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Disruption of thyroid hormone levels by decabrominated diphenyl ethers (BDE-209) in occupational workers from a deca-BDE manufacturing plant

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ABSTRACT

While there is some evidence that exposure to decabrominated diphenyl ethers (BDE-209) affects thyroid function, the results obtained to date have been inconsistent. No studies have been performed on workers in deca-BDE manufacturing who had a high level of exposure to BDE-209 and relatively little exposure to other contaminants. In the present study, the relationship between BDE-209 exposure and thyroid hormone in occupational workers from a deca-BDE manufacturing plant was investigated. The serum and urine levels of polybrominated diphenyl ethers (PBDEs) and serum thyroid hormones were measured in 72 workers recruited from the deca-BDE manufacturing plant. The associations between their thyroid hormone levels and their exposure to BDE-209 were examined using multiple linear regression models. Serum concentrations of BDE-209 ranged from 67.4 to 109,000 ng/g lipid weight (lw), with a median of 3420 ng/g lw, contributing to 93.1% of the total PBDEs. The concentration of BDE-209 in urine was highly correlated with that in the serum ($r^2 = 0.440$, $p < 0.001$), indicating that urine may be a good non-invasive biomonitoring medium of BDE-209 body burden in occupational workers. BDE-209 in the serum was significantly and positively correlated with total thyroxine (tT4, $r = 0.270$, $p = 0.029$) and marginally and positively correlated with total triiodothyronine (tT3, $r = 0.232$, $p = 0.061$) in all occupational workers after adjusting for gender, age, BMI, and occupational exposure duration. A 10-fold increase in the serum BDE-209 concentration was associated with an increase in tT4 (8.63 nmol/L) [95% confidence interval (CI): 0.930–16.3] and tT3 (0.106 nmol/L) [95% confidence interval (CI): −0.005-0.219], corresponding to the increase of 7.8% in tT4 level and 5.4% in tT3 level. Associations between urine BDE-209 levels and thyroid hormones were similar to the results for the serum levels. These findings offer new evidence for proving the thyroid disrupting effects of BDE-209, impacting the direction of hyperthyroidism.

1. Introduction

Brominated flame retardants (BFRs) are a large group of chemicals that have been commonly used as fire-retardants in a variety of products (electronic devices, foams and padding materials, textiles etc.). Polybrominated diphenyl ethers (PBDEs) have been used as BFRs since the 1970s. There are three types of commercial PBDEs: penta-BDE, octa-BDE and deca-BDE. Commercial penta-BDE and octa-BDE have been phased out after they were listed as persistent organic pollutants (POPs) under the Stockholm Convention in 2009 (http://chm.pops.int/TheConvention/ThePOPs). However, commercial deca-BDE mixtures, which are mainly composed of decabrominated diphenyl ethers (BDE-209), are still produced and consumed in China and many other developing countries in Asia (Ji et al., 2017; Yu et al., 2016), even though it has been added to the list of POPs in 2017 (http://chm.pops.int/TheConvention/ThePOPs).

Deca-BDE is normally used as an additive flame retardant in electronic products and can therefore leach or volatilize from products and

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enter the surrounding microenvironments. China is the largest producer and consumer of deca-BDE in the world (Ji et al., 2017). Moreover, there are a considerable number of electronic waste (e-waste) recycling regions in southern and southeastern China. Therefore, numerous investigations throughout various different environmental matrices have shown that BDE-209 has become the dominant BDE congener in most areas of China and even accounts for > 75% of the total PBDEs in human serum in northern China (Huang et al., 2014; Ji et al., 2017; Zhu et al., 2015).

In the past, bioaccumulation of BDE-209 was assumed to be low due to its large molecular size, extreme hydrophobicity and low bioavailability. However, recent results from both aquatic and terrestrial food web studies have demonstrated that BDE-209 bioaccumulates (Chen et al., 2008; Chen et al., 2007; deBruyn et al., 2009; Law et al., 2006; Shaw et al., 2009). There is ongoing human exposure to BDE-209 from dust in indoor environments (Wang et al., 2018; Zhu et al., 2015) and from diet (Shi et al., 2018), particularly seafood (Ji et al., 2017; Shaw et al., 2009). Correspondingly, high levels of BDE-209 were also found, and BDE-209 has become the dominant BDE congener in human samples such as hair (Qiao et al., 2018; Yuan et al., 2016; Zheng et al., 2011), breast milk (Shi et al., 2013), blood (Li et al., 2017) and even feces (English et al., 2017). Thus, a risk assessment of BDE-209 exposure is still important, especially for China. China has the largest population exposed to high levels of BDE-209 in manufacturing sites and e-waste recycling sites (Zheng et al., 2017). The concentration of BDE-209 in humans from these contaminated areas is over 100-fold higher than that from European or American areas (Bjermo et al., 2017; Darrow et al., 2017; Xu et al., 2014; Zheng et al., 2017).

The adverse effect of PBDEs on thyroid function is of particular concern because of their structural similarity to thyroid hormones. Thyroid hormones are essential for normal development and maintenance of normal physiological functions. While previous studies have reported that BDE-209 could disturb thyroid hormones homeostasis in laboratory animals, the obtained results are inconsistent. For example, two studies have reported that BDE-209 exposure in rats can reduce the blood levels of thyroxine (T4) or triiodothyronine (T3) (Kim et al., 2009a; Lee et al., 2010), whereas another study found that T3 in the rats from the BDE-209 treatments increased significantly compared to the control group (Wang et al., 2011). Human studies that have investigated the associations between BDE-209 and thyroid hormone levels are limited, and the results are also inconsistent (Byrne et al., 2018; Huang et al., 2014; Xu et al., 2014; Zheng et al., 2017; Zota et al., 2011). The participants in these previous studies were drawn either from non-occupational population or from e-waste recycling related population and were exposed to a mix of endocrine disruptors at the same time. For example, the e-waste recycling related populations had a high exposure to BDE-209 but were also highly exposed to other endocrine disruptor pollutants such as polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) (Man et al., 2017; Xu et al., 2014; Zheng et al., 2017). In addition, in most cases, these endocrine disruptors were highly correlated with each other, making it difficult to identify the unique effect of BDE-209 when these independent effects show severe collinearity. This collinearity may be an important reason for the inconsistent results of human studies.

Given the inconsistent results of the studies linking BDE-209 and thyroid hormones, we examined the relationships between BDE-209 exposure and thyroid hormone concentrations measured in occupational workers, who are drawn from the workforce of a deca-BDE manufacturing plant and have a high and primary exposure to BDE-209. In addition, as a non-invasive and easily acquired matrix, urine may be suitable for monitoring internal BDE-209 exposure in occupational workers. Thus, the second objective of this study is to measure BDE-209 in urine samples and test the correlations between serum and urine concentrations of BDE-209.

2. Materials and methods

2.1. Sample collection

This study was launched with the authorization of the Ethics Committee of Capital Medical University and Shandong Center for Disease Control and Prevention. Sample collection was conducted in a deca-BDE manufacturing plant located in Shandong province. Most of the deca-BDE manufacturing facilities in China are located in Shandong province (Ji et al., 2017), where BDE-209 concentrations in the soil are markedly high and account for 88–99% of the total PBDEs (Li et al., 2015). The production line of deca-BDE in this plant was divided into six workshops, including a bromination workshop, a distillation workshop, a washing workshop, a filter pressing workshop, a drying workshop, and a packaging workshop; deca-BDE synthesis is carried out in the first three workshops, and therefore, deca-BDE levels in these workshops should be relatively limited, whereas the last three workshops address the already produced deca-BDE and therefore, in these workshops, the levels of deca-BDE should be relatively high due to the emission and volatilization of the deca-BDE product. Except for the workers who were pregnant or refused to sign the informed consent, all of the workers who work in these six workshops were included. From a total of 78 workers work in these six workshops, four workers were on vacation during the survey period, one female worker just became pregnant, and for one worker, blood draw was not performed because of homophobia. Finally, 72 workers were recruited into our study in 2016. To eliminate the influence of the thyroid hormones fluctuations at different times of the day, blood samples were obtained from these workers between 8:00–9:30 am on the same day. At the same time, paired urine samples were collected from these workers. However, only 67 urine samples were acquired because several participants in the study declined to participate in urine collection.

With the consent from the participants after clearly informing them of the study objectives, serum samples were collected by medical staff from the local Centers for Disease Control and Prevention (CDC). Approximately 10 mL of blood was collected with an anticoagulant-free tube (Franklin Lakes, NJ, US). Serum was isolated by centrifugation at 3000 rpm for 15 min within 2 h after collection. Approximately 1 mL of serum was stored at 4 °C and used to measure the circulating thyroid hormones, thyroid antibodies, total triglyceride (TG), and cholesterol (CHOL) levels within two days. The remaining serum samples were kept at −80 °C until chemical analysis. 40–45 mL of urine was collected from each donor with a 50 mL polypropylene (PP) tube. A short questionnaire and general physical examination, concerning the participants' gender, age, weight, height, occupational history, vocational prevention and protection, educational level, place and time of residence, smoking habits, iodized salt eating, etc. were conducted.

2.2. Reagents and chemicals

All the HPLC-grade organic solvents were obtained from Merck (Darmstadt, Germany). Sulfuric acid (98%), anhydrous $MgSO_4$ and NaCl were provided by Tianjin Fuchen Chemical Factory (Tianjin, China). Octadecyl-modified silica (C18) was obtained from Agilent Technologies (Palo Alto, CA, USA). The standard reference material (organic contaminants in fortified human serum) SRM 1958 was purchased from the National Institute of Standards and Technology (Gaithersburg, MD, USA).

Individual PBDE standards, including BDE-28, 47, 77, 99, 100, 128, 153, 154, 183, and 209, were obtained from AccuStandard Inc. (New Haven, CT, USA). The ^{13}C-labeled internal standard, $^{13}C_{12}$-BDE-209, was obtained from Wellington Laboratories (Guelph, Ontario, Canada).

2.3. Sample preparation and analysis

Serum and urine samples were analyzed for eight PBDEs congeners

(BDE-28, 47, 99, 100, 153, 154, 183, and 209) using gas chromatography–mass spectrometry (GC–MS, Agilent 7890B-5977A) in Capital Medical University. A slightly modified method described in previous study was used for chemical analysis (Gao et al., 2016). By enzymatically measuring the total triglyceride (TG) and cholesterol (CHOL) levels, the serum lipid content was calculated as described by Covaci et al. (2006). Detail information of sample preparation and instrumental analysis was described in Supplementary.

2.4. Quality assurance/quality control

Method blank samples were run every 10 samples to check for interference or contamination from the solvents and glassware. To minimize background contamination, the entire glassware was baked in a muffle furnace at 400 °C for 5 h before use. No PBDE congeners were detected in the method blanks. For recovery testing, matrix spiking tests using fetal bovine serum and rat urine were conducted. The recoveries of the analytes were in the 82.7% to 121.3% range with RSDs < 11.5% (n = 5). We did not correct the reported concentrations based on the recovery data. During the detection of serum samples, SRM 1958 was used as a quality control sample, the average values of most target congeners were in agreement with the corresponding certified values in SRM 1958 (Supplementary Table S1). The LOD of BDE-209 in serum was 50 pg/mL, whereas those of BDE-28, 47, 99, 100, 153, 154 and 183 were 2.5, 3, 5.5, 6, 9, 6.5 and 14 pg/mL, respectively. Furthermore, the LODs of BDE-209 and tri- to hepta-BDEs in urine were relatively low (20 pg/mL for BDE-209 and 0.5, 0.6,1, 1.2, 2, 1.2 and 3 pg/mL for BDE-28, 47, 99, 100, 153, 154 and 183, respectively).

2.5. Thyroid hormone analysis

Thyroid hormones and other thyroid markers were analyzed at the Shandong Academy of Occupational Health and Occupational Medicine. Following the standard methodologies, thyroid-stimulating hormone (TSH), total thyroxine (tT4), total triiodothyronine (tT3), free T4 (fT4), free T3 (fT3), thyroid antibodies (including thyroglobulin antibody (TG-Ab) and thyroid peroxidase antibody (TPO-Ab)) were analyzed using Roche's technique for immunoassay detection (Cobas e601 analyzer, Roche Diagnostics Ltd.) with accessory materials, including reagent standards and quality controls. Reference intervals for all of the thyroid tests that Roche suggests for immunoassay analyzer (Cobas e 601 analyzer) were used in data analysis. Reference intervals for healthy adults are as followed: TSH, 0.27–4.2 μIU/L; tT4, 66–181 nmol/L; tT3, 1.3–3.1 nmol/L; fT4, 12–22 pmol/L; fT3, 3.1–6.8 pmol/L; TG-Ab, 0–115 IU/mL; TPO-Ab, 0–34 IU/mL. Reference intervals of TSH, tT4, tT3, fT4, and fT3 corresponds to the 2.5% and 97.5% quantile; 115 for TG-Ab and 34 for TPO-Ab is the 95% quantile. The recoveries of the thyroid hormones and thyroid antibodies in dilutions (1:2, 1:4 and 1:8, v/v) from five serum samples ranged from 89.6% to 106.4%, and the recoveries ranged from 91.8% to 110.5% in the spiked matrices. Standard reference materials for tT4, tT3, fT4, fT3, TSH, TG-Ab, and TPO-Ab were tested three times prior to measuring the serum samples. The coefficients of variations were < 7.2%, and the deviations of standard reference materials were < 10.8%.

2.6. Data analysis

Descriptive statistics were used to represent the characteristics of the study population, individual PBDEs congeners, thyroid hormones, and thyroid antibodies. *t*-test was used to identify the differences in the characteristics between the genders. For the results below the limit of detection (LOD), we assigned BDE congener concentrations as the LOD for the individual congener divided by √2. We generated a sum (ΣPBDEs) based on the congeners with detection frequencies > 60% (BDE-28, 47, 153, 183, 209). We used $\log_{10}$ transformations of BDE congeners to approximate a normal distribution.

Most thyroid hormones (tT4, fT4, tT3, and fT3) levels were normally distributed, whereas the distributions of TSH, TG-Ab and TPO-Ab were skewed and natural log-transformed values were used for correlation and regression analysis. Additionally, significant differences between genders were observed in the tT3, fT4, and fT3 levels and a marginal difference between genders was observed in TG-Ab. Thus, gender is a very important factor that affects the correlation between the PBDEs levels and thyroid hormones. In the subsequent analysis, we adjusted gender in the entire population and further fit separate multivariable linear regression models for each gender population.

The correlations between the different BDE concentrations and between the BDE-209 and occupational exposure durations were examined using Pearson correlation analysis. Associations of the hormones with BDE-209 in both serum and urine were modeled using linear regression. Pearson's partial correlation coefficients for the associations of the hormones with exposures were estimated using the same variables as those used in the multiple linear regression models. We considered age (yr), body mass index (BMI, kg/m^2), gender (male/female), and occupational exposure duration (yr) to be important covariates and included them into all multivariate models. In this study, we considered $p < 0.05$ to be statistically significant and $p < 0.1$ to be marginally significant. The statistical analyses were performed using SPSS software version 23 (SPSS Inc., Chicago, IL, USA).

3. Results and discussions

3.1. Characteristics of participants

The sociodemographic characteristics of the participants are shown in Table 1. The 72 workers consist of 43 males and 29 females. The ages of the workers varied from 25 to 55 yrs. with the average of 34.9 yrs. Occupational exposure duration (the years that they worked at the deca-BDE manufacturing plant) ranges from 1 to 18 yrs. (average of 7.04 yrs). Thirty participants (42%) had a work history of working in other factories or as farmers and the total of working years ranges from 1 to 35 years (data not shown). To identify the gender difference, we found that the females had a higher serum lipid concentration and smaller smoking frequency than the males. None of the participants reported a personal or family history with thyroid problems.

3.2. PBDEs levels in serum and urine

3.2.1. PBDEs in serum and congener profile

The concentrations of PBDEs in serum and urine are summarized in Table 2, and the descriptive statistics of the congener-specific values are shown in Supplementary Table S2. The concentrations of BDE-209 in serum ranged from 67.4 ng/g lipid weight (lw) to 109,000 ng/g lw, with the median of 3420 ng/g lw. Clearly, BDE-209 was the primary PBDE congener in the serum, that was detected in all serum samples and contributed 93.1% of the total PBDEs. The maximum concentration of BDE-209 was observed in a female worker who was a packing workshop worker for 5 years.

The results obtained in this study imply that in spite of its larger molecular size and lower water solubility compared to lower brominated congeners, BDE-209 does accumulate in the human body (Ni et al., 2013). In recent years, an increasing number of studies carried out in China have reported that BDE-209 has become the major PBDE congener in human serum, whereas in other areas outside China, such as USA (< LOD-9.6 ng/g lw), Iran and Sweden (< LOD-78 ng/g lw), BDE-209 was still in low abundance compared to other congeners (Table 3) (Bjermo et al., 2017; Darrow et al., 2017; Eslami et al., 2016; Wu et al., 2015).

Domestic and global comparisons of PBDE levels in the serum are shown in Table 3. The serum BDE-209 concentration found in the present study was several orders of magnitude higher than those observed in the general population, and much higher than those from the

Table 1
Basic sociodemographic characteristics of workers from the deca-BDE manufacturing plant.

	Range (mean ± SD) or percentage			P^b
	All (n = 72)	Male (n = 43)	Female (n = 29)	
Age (yr)	25–55 (34.9 ± 6.98)	26–55 (35.65 ± 7.50)	25–46 (33.79 ± 6.08)	0.271
OED (yr)[a]	1–18 (7.04 ± 4.52)	1–18 (7.42 ± 4.47)	1–17 (6.46 ± 4.62)	0.318
BMI (kg/m^2)	17.71–33.06 (23.9 ± 3.44)	17.71–30.45 (24.14 ± 3.49)	18.83–33.06 (23.61 ± 3.41)	0.527
Serum lipid (g/L)	3.32–10.96 (5.06 ± 1.24)	3.32–10.96 (5.41 ± 1.46)	3.64–5.51 (4.54 ± 0.51)	0.002**[c]
Smoke	23.6% (17/72)	39.5% (17/43)	0% (0/29)	< 0.001**[d]
Anti-dust Mask usage	63.9% (46/72)	58.1% (25/43)	72.4% (21/29)	0.216[e]
High exposure workshop[f]	36.1% (26/72)	53.5% (23/43)	10.3% (3/29)	< 0.001**[e]

[a] OED, occupational exposure duration, there are one female which has missing data for OED.
[b] The value is from *t*-test or Fish's exact test between gender.
[c] $*p < 0.05$, $**p < 0.01$.
[d] The result is from Fisher's exact test between gender.
[e] The result is from Pearson Chi-Square test between gender.
[f] High exposure workshop includes filter pressing workshop, drying workshop, and packaging workshop.

Table 2
Serum concentrations (ng/g lw) and urine concentrations (ng/mL) of PBDEs in occupational workers.

	All (n = 72)			Gender						
				Male (n = 43)			Female (n = 29)			*t*-test
	DF	Median[a]	Geo mean	DF[b]	Median	Geo mean[a]	DF	Median	Geo mean	P^b
BDE-209	100	3420	3640	100	7130	6390	100	1700	1580	0.000**
BDE-28	81.9	33.8	21.5	78.6	29.5	19.0	86.2	22.6	25.8	0.998
BDE-47	79.2	22.7	14.8	76.2	22.7	14.7	82.8	22.6	15.0	0.238
BDE-100	12.5	n.d.	–	16.7	n.d.	–	6.90	n.d.	–	0.029*
BDE-99	20.8	n.d.	–	26.2	n.d.	–	10.3	n.d.	–	0.217
BDE-154	16.7	n.d.	–	23.8	n.d.	–	3.40	n.d.	–	0.321
BDE-153	77.8	48.3	33.0	76.2	49.8	35.7	79.3	28.4	29.3	0.113
BDE-183	90.3	61.2	50.8	95.2	89.0	79.9	82.8	30.4	25.9	0.000**
ΣPBDEs	100	3710	4010	100	7650	6970	100	2060	1770	0.000**
Urine BDE-209[c]	100	1.31	1.31	100	2.64	1.59	100	0.97	1.02	0.199

n.d.: not detected or value lower than LOD; DF: detection frequency; Geo mean: geometric mean; −:Geometric means of BDE-100, 99 and 154 were not calculated due to low detection frequency; ΣPBDEs: sum of PBDEs (BDE-28,47, 153,183, 209).
[a] Values bellowed the limitation of detection imputed as LOD/√2.
[b] When comparing difference between gender, the values of PBDEs was log10 transformed to getting a normal distribution.
[c] n for male is 41 and n for female is 26.
* $p < 0.05$.
** $p < 0.01$.

Table 3
Concentrations (ng/g lw) of PBDEs in human serum from various areas.

Region	Population	Year	n	Concentration of PBDEs (ng/g lw)				Reference
				BDE-209		ΣPBDEs[b] (include BDE-209)		
				Mean[a]/median	Range	Mean/median	Range	
China	deca-BDE workers	2016	72	9850/3420	67.4–1.09 × 10^5	10,200/3710	67.4–1.1 × 10^5	This study
China	E-waste workers	2011	79	509/409	65–1490	690/572	105–1810	(Zheng et al., 2017)
China	E-waste workers	2015	9	521/−	123–2140	656/−	167–2530	(Liang et al., 2016)
China	E-waste workers	2011	32	−/256	4–2716	−/753	105–4099	(Zheng et al., 2014)
China	Resident in e-waste area	2010	167	184.19/146.1	nd-470.29	−/208.08	16.56–582.35	(Xu et al., 2014)
China	Resident in e-waste area	2011	64	6.93/2.39	nd-80.3	22.7/9.77	0.4–370	(Lv et al., 2015)
China	General population	2010–11	124	2.25/5.02	< LOQ-157.1	11.02/7.16	2.09–160.3	(Huang et al., 2014)
China	General population	2015	10	7.5/−	nd-14.6	24.6/−	10.1–48.2	(Liang et al., 2016)
USA	General population	2011–12	80	< LOD	< LOD	52.2/53.9	6.5–9.7.1	(Darrow et al., 2017)
Korea	General population	2009	720	3.11/4.97	nd-84	8.06/6.04	nd-84	(Kim et al., 2012)
Iran	General population	2013–15	70	0.01/0.01	–	2.01/1.35	–	(Eslami et al., 2016)
Sweden	General population	2010–11	170	−/0.95	nd-78			(Bjermo et al., 2017)

[a] Mean level in this table is arithmetic mean.
[b] ΣPBDEs in our study is the sum of BDE-28, 47, 153, 183 and 209. In Darrow et al., 2017, ΣPBDEs is the sum of BDE-47, 99 and 100. In other studies listed in this table ΣPBDEs is the sum of all the tested congeners.

workers in the e-waste recycling regions. For example, in a study conducted in Southeastern China, the mean level of BDE-209 in the serum from e-waste disassembly workers was 521 ng/g lw, which is approximately 20 times lower than the results of our study (mean: 9850 ng/g lw); additionally, the BDE-209 contribution to total PBDEs was only 75% in serum samples from e-waste workers, which was also much lower than that found in our study (93.1%) (Liang et al., 2016). In the general population from North China, the median serum BDE-209 level was 5.02 ng/g lw, which is three orders of magnitude lower than our result (Huang et al., 2014). Due to the short half-life (15 days) of BDE-209 in human blood (Thuresson et al., 2006), BDE-209 level in human blood has been regarded as an indicator of recent exposure to deca-BDE (Sudaryanto et al., 2008). Thus, the high serum BDE-209 level in this study indicated that the workers are continuously exposed to high levels of BDE-209 during their daily work. Correlation analysis (Supplementary Table S3) showed that there was significant correlation between the serum BDE-209 level ($r = 0.352$, $p = 0.003$) and the occupational exposure duration, also indicating that occupational contact with deca-BDE resulted in a considerable BDE-209 accumulation in the human body. Vocational prevention and protection strategies should be strengthened to reduce such a high exposure.

Levels of tri- to hepta-BDE were significantly lower than those of BDE-209, with median levels ranged from < LOD to 61.2 ng/g lw. Among the tri- to hepta-BDE congeners, the highest detection frequency and concentration was obtained for BDE-183 with the median level of 61.2 ng/g lw. High detection frequencies and concentrations were also obtained for BDE-28 and BDE-47 and in particular for the BDE-153 that was the second most predominant congener in the serum. However, low detection frequencies (< 25%) and low concentrations were obtained for BDE-99, BDE-100 and BDE-154, and the median levels of all of these three congeners were lower than the LOD. We inferred that either a relatively low accumulation potential or a fast metabolic rate may produce the relatively low levels of these three congeners. McKinney et al. (2006) reported that rapid metabolism of BDE-99 and BDE-154 was observed in a rat model, and BDE-154 was biotransformed to hydroxylated metabolites to a significant extent, which can explain the low detection frequency of BDE-154 in the serum. On the other hand, a human liver microsome model demonstrated that human liver microsomes metabolized BDE-99 and BDE-47 but not BDE-153; therefore, a high bioaccumulation rate of BDE-153 in humans was observed, resulting in the relatively high concentration of BDE-153 in serum (Lupton et al., 2009).

During serum collection, we also collected and tested some workshop air samples from this factory, and it was found that BDE-209 was the predominant congener in the workshop air with a median concentration of 45.8 μg/m^3, whereas tri- to hepta-BDEs (median: 6.89 ng/m^3) could still be detected in these air samples albeit at low levels (Supplementary Table S4), indicating that tri- to hepta-BDEs are generated simultaneously with the BDE-209, and therefore tri- to hepta-BDEs were also found in the serum obtained from the workers. The photolytic debromination and short half-life of BDE-209 is a possible pathway for the formation of the lower brominated BDEs in the workshop (Chen et al., 2015). Soderstrom et al. (2004) reported that deca-BDE is photolytically labile and formed a series of debromination products including nona- to tetra-BDEs under sunlight. Additionally, short half-lives of deca-BDE were also observed in Soderstrom's study, and the half-life of BDE-209 on a silica gel under sunlight was shorter than 15 min, and ranged between 40 and 200 h on other matrices such as sediment, soil and sand. Photodegradation of deca-BDE under sunlight was also observed by Stapleton and Dodder (2008), resulting in the formation of lower brominated BDEs including octa- and nona-BDEs. In another study, production of tri- to nona-BDEs was also found after the irradiation of BDE-209 by sunlight (Grant et al., 2013). In summary, photolytic debromination of deca-BDE is likely to be a source of the tri- to hepta-BDEs found in this factory. In addition, commercial octa-BDE was produced in this factory until it was phased out by Chinese government in 2014. Octa-BDE can stay in environmental metrics for a long time (approximately 2–5 years) and have long half-lives in humans (3 months) after entering the human body via food or inhaling air (Andrade et al., 2017; Thuresson et al., 2006). Since BDE-183 (approximately 44%) and BDE-153 (approximately 12%) are the major components of commercial octa-BDE products, it is not surprising that the serum levels of BDE-183 (median: 61.2 ng/g lw) and BDE-153 (median: 48.31 ng/g lw) obtained in this study were more than ten times higher than those in the non-occupational population in China and other countries (Abou-Elwafa Abdallah et al., 2017; Bjermo et al., 2017; Liang et al., 2016; Marchitti et al., 2017). The correlation analysis (Table S3) between the PBDE congeners showed that the concentration of BDE-209 was highly correlated with the concentrations of BDE-153 and BDE-183 but had no significant correlations with the concentrations of BDE-28 and BDE-47. This implied that further investigations are necessary to identify the source of BDE-28 and BDE-47.

3.2.2. Serum BDE-209 levels between males and females

The serum concentrations of BDE-209 in male workers were much higher than those in the female workers ($p < 0.001$), and BDE-100 and BDE-183 showed the same tendency ($p = 0.029$ and $p < 0.001$). This finding is consistent with other studies on human blood (Thomas et al., 2006; Thomsen et al., 2002) and adipose tissue (Kunisue et al., 2007) that showed that women had lower PBDEs burden levels compared to men. In previous studies, along with placenta transfer (Leonetti et al., 2016b) and the elimination of PBDEs during lactation in women (Yang et al., 2016), the difference between the genders in the ability to excrete lipophilic contaminants was found to be helpful for explaining the different levels of PBDEs. However, for the workers examined in our study, differences in the occupational exposure may be the primary origin of the gender difference in the PBDE levels. More male workers work in the high exposure workshops, namely, the filter pressing workshop, the drying workshop, and the packaging workshop (Table 1), that address the produced deca-BDE, and therefore, the workers in these workshops were exposed to a higher level of BDE-209 due to the emission and volatilization of the deca-BDE product, resulting in higher serum BDE-209 levels. Thus, we infer that the difference in the BDE-209 levels in different workshops is the primary factor explaining the difference in the serum BDE-209 level between the genders.

3.2.3. PBDEs in urine

Currently, the information regarding PBDEs in urine is rather limited. Urine is not a commonly used matrix for monitoring internal PBDEs exposure due to the poor water solubility of PBDEs. However, as a non-invasive and easily acquired matrix, urine may be suitable for monitoring internal PBDE exposure in occupational workers who have a high body burden of PBDEs. The levels of BDE congeners in urine are listed in Supplementary Table S2, and an examination of these results showed that BDE-209 can be detected in all the urine samples but a low detection frequency was obtained for other congeners. In a previous study, several body fluids (blood, urine and perspiration) were used as PBDE biomonitoring media to assess the excretion of several congeners (BDE-28, 47, 99, 100 and 153), and these congeners were found in blood and perspiration but not in urine (Genuis et al., 2017). Hakk also reported that < 1% penta-BDE was excreted in urine after a single oral dose of penta-BDE in rats (Hakk et al., 2002). Dareer reported that only 0.129% of the deca-BDE administered intravenously to rats appeared in urine (el Dareer et al., 1987). In this study, PBDEs congeners other than BDE-209 had a low detection frequency (< 30%) in urine (Table S2), and even their serum levels were much higher than those in the non-occupational populations. Thus, urine is not an effective biomonitoring medium for the measurement of the unmetabolized parent compound when the body burden of PBDEs is low. Although hydroxylated PBDEs (OH-PBDEs) were not measured in our study, these metabolites, with better water solubility and can be detected in urine even in the non-

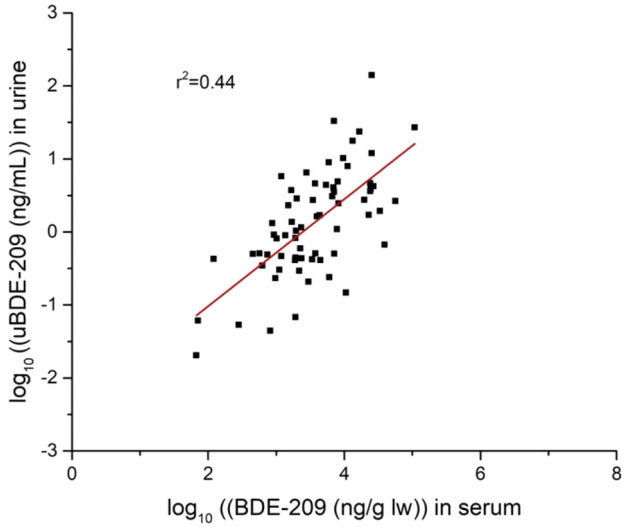

Fig. 1. Pearson's correlations between $\log_{10}$-transformed serum and urine concentrations of BDE-209 (n = 67).

occupational population, may be better biomarkers of the human body burden of PBDEs in the urine medium (Feng et al., 2016; Hakk and Letcher, 2003; Riu et al., 2008).

Although measurement of PBDEs in feces has been successfully used as a non-invasive method to estimate the serum concentrations of PBDEs in toddlers (Sahlstrom et al., 2015), it is clear that the collection, conservation and analysis of urine are easier than those of feces, and therefore, the feasibility of using urine as a non-invasive matrix to estimate the serum concentrations of PBDEs was investigated in this occupational population. Since BDE-209 could be found in all of the paired serum and urine samples, the correlation between the levels of BDE-209 in serum and urine was investigated. It was found that BDE-209 levels in the serum were significantly and positively correlated with those in urine ($r^2 = 0.44$, $p < 0.001$) (Fig. 1). The significant correlation reveals that the concentration of BDE-209 in urine is linearly proportional to that in the serum of the workers. Therefore, we suggest that urine can be used as a biomonitoring medium for predicting the body burden of BDE-209 in an occupational population.

3.3. Thyroid hormones and thyroid antibody levels

Seven participants had positive TG-Ab and four participants had positive TPO-Ab, but all of these participants had normal circulating thyroid hormones levels (Table 4). Females tended to have a higher prevalence of positive TG-Ab than males (17.24% vs 4.65%, $p = 0.173$) and the TG-Ab levels of the females were marginally significantly higher than those of the males (19.0 IU/mL vs 17.6 IU/mL, $p = 0.084$). However, we cannot conclude that the thyroid function of the females is more sensitive to BDE-209 than that of the males, because a positive antibody of TG was also found to be more prevalent in women than men in normal adult population (Hollowell et al., 2002; Quinn et al., 2009), and the 5.56% prevalence of TPO-Ab in this deca-BDE occupational study is smaller than the rate in normal Chinese adults (12.1%) (Quinn et al., 2009). No significant relationship was detected between BDE-209 and thyroid antibody concentrations in the full population (Table 5 and Supplementary S5). However, TPO-Ab was significantly correlated with BDE-209 in the female population ($r = 0.453$, $p = 0.045$). Several studies have reported that PBDE exposure is associated with increased thyroid antibodies (Turyk et al., 2008), and which may lead to the change of thyroid hormones levels (Vuong et al., 2015). However, in our study, we did not find a higher BDE-209 level in the positive thyroid antibody workers (geometric mean levels of serum BDE-209 for thyroid antibody positive workers and negative workers were 1610 and 3820 ng/g lw, respectively, p value of t-test after log-transformation is 0.117). Due to the limitation of the small sample size used in our study, it is difficult to draw conclusions regarding the effects of BDE-209 exposure on thyroid autoimmune diseases.

Table 4
Serum levels of thyroid hormones and thyroid antibodies in occupational workers.

	Median or mean[a]			t-Test
	All (n = 72)	Male (n = 43)	Female (n = 29)	p[b]
TG-Ab (IU/mL)[c]	17.9	17.6	19.0	0.084
TG-Ab positive[d]	7/72 (9.72%)	2/43 (4.65%)	5/29 (17.2%)	0.173[e]
TPO-Ab (IU/mL)[c]	18.73	18.03	19.15	0.659
TPO-Ab positive[d]	4/72 (5.56%)	1/43 (2.33%)	3/29 (10.3%)	0.351[e]
tT4 (nmol/L)	111	110	113	0.480
tT3 (nmol/L)	1.98	2.02	1.90	0.041*
fT4 (pmol/L)	17.4	17.9	16.6	0.003**
fT3 (pmol/L)	5.37	5.65	4.94	0.000**
TSH (μIU/mL)	1.92	1.92	1.95	0.616

[a] Median values are for TSH, TG-Ab and TPO-Ab, mean values are for tT4, fT4, tT3, fT3.
[b] When comparing difference between gender, the values of TG-Ab, TPO-Ab and TSH was $\log_{10}$ transformed to getting a normal distribution, except tT4, tT3, fT4, and fT3.
[c] For TG-Ab and TPO-Ab, n of male is 41 and n of female is 23. Participants with value > 115 IU/mL and > 34 IU/mL were considered as TG-Ab and TPO-Ab positive, respectively. Seven of the participates having positive TG-Ab or TPO-Ab were not included.
[d] Values are positive no./total (%).
[e] The value was from Chi-Square test.
* $p < 0.05$.
** $p < 0.01$.

The levels of circulating thyroid hormones in the BDE-209 occupational workers are listed in Table 4, and it is observed that the results were generally within the population reference ranges suggested by (Quinn et al., 2009). One participant had a fT3 level above the reference range, one had a TSH level above the reference range, and one had a tT4 level below the reference range. The levels of tT3, fT4 and fT3 in the males were higher than those in the females, but this was not true for TSH and tT4. Additionally, the levels of BDE-209 in the males were significantly higher than those in the females. Therefore, gender is a very important factor that affects the correlations between the PBDEs levels and thyroid hormones. In the subsequent analysis, we adjusted the gender in the entire population and further fit separate multivariable linear regression models for each gender population.

3.4. Association between thyroid hormones and PBDEs

Our study suggests that thyroid function may be changed in the direction of hyperthyroidism after BDE-209 exposure. BDE-209 in the serum was significantly and positively correlated with tT4 ($r = 0.270$, $p = 0.029$) and was marginally positively correlated with tT3 ($r = 0.232$, $p = 0.061$) in occupational workers (Table 5). Additionally, we found generally similar correlations in male workers who showed significantly positive correlations between BDE-209 and tT3, and marginally positive correlations between BDE-209 and tT4 and fT3. However, with the exception of free T4 ($r = 0.402$, $p = 0.046$), no significant correlations to BDE-209 were found for female workers. Similar correlations between these thyroid hormones and BDE-209 in urine were also found for all workers and for male workers, but not for the females (Supplementary Table S5). In female workers, BDE-209 in urine was not significantly correlated with fT4 ($r = 0.015$, $p = 0.949$) but was marginally significantly correlated with TSH ($r = -0.390$, $p = 0.082$).

The results of the multiple linear regressions for the associations between the circulating thyroid hormone levels and BDE-209

Table 5
Correlations of thyroid hormones and thyroid antibodies with BDE-209 in serum: Pearson's correlation coefficients.[a]

		All		Male		Female	
	Measure	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[c]	Unadjusted	Adjusted[c]
Ln TG-Ab (IU/mL) [d]	*r*-Value[e]	0.008	0.054	0.041	−0.067	0.208	0.179
	p-Value	0.950	0.683	0.801	0.693	0.341	0.450
Ln TPO-Ab (IU/mL) [d]	*r*-Value[e]	0.149	0.144	0.016	−0.033	0.361[#]	**0.453**[*]
	p-Value	0.245	0.277	0.921	0.848	0.090	0.045
tT4 (nmol/L)	*r*-Value[e]	**0.264**[*]	**0.270**[*]	**0.339**[*]	0.269[#]	0.351[#]	0.293
	p-Value	0.026	0.029	0.028	0.098	0.062	0.155
tT3 (nmol/L)	*r*-Value[e]	**0.341**[**]	0.232[#]	**0.424**[**]	**0.380**[*]	−0.094	−0.099
	p-Value	0.004	0.061	0.005	0.017	0.626	0.639
fT4 (pmol/L)	*r*-Value[e]	**0.332**[**]	0.163	0.166	0.070	0.327	**0.402**[*]
	p-Value	0.005	0.191	0.295	0.673	0.083	0.046
fT3 (pmol/L)	*r*-Value[e]	**0.377**[**]	0.125	**0.344**[*]	**0.309**[#]	−0.258	−0.214
	p-Value	0.001	0.317	0.026	0.050	0.167	0.305
Ln TSH (μIU/mL)	*r*-Value[c]	−0.167	−0.123	−0.204	−0.207	−0.107	−0.069
	p-Value	0.163	0.327	0.196	0.206	0.580	0.745

[a] The concentrations of BDE-209 was $\log_{10}$ transformed for the correlation analysis.
[b] Adjusted for genders, age, BMI, and occupational exposure duration.
[c] Adjusted for age, BMI, and occupational exposure duration.
[d] The participants that had positive TG-Ab or TPO-Ab were excluded.
[e] *p*-values < 0.05 are highlighted.
[#] $p < 0.1$.
[*] $p < 0.05$.
[**] $p < 0.01$.

concentrations are shown in Table 6. A 10-fold increase in the serum BDE-209 concentration was associated with elevated tT4 level (8.632 nmol/L) [95% confidence interval (CI): 0.930,16.33], corresponding to an increase of 7.8%. Additionally, a 10-fold increase in the serum BDE-209 concentration was associated with elevated tT3 level (0.106 nmol/L) [95% confidence interval (CI): −0.005, −0.219], corresponding to an increase of approximately 5.4%. A previous study reported that 10-fold increases in certain lower-brominated BDEs (BDE-47, −66, or −85) were associated with a 6.5–9.6% increase of tT3 but a much smaller increase of tT4 (approximately 0.15%–0.16%) in e-waste recycling workers (Zheng et al., 2017).

To elucidate the exact mechanisms of the PBDEs affecting thyroid hormonal status, at least four different levels at which the PBDEs are known to interact with the thyroid hormone system were explored, namely, the thyroid gland level, thyroid hormone transport proteins level, thyroid hormone activation level, and thyroid hormone metabolism level. For the thyroid gland level, several in vivo experiments showed that the thyroid gland could be damaged through the thyroid gland weight increase, slight follicular epithelium degeneration and swelling, but with different trends of thyroid hormone synthesis function after BDE-209 exposure (Chan and Chan, 2012; Lee et al., 2010; Noyes et al., 2011; Tseng et al., 2008). A recent study investigated the direct effects of PBDEs on the thyroid gland using primary human thyroid cells after exposure to BDE-71. The results showed that BDE-71 can inhibit thyroid functions by inhibiting Tg-release and reducing TPO mRNA expression in the absence of cytotoxicity (Kronborg et al., 2017). For the thyroid hormone transport proteins level, several studies showed that OH-PBDEs had the potential to disrupt thyroid homeostasis

Table 6
Multiple linear regression coefficients (95% CI) between BDE-209 and thyroid hormones, and thyroid antibody levels.[a]

	BDE-209s [b]	All workers[a]			Male workers[a]			Female workers[a]		
		β	95% CI	*p*-Value[d]	β	95% CI	*p*-Value[d]	β	95% CI	*p*-Value[d]
Ln TG-Ab (IU/mL)[c]	BDE-209	0.037	(−0.138, 0.212)	0.683	−0.030	(−0.189, 0.127)	0.693	0.173	(−0.297, 0.643)	0.450
	uBDE-209	0.037	(0.002, 0.910)	0.586	0.032	(−0.076, 0.140)	0.537	−0.094	(−0.608, 0.421)	0.705
Ln TPO-Ab (IU/mL)[c]	BDE-209	0.064	(−0.053, 0.180)	0.277	−0.012	(−0.127, 0.104)	0.848	0.290	(0.007, 0.571)	**0.045**[*]
	uBDE-209	0.048	(−0.039, 0.136)	0.280	0.009	(−0.069, 0.090)	0.795	0.306	(0.009, 0.606)	**0.044**[*]
tT4 (nmol/L)	BDE-209	8.632	(0.930, 16.33)	**0.029**[*]	8.185	(−1.596, 17.97)	**0.098**[#]	10.336	(−4.201, 24.88)	0.155
	uBDE-209	5.928	(0.387, 11.47)	**0.036**[*]	5.988	(−0.251, 12.227)	**0.059**[#]	5.536	(−10.27, 21.35)	0.474
tT3 (nmol/L)	BDE-209	0.106	(−0.005, 0.219)	**0.061**[#]	0.164	(−0.032, 0.297)	**0.017**[*]	−0.051	(−0.269, 0.168)	0.639
	uBDE-209	0.071	(−0.014, 0.157)	**0.099**[#]	0.088	(−0.009, 0.182)	**0.074**[#]	0.007	(−0.226, 0.240)	0.950
fT4 (pmol/L)	BDE-209	0.501	(−0.258, 1.257)	0.191	0.210	(−0.788, 1.207)	0.673	1.251	(0.023, 2.480)	**0.046**[*]
	uBDE-209	0.134	(−0.440, 0.709)	0.642	0.207	(−0.477, 0.891)	0.541	0.044	(−1.370, 1.458)	0.949
fT3 (pmol/L)	BDE-209	0.104	(−0.101, 0.304)	0.317	0.208	(−0.005, 0.421)	**0.056**[#]	−0.210	(−0.622, 0.203)	0.305
	BDE-209	0.023	(−0.134, 0.177)	0.774	0.071	(−0.083, 0.226)	0.359	−0.151	(−0.587, 0.288)	0.484
Ln TSH (μIU/mL)	BDE-209	−0.115	(−0.345, 0.117)	0.327	−0.152	(−0.392, 0.088)	0.206	−0.083	(−0.596, 0.433)	0.745
	uBDE-209	−0.085	(−0.256, 0.088)	0.329	−0.041	(−0.210, 0.127)	0.619	−0.463	(−0.979, 0.051)	**0.075**[#]

[a] Adjusted for genders, age, BMI, and occupational exposure duration in all the occupational workers, and adjusted for age, BMI, and occupational exposure duration in male and female workers. The concentration of BDE-209 was $\log_{10}$ transformed.
[b] BDE-209s means BDE-209 in serum (BDE-209) and in urine (uBDE-209).
[c] The participants that had positive TG-Ab or TPO-Ab were excluded.
[d] *p*-values < 0.1 are highlighted.
[#] $p < 0.1$.
[*] $p < 0.05$.

by competitive binding with thyroid hormone transport proteins (TBG and TTR) and the binding affinity appeared to be more efficient with a high degree of brominated congeners (Meerts et al., 2000; Ren and Guo, 2012). Even though we did not measure the metabolites of BDE-209 in our study, several previous studies have shown that BDE-209 can debrominate to PBDEs with fewer bromine atoms and metabolize into phenolic metabolites (mainly OH-PBDEs) (Chen et al., 2012; Huang et al., 2010; Noyes et al., 2011; Stapleton et al., 2006), implying that BDE-209 metabolites may also disturb the thyroid hormone homeostasis by competitive binding with thyroid hormone transport proteins. For the thyroid hormone activation level, deiodinases can locally modify the thyroid hormone bioactivity independent of serum thyroid hormone concentrations that play an important role in thyroid hormone homeostasis. Several in vivo animal studies showed that TH-regulating deiodinases changed after BDE-209 exposure, but the directions of the change in different tissues or at different times were different, which may be caused by a compensatory response to the changes in the circulating thyroid hormones (Chen et al., 2012; Li et al., 2014; Noyes et al., 2011; Noyes et al., 2013; Tseng et al., 2008). For the thyroid hormone metabolism level, uridine diphosphate glucoronosyltransferases (UGT) play important roles in TH homeostasis. A previous in vivo study showed that decreased tT4 levels and increased tT3 were accompanied by decreased UGT gene transcription after BDE-209 exposure (Chen et al., 2012), which was not consistent with other BDE congeners, for which the decreased T4 levels were accompanied with increased UGT gene transcription (Kim et al., 2009b; Richardson et al., 2008). One study showed that UGT gene transcription was inhibited by BDE-47 but was up-regulated by BDE-99 exposure, implying that different congeners may have different substrate metabolizing activities (Yang and Chan, 2015).

In our study, positive correlations were observed between tT4, tT3 and BDE-209 in occupational workers but TSH, fT3, fT4 showed no correlation with BDE-209, possibly due to the regulation of the pituitary-thyroid axis and the thyroid hormone activation system. Free thyroid hormones are the main biologically active hormones and must stay in a narrow concentration range to maintain normal function. BDE-209 exposure may disturb thyroid homeostasis through thyroid gland damage, competitive binding with thyroid hormone transport proteins, and changes in the thyroid hormone metabolism, but at the same time, the pituitary-thyroid axis and thyroid hormone activation system will work together to correct the free thyroid hormone concentration to a certain level through a feedback response to thyroid hormones. Because biological systems such as the human body include many interactions and feedback systems, it is difficult to precisely determine the regulation mechanism in this study. Nevertheless, the more dramatic increase in the concentrations of the total thyroid hormones (tT4 and tT3) compared to the free thyroid hormones (fT4 and fT3) observed in our study after BDE-209 exposure indicated that tT4 and tT3 may be sensitive monitoring biomarkers of adverse effects to thyroid function for BDE-209 exposure.

In our study the increases in mean TT4 and TT3 were below the clinical thresholds, however, the difference may be important as Miller et al. (2009) concluded that small shift in the distribution may have a substantial impact. Additionally, Andersen et al. (2002) pointed out that the ranges of the concentrations of the individual thyroid hormones are narrow compared to the used laboratory reference ranges, suggesting that the margins of changes for individual are smaller than that for population level. As a result, the estimated small increases in TT4 and TT3 in the whole BDE-209 manufacturing workers reflected relatively large increases on an individual level, which might exceed the margins of certain individual levels. Additionally, THs play an important role in regulating physiological processes, largely through binding to the nuclear thyroid hormone receptor (TR) α and β. BDE-209 could directly suppress TRβ action and inhibit normal neurodevelopment (Ibhazehiebo et al., 2011), implying that BDE-209 could bind to TR and alter transcriptional activities even though the thyroid hormone concentration remain normal. The adverse effect of BDE-209 exposure could be more serious among the subpopulations that may be more sensitive to thyroid hormones disruption such as pregnant women, and individuals with clinical hyperthyroidism.

Many human studies have been performed to investigate the associations between the thyroid hormone levels and PBDE exposure, but most of these were carried out in pregnant women. It is difficult to compare the results from pregnant women with the results obtained from the occupational workers in our study. tT4 was found to be increased by up to 50% in the first trimester of pregnancy due to the estrogen-induced elevations of serum thyroxine-binding globulin (TBG) (Alexander et al., 2017). The correlations between thyroid hormones and PBDEs may be modified further because of the different feedback regulation capabilities to the thyroid hormone changes between the pregnant populations and the non-pregnant populations. Only a few studies used the normal adult population (summarized in Supplementary Table S6).

Because of its lower bioavailability, measurement of serum BDE-209 was rarely included in previous studies (Brasseur et al., 2014; Kim et al., 2009b; Lin et al., 2011; Roze et al., 2009; Sjödin et al., 2008; Turyk et al., 2008). To date, few studies have estimated the association between thyroid hormones and highly brominated BDEs, and the results are also inconsistent (Huang et al., 2014; Xu et al., 2014; Zheng et al., 2017). A study carried out in a general population in Northern China, reported that BDE-209 was the most abundant PBDE congener in participants' blood and was positively correlated with T3 in 124 serum samples (Huang et al., 2014), which is consistent with our results. Zheng et al. reported that the circulating TSH levels showed inverse associations with some highly brominated BDEs (202, 203, and 208) in e-waste recycling workers (Zheng et al., 2017). However, one study reported hypothyroid-like effect (e.g., decreased T4/T3 or increased TSH) in relation to BDE-209 exposure. Xu et al. (2014) found that BDE-209 was positively associated with TSH and was negatively associated with fT3 levels in children from e-waste sites in China.

Several studies suggested that many factors may modify the associations between PBDEs and the thyroid hormones, which may partly explain these discrepancies. For example, a recent meta-analysis reported that the relationships between PBDEs and thyroid hormones followed U-shaped patterns, with low exposure level inversely associated with thyroid hormones and higher exposure level associated with increased levels of thyroid hormones (TSH and tT4) (Zhao et al., 2015). In our study, the median level of BDE-209 in serum was over 100 ng/g lw, and according to this meta-analysis, correlations between PBDE exposure and serum tT4 should show a positive correlation, which was consistent with our results. However, the U-shaped pattern of TSH change caused by BDE-209 cannot explain the results of our study. Several studies also suggested that the associations between PBDEs and thyroid hormones are modified by gender. A study conducted in a remote Alaska Native population showed that gender modified the effect of BDE-47 and BDE-100 on fT4, with a positive effect in the females and a negative effect in the males (Byrne et al., 2018). Another study investigating the associations between placental PBDEs and thyroid hormones in infants of different gender showed that the concentrations of PBDEs in the placenta were positively associated with female infants but were null associated with male infants (Leonetti et al., 2016a). An in-vivo animal study also showed that the thyroid hormones in female nestlings could be more significantly influenced by DE-71 exposure than those in male nestlings (Fernie and Marteinson, 2016). The fluctuation of thyroid hormones in different stages of life cycle could also be a confounding factor that may modify the associations between PBDEs and thyroid hormones. tT4 and tT3 can be increased by up to 43% and 38% in the first trimester of pregnancy and fluctuate throughout pregnancy (Soldin et al., 2004). Thus, the different capabilities of feedback regulation of thyroid hormone changes may occur in different stages of life, and further modify the correlations between thyroid hormones and certain exposed chemicals. Additionally, several

studies reported that other POPs (including PCBs, dioxins, etc.) can also disturb thyroid hormones (Grant et al., 2013; Schell et al., 2008). Concurrent exposure to PBDEs and other POPs may have additive or synergistic effects on thyroid hormone concentrations (Crofton et al., 2005). Collectively, the literature suggests a complex association between PBDEs exposure and thyroid hormones, potentially modified by dosage, sex, time of thyroid hormone measure, and exposure to other POPs.

Several studies reported opposite associations between thyroid hormones and lower- and higher-brominated congeners. A study carried out in a general population in Northern China, reported that T3 was positively correlated with BDE-209 and was inversely correlated with BDE-17, 28, 47, 153, and 183 (Huang et al., 2014). Zota et al. observed a positive association between TSH and lower brominated congeners (BDE-47 and BDE-85) and an inverse association with BDE-207 (Zota et al., 2011). Several in vitro or in vivo studies imply that thyroid function response varies by PBDE structure. BDE-28 was found to be a potentiator on TRβ, while BDE-206 was antagonistic on TRβ (Schriks et al., 2007). One study further reported that unlike the lower-brominated congeners (BDE-47), BDE-209 could suppress TRβ action and inhibit the development of Purkinje cell dendrites (Ibhazehiebo et al., 2011). Further study is required for further elucidation of the different actions of PBDE congeners.

In the present study, BDE-209 was the primary PBDEs congener that provided a possible adverse effect on the thyroid function that was caused by long-term exposure to BDE-209. However, our study also had some limitations. First, this study is a cross-sectional study with a small population that cannot determine the temporal relationship between the exposure and the outcome. The small sample size reduces the statistic power and increases the margin of type 2 error of the study. Second, we did not measure the OH-PBDEs metabolites that may be more detrimental to the thyroid system than their parent congeners, because OH-PBDEs more closely resemble T3 and T4, and therefore have a higher affinity to TBG and TTR (Marchesini et al., 2008; Meerts et al., 2000). Third, urinary iodine was not measured because all of the participants are local residents who live in Shouguang city that is located in the coastal regions of the Shandong province in China. A previous study reported that adults from Shandong province have more than adequate iodine nutrition (Xu et al., 2016). In addition, most of the participants (65/72) in our study consume iodized-salt during the meals with their families. Thus, it is plausible that the iodine levels of our participants are sufficient. Therefore, we did not include iodine as a covariate. Last, our study showed that BDE-209 exposure can influence thyroid function in the occupational workers in the direction of hyperthyroidism, but none of them could be diagnosed with hyperthyroidism. Accordingly to the response to the questionnaire, only one female reported that she had thyroid nodules, while the rest of the participants reported no thyroid disorders (hypothyroidism, hyperthyroidism, goiter, thyroid nodules or thyroid cancer). Based on the thyroid hormone determination, three participants had a single thyroid hormone abnormality, but none of them could be diagnosed as hyperthyroidism. The prevalence of hyperthyroidism ranges from 0.2 to 1.3% in iodine-sufficient areas (Taylor et al., 2018). The selection bias from the healthy worker effect can underestimate the prevalence of outcomes in occupational epidemiology. However, in this cross-sectional study, the small population limited our ability to estimate the prevalence of hyperthyroidism. However, this work still provided new evidence of the correlation between BDE-209 and thyroid function and highlighted the importance of considering the elimination of BDE-209 production throughout the world.

4. Conclusion

This work is the first study to investigate the relationship between the BDE-209 levels and thyroid hormone concentrations that was carried out in occupational workers from a deca-BDE manufacturing plant. High levels of BDE-209 that were considerably higher than those in previous studies were detected in the serum samples obtained from the workers, indicating that the workers were continuously exposed to high levels of BDE-209. BDE-209 was associated with greater tT4 and tT3 concentrations in the occupational workers, consistent with a physiological pattern in the direction of hyperthyroidism. In addition, BDE-209 concentration in urine was highly correlated with that in the serum, indicating that urine may be a good non-intrusive biomonitoring medium of BDE-209 body burden in occupational workers. Given that this population is highly exposed to BDE-209 and has relative little exposure to other contaminants, these findings provided new evidence of possible adverse effect on thyroid function caused by long term exposure to BDE-209. This study supports previous research that suggested that higher-brominated flame retardants can also influence thyroid function. Future studies are also needed to explore the mechanisms by which BDE-209 and their metabolites act on the thyroid system because thyroid hormones are critical to health, in particular for pregnant women and child development.

Conflict of interest statements

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.08.032.

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