209, e.g., though eight components were negatively associated with FT_4 (Table 2), their sum relative abundance in ΣPBDE+NFR (11%) was much lower than those of BDE-209 (25%). Different from ΣPBDE, Σ_{12}PBDE was negatively associated with FT_4. This may possibly because without BDE-209, the relative abundance of other components that are negatively associated with FT_4

contributed a high proportion (25%) in Σ_{12}PBDE. No TH disrupting effects were observed for ΣNFR levels, possibly because the TH disrupting components had low relative abundance in ΣNFR, e.g., 2.8%, 1.5% and 1.7% for HCDBCO, TBB and TBPH, respectively. Thus, ΣNFR showed weaker TH disrupting effects comparing to ΣPBDE, Σ_{12}PBDE and ΣPBDE+NFR. It can thus be inferred that the overall TH disrupting effects of ΣPBDE+NFR may be reduced in years to come as the serum concentration PBDEs are expected to decrease after the discontinuation of PBDEs in new products. Though these findings confirm a more positive health outcome for the use of NFRs, more work is needed to clarify whether these results are applicable to other populations.

The strength of this study is the analysis of eight components of NFRs; the TH disrupting effects of which have seldom been examined. Also, the participates had similar age and living conditions, reducing the risk of confounding. However, our findings were subject to some limitations. First, the results of this study reflected the TH disrupting effect of 10 year old children near a petrochemical complex in South China and hence the generalizability of these results to other populations, e.g., e-waste dismantling worker and general population, is questionable. Additional study, which aims at other groups of persons, was needed. Second, we were unable to determine the hydroxylated-PBDEs (OH-PBDEs), which were highly correlated with their parent congers and also have strong associations with TH (Marchesini et al., 2008; Stapleton et al., 2009). Also, β-coefficients in regression were not the perfect choice to evaluate the importance of associations between PBDEs, NFRs and THs. More effective statistics method were needed to perform comparisons among associations and revel potential mechanisms. Future studies should attempt to overcome these limitations in order to build a more comprehensive picture of populations at risk to these existing and emerging groups of chemicals.

5. Conclusion

The serum levels for PBDEs and NFRs identified in our population of students aged 10 were greater than most of the general population in previous reports, and a greater relative abundance was identified for NFRs than for PBDEs. Nonmonotonic relationships were observed between PBDEs, NFRs, TH and TSH. Due to the dominant component BDE-209, the ΣPBDE+NFR level in serum was positively associated with T_3 levels. Based on the weaker TH disrupting effect of ΣNFR, the current TH disrupting effects of ΣPBDE+NFR may be weakened in years to come as the serum concentration of PBDEs is expected to decrease after production of PBDEs ended. These findings help build our understanding of the mechanism of TH disrupting of PBDEs and NFRs, and confirm that policy decisions to reduce PBDEs and replace them with NFRs reduce the risk of harm to exposed populations.

Acknowledgements

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Table 1 Serum levels of PBDEs, NFRs, lipid, thyroid hormone, thyroid-stimulating hormone and BMI index in school students.

	Median	Mean ± SD	Range	Frequency of Detection
PBDEs and NFRs (ng g^{-1} lipid)				
BDE-28	9.9	11 ± 6.1	3.7–40	100%
BDE-47	4.4	5.0 ± 2.8	0.98–22	100%
BDE-85	0.77	1.1 ± 1.5	nd–18	80%
BDE-99	4.5	5.7 ± 4.5	nd–29	98%
BDE-100	1.8	2.6 ± 2.5	nd–21	97%
BDE-153	2.9	3.7 ± 2.7	0.62–25	100%
BDE-154	2.4	2.7 ± 1.7	0.98–15	100%
BDE-183	2.4	3.1 ± 3.1	nd–23	93%
BDE-196	2.6	4.5 ± 5.8	nd–49	89%
BDE-204	4.6	9.6 ± 15	nd–84	61%
BDE-206	2.2	3.6 ± 3.9	nd–24	86%
BDE-207	2.1	6.1 ± 32	nd–400	78%
BDE-209	95	120 ± 100	nd–760	98%
TBECH	30	34 ± 16	1.0–110	100%
HCDBCO	10	14 ± 12	nd–67	95%
TBB	5.6	7.5 ± 7.1	nd–46	97%
BTBPE	0.83	1.3 ± 1.8	nd–14	70%
TBPH	6.6	11 ± 13	nd–78	83%
DPs	4.9	5.8 ± 4.6	nd–40	95%
DPa	7.4	8.7 ± 6.9	1.2–74	100%
DPDBE	180	210 ± 140	nd–690	99%
Σ_{12}PBDE[a]	41	59 ± 120	41–790	-
ΣPBDE[b]	140	180 ± 48	14–460	-
ΣNFR[c]	240	290 ± 150	88–940	-
ΣPBDE+NFR[d]	380	470 ± 240	150–1460	-
Lipid (g L^{-1})				
Total lipid	1.6	1.6 ± 0.27	1.1–2.4	100%
Total cholesterol	0.49	0.55 ± 0.23	0.19–1.6	100%

Triglycerides	3.7	3.7 ± 0.64	0.96–5.3	100%
Thyroid hormone (nmol L^{-1} for T_3 and T_4, pmol L^{-1} for FT_3 and FT_4) and Thyroid-stimulating hormone (mIU L^{-1})				
T_3[e]	2.2	2.2 ± 0.41	0.72–3.2	100%
T_4[f]	120	120 ± 20	18–160	100%
FT_3[g]	6.4	6.4 ± 0.54	4.5–7.7	100%
FT_4[h]	16	16 ± 1.7	11–22	100%
TSH[i]	1.8	1.9 ± 0.81	0.44–5.4	100%
BMI index	16	17 ± 3.6	12–32	-

[a]Sum of 12 congeners of PBDEs, including BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-196, BDE-204, BDE-206 and BDE-207. [b]Sum of 13 congeners of PBDEs, including BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-196, BDE-204, BDE-206, BDE-207 and BDE-209. [c]Sum of 8 species of NFRs, including TBECH, HCDBCO, TBB, BTBPE, TBPH, DPs, DPa and DBDPE. [d]Sum of 13 congeners of PBDEs and 8 species of NFRs listed above. [e]T_3 refers to triiodothyronine. [f]T_4 refers to thyroxine. [g]FT_3 refers to free triiodothyronine. [h]FT_4 refers to free thyroxine. [i]TSH refers to thyroid-stimulating hormone.

Table 2 Regression coefficients (β) for associations between serum PBDEs and NFRs concentrations and thyroid hormone (T_3, T_4, FT_3, FT_4) and thyroid-stimulating hormone (TSH) concentrations.

	T_3		T_4		FT_3		FT_4		TSH	
	β^a	95% CI	β^a	95% CI	β^a	95% CI	β^a	95% CI	β^a	95% CI
BDE-28	-0.018	(-0.16, 0.13)	-4.3	(-11, 2.8)	0.13	(-0.050, 0.32)	-0.063	(-0.66, 0.53)	-0.16	(-0.46, 0.14)
BDE-47	-0.067	(-0.20, 0.067)	**-8.1**	**(-15, -1.6)***	0.058	(-0.11, 0.23)	**-0.82**	**(-1.4, -0.28)***	-0.18	(-0.45, 0.10)
BDE-85	-0.0050	(-0.078, 0.067)	-1.9	(-5.5, 1.7)	-0.056	(-0.15, 0.036)	-0.27	(-0.57, 0.028)	0.019	(-0.13, 0.17)
BDE-99	-0.018	(-0.11, 0.074)	-3.4	(-7.9, 1.1)	-0.013	(-0.13, 0.11)	**-0.54**	**(-0.91, -0.16)***	-0.035	(-0.23, 0.16)
BDE-100	0.013	(-0.079, 0.11)	-3.8	(-8.3, 0.69)	-0.041	(-0.16, 0.077)	**-0.67**	**(-1.0, -0.31)***	-0.020	(-0.21, 0.17)
BDE-153	-0.049	(-0.16, 0.063)	-1.3	(-6.9, 4.3)	0.0050	(-0.14, 0.15)	-0.29	(-0.76, 0.18)	-0.068	(-0.30, 0.17)
BDE-154	0.031	(-0.12, 0.18)	-6.3	(-14, 1.2)	0.0060	(-0.19, 0.20)	-0.44	(-1.1, 0.19)	0.049	(-0.27, 0.37)
BDE-183	0.002	(-0.079, 0.084)	**-4.4**	**(-8.4, -0.42)***	0.016	(-0.088, 0.12)	**-0.40**	**(-0.73, -0.069)***	-0.081	(-0.25, 0.088)
BDE-196	0.010	(-0.039, 0.059)	-1.6	(-4.0, 0.8)	0.012	(-0.051, 0.075)	-0.13	(-0.34, 0.071)	-0.024	(-0.13, 0.078)
BDE-204	-0.019	(-0.061, 0.023)	-1.8	(-3.9, 0.24)	-0.045	(-0.098, 0.0090)	**-0.22**	**(-0.39, -0.048)***	-0.0080	(-0.096, 0.080)
BDE-206	0.011	(-0.046, 0.068)	-0.54	(-3.4, 2.3)	-0.032	(-0.10, 0.041)	-0.17	(-0.41, 0.062)	0.041	(-0.077, 0.16)
BDE-207	-0.011	(-0.059, 0.038)	-1.9	(-4.3, 0.55)	-0.015	(-0.076, 0.046)	-0.18	(-0.39, 0.021)	0.068	(-0.029, 0.17)
BDE-209	**0.080**	**(0.011, 0.15)***	1.4	(-2.0, 4.9)	0.038	(-0.051, 0.13)	0.0030	(-0.29, 0.29)	0.024	(-0.12, 0.17)

TBECH	-0.094	(-0.23, 0.038)	-4.2	(-11, 2.4)	0.094	(-0.076, 0.26)	0.14	(-0.41, 0.69)	-0.14	(-0.41, 0.14)
HCDBCO	**-0.064**	**(-0.12, -0.0040)***	**-3.7**	**(-6.6, -0.7)***	-0.075	(-0.15, 0.0020)	**-0.31**	**(-0.56, -0.062)***	**-0.13**	**(-0.26, -0.0070)***
TBB	-0.028	(-0.11, 0.053)	-2.5	(-6.4, 1.5)	0.018	(-0.085, 0.12)	**-0.48**	**(-0.80, -0.15)***	0.15	(-0.016, 0.31)
BTBPE	-0.013	(-0.075, 0.049)	-0.3	(-3.4, 2.8)	-0.038	(-0.12, 0.041)	-0.2	(-0.46, 0.056)	0.12	(-0.012, 0.24)
TBPH	0.026	(-0.023, 0.076)	-0.37	(-2.8, 2.1)	0.002	(-0.061, 0.065)	**-0.21**	**(-0.42, -0.009)***	-0.067	(-0.17, 0.034)
DPs	-0.043	(-0.12, 0.033)	-0.77	(-4.6, 3.0)	-0.096	(-0.19, 0.0020)	-0.11	(-0.43, 0.21)	0.030	(-0.13, 0.19)
DPa	0.021	(-0.086, 0.13)	-1.8	(-7.1, 3.5)	-0.058	(-0.19, 0.079)	-0.39	(-0.83, 0.052)	-0.025	(-0.25, 0.20)
DPDBE	0.038	(-0.061, 0.14)	-1.6	(-6.4, 3.3)	0.013	(-0.11, 0.14)	0.13	(-0.28, 0.54)	-0.11	(-0.31, 0.096)
ΣPBDE[b]	**0.13**	**(0.029, 0.24)***	-0.18	(-5.5, 5.2)	0.083	(-0.055, 0.22)	-0.15	(-0.59, 0.30)	0.046	(-0.17, 0.26)
Σ_{12}PBDE[c]	0.01	(-0.098, 0.12)	-4.4	(-9.9, 1.1)	0.019	(-0.12, 0.16)	**-0.66**	**(-1.1, -0.21)***	-0.048	(-0.27, 0.18)
ΣNFR[d]	0.049	(-0.077, 0.18)	-3	(-9.2, 3.3)	0.028	(-0.14, 0.19)	0.001	(-0.52, 0.53)	-0.085	(-0.34, 0.17)
ΣPBDE+NFR[e]	**0.13**	**(0.0010, 0.25)***	-1.8	(-8.3, 4.7)	0.089	(-0.078, 0.26)	-0.042	(-0.58, 0.50)	-0.024	(-0.29, 0.24)

[a]Adjusted for BMI, sex, lung function, secondhand smoke and personal symptoms (running nose, sore throat, fever, headache, night cough, loose cough, asthma, chest tightness, dyspnea). [b]Sum of 12 congeners of PBDEs, including BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-196, BDE-204, BDE-206 and BDE-207. [c]Sum of 13 congeners of PBDEs, including BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-196, BDE-204, BDE-206, BDE-207 and BDE-209. [d]Sum of 8 species of NFRs, including TBECH, HCDBCO, TBB, BTBPE, TBPH, DPs, DPa and DBDPE. [e]Sum of 13 congeners of PBDEs and 8 species of NFRs listed above. * Significant at the 0.05 level.

Greater levels occurred for ΣNFR than for ΣPBDE in the serum of study students.

Nonmonotonic relationships occurred between quartile levels of PBDEs, NFRs and TH.

Influenced by BDE-209, ΣPBDE and ΣPBDE+NFR were positively associated with T_3.