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Thyroid function and decabromodiphenyl ethane (DBDPE) exposure in Chinese adults from a DBDPE manufacturing area

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ABSTRACT

Polybrominated diphenyl ethers (PBDEs), which are persistent organic pollutants, affect thyroid function. Human exposure to decabromodiphenyl ethane (DBDPE), which has a similar structure to PBDEs, has recently increased, and the health effects of DBDPE have not been well studied. The objective of this study was to determine whether human exposure to DBDPE was associated with thyroid hormone levels in adults from a DBDPE manufacturing area. Three hundred-two blood samples were collected from two populations in the largest DBDPE manufacturing area located in North China: 133 DBDPE occupationally exposed workers from a DBDPE manufacturing plant and 169 non-DBDPE occupationally exposed residents from a nearby food processing plant. The levels of DBDPE, and thyroid function parameters [total thyroxine (TT4), free T4 (FT4), total triiodothyronine (TT3), free T3 (FT3), thyroid-stimulating-hormone (TSH), thyroglobulin antibody (TG-Ab), and thyroid peroxidase antibody (TPO-Ab)] were measured in serum samples. Serum concentrations of DBDPE ranged from 3.148 to 54,360 ng g^{-1} lipid weight (lw), with a geometric mean of 332.6 ng g^{-1} lw. A 10-fold increase in the DBDPE concentration was associated with increase of 4.73 nmol L^{-1} [95% confidence interval (CI): 2.75, 6.71] TT4 and 0.046 nmol L^{-1} TT3 [95% CI: 0.012, 0.081], corresponding to increases of approximately of 4.73% (95% CI: 2.75%–6.71%) and 2.38% (95% CI: 0.62%–4.20%), respectively. DBDPE in serum was also significantly and positively associated with the concentrations of TG-Ab and TPO-Ab. Our study found that exposure to DBDPE was associated with changes in thyroid activity in adults exposed to a high concentration of DBDPE, mainly increases of TT4, TT3, TPO-Ab, and TG-Ab. The association between DBDPE exposure and thyroid homeostasis requires further investigation because increasing DBDPE exposure has emerged in recent years.

1. Introduction

Decabromodiphenyl ethane (DBDPE) is produced as a replacement and alternative retardant to decabrominated diphenyl ether (deca-BDE) and was introduced into the Chinese market in the beginning of the 21st century. Since the use of deca-BDE has been restricted because of its adverse effects on the environment and human health, DBDPE has become one of the most widely used brominated flame retardants (BFRs) around the world (Vuong et al., 2015). In 2017, deca-BDE was added as a new persistent organic pollutant under the Stockholm Convention (http://chm.pops.int/TheConvention/ThePOPs). Obviously, with the regulation of deca-BDE, demand for DBDPE will continue to increase.

DBDPE has similar applications to deca-BDE and is used in various products such as electronic products, furniture and children's toys. As a BFR, DBDPE can leach or volatilize from these products and enter the surrounding microenvironments. DBDPE is not only similar to deca-BDE in structure but also in its persistence properties. DBDPE was first identified in sewage sludge, sediment, and indoor air samples collected in 2000 in Sweden (Kierkegaard et al., 2004). Recently, Hsu et al. (2018) summarized the levels of novel brominated flame retardants (NBFRs) in indoor dust, and they found that DBDPE had become the dominant NBFR in many countries, including Spain (Cristale et al., 2016), the United Kingdom (Kuang et al., 2016), Norway (Cequier et al., 2014), Pakistan (Khan et al., 2016), and especially China (Cao

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Table 1
Concentrations (ng g^{-1} lw) of DBDPE in human serum from various regions.

Region	Population	Year	*n*	Concentration of DBDPE (ng g^{-1} lw)				Reference
				LOD	%DF	Mean[a]/ median	Range	
Shandong, China	DBDPE occupationally exposed workers	2016–2017	133	0.01 ng mL^{-1}	100	7020/4170	236–54,400	This study
	Residents from DBDPE manufacturing contaminated areas	2016–2017	169	0.01 ng mL^{-1}	100	148/33.4	3.15–3740	This study
Tianjin, China	General population	2006	115	15 ng g^{-1} lw	0	n.d./n.d.	n.d.	Zhu et al., 2009
Zhejiang, China	e-Waste workers	2015	9	2.5 ng g^{-1} lw	100	125/–	26.7–440	Liang et al., 2016
	Resident lived in e-waste area	2015	21	2.5 ng g^{-1} lw	100	56.1/–	4.2–128	
	General population	2015	10	2.5 ng g^{-1} lw	–	13.8/–	n.d.–33.2	
China	General population	2016	12	0.5 ng mL^{-1}	25	–/n.d.	n.d.–43.9	Gao et al., 2016
Guangzhou, China	General population	2014	43	5.59 ng g^{-1} lw	100	–/39.2	–	Qiao et al., 2018
	General population	2014	12	5.59 ng g^{-1} lw	100	–/38.0	30.9–65.0	
Sweden	Aircraft maintenance workers (*n* = 27), pilots (*n* = 41), general population (*n* = 31)	2010–2011	99	–	0	n.d./n.d.	n.d.	Strid et al., 2014
Sherbrooke, Canada	General population	2008–2009	102	3.5 ng g^{-1} lw	5.9	–/n.d.	n.d.–123	Zhou et al., 2014

LOD: limit of detection; n.d.: not detected or value lower than LOD; DF: detection frequency.
[a] Arithmetic mean.

et al., 2014; Malliari and Kalantzi, 2017; Peng et al., 2017; Qi et al., 2014; J. Wang et al., 2010, 2018; Zheng et al., 2015; Zheng et al., 2014). As an important electronic product manufacturer, China is the major producer and consumer of DBDPE. Moreover, there are a considerable number of electronic waste (e-waste) recycling regions in Southern and Southeastern China. Studies have shown that the levels of DBDPE in indoor dust collected from China are from several to hundreds of orders of magnitude higher than those from other countries, suggesting that DBDPE has been used or released in large amounts in China (Hsu et al., 2018; Malliari and Kalantzi, 2017).

Bioaccumulation of DBDPE is assumed to be relatively low due to its large molecular size and high hydrophobicity. However, recent results from both aquatic and terrestrial food web studies have demonstrated that DBDPE bioaccumulates (Gao et al., 2009; Law et al., 2006; Luo et al., 2009; Zheng et al., 2014). DBDPE can accumulate in human serum (Table 1). DBDPE was not detected in serum samples collected in 2006 from cleaners, university students and policemen in Tianjin, China (Zhu et al., 2009). However, the detection frequencies and levels of DBDPE have been increasing, especially in adults from e-waste recycling areas in China (Gao et al., 2016; Liang et al., 2016; Qiao et al., 2018). DBDPE was also detected in human milk (Shi et al., 2016) and hair samples (Qiao et al., 2018) at levels higher than most other BFRs.

The adverse effect of DBDPE on thyroid function is of great concern (Noyes et al., 2013). A previous study showed that DBDPE could increase serum triiodothyronine (T3) levels in laboratory rats after a 90-day oral exposure (F. Wang et al., 2010; J. Wang et al., 2010). However, a recent study reported an induction in total T3 (TT3), free T3 (FT3) and thyroid-stimulating-hormone (TSH) in mice treated with 30-day dietary exposure to DBDPE (Sun et al., 2018). Although the results of these studies are inconsistent, both studies suggest that DBDPE can increase the risk of thyroid hormone homeostasis disruption (Noyes et al., 2013). In humans, deca-BDE has been found to be associated with the disruption of thyroid hormone homeostasis (Chen et al., 2018; Turyk et al., 2008; Zheng et al., 2017), whereas the effects of DBDPE on thyroid hormones have not yet been reported.

In the present study, the effects of DBDPE exposure on thyroid hormones in residents from a DBDPE manufacturing area located in North China (Shandong province) are reported. China is one of the major producers of DBDPE, and most DBDPE plants are located in Shandong Province, China (http://www.polymer.cn/). The production volume of DBDPE in China in 2006 was 12,000 tons, and with an increase of 80% per year (Covaci et al., 2011). Local residents, especially workers from DBDPE manufacturing plants, are exposed to high concentrations of DBDPE. In this study, blood samples were collected and tested from two groups in Shandong Province: DBDPE occupational workers from a DBDPE manufacturing plant and non-DBDPE occupational residents from a food processing plant located in a DBDPE contaminated area. The serum concentrations of DBDPE and thyroid hormones were measured, and the relationships of DBDPE exposure with thyroid hormone homeostasis were studied.

2. Materials and methods

2.1. Study design and population

Two groups of residents were recruited in our study during 2016–2017. One group was composed of DBDPE manufacturing workers from a DBDPE manufacturing plant located in Shandong Province. The process of producing DBDPE involves six workshops: a brominating workshop, a distillation workshop, a washing workshop, a filter pressing workshop, a drying workshop, and a packaging workshop. DBDPE is synthesized in the first three workshops and is purified and dried in the last three workshops. Therefore, workers who work in the last three workshops are exposed to relatively higher levels of DBDPE. From a total of 152 workers working in these six workshops, ten workers worked in this plant for less than one year, six workers were on vacation during the survey period, and three workers failed to provide blood samples. 133 workers in the DBDPE manufacturing plant were recruited into our study. The other group was composed of non-DBDPE manufacturing residents (food processing workers) from a food processing plant that is located 30 km from the DBDPE manufacturing plant, in which no BFRs are used during the manufacturing process. From a total of 183 workers working in the food processing plant, eight workers worked in this plant less than one year, two workers were on vacation during the survey period, one female worker just became pregnant, and three workers failed to provide blood samples. 169 workers in the food processing plant were recruited into our study. We obtained written informed consent before participation, and this study was launched with the authorization of the Ethics Committee of Capital Medical University and Shandong Center for Disease Control and Prevention (CDC).

2.2. Serum collection and analysis

2.2.1. Serum collection and thyroid hormone analysis

Before serum collection, a short questionnaire and general physical examination, concerning participants' gender, age, weight, height, occupational history, vocational prevention and protection, educational level, place and time of residence, smoking habits, seafood consumption, iodized salt consumption, etc. were conducted.

Blood samples were collected from all 302 participants in routine physical examinations performed by medical staff from the local CDC.

Blood samples were obtained from these participants between 8:00–9:30 am to eliminate the influence of thyroid hormone fluctuation at different times of the day. After fasting for a whole night, approximately 10 mL of blood was collected in 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 total thyroxine (TT4), free T4 (FT4), TT3, FT3, TSH, thyroglobulin antibody (TG-Ab), and thyroid peroxidase antibody (TPO-Ab), total triglyceride (TG) and cholesterol (CHOL) at the Shandong Academy of Occupational Health and Occupational Medicine within two days. Thyroid function parameters were measured by Roche's technology for immunoassay detection (Cobas e601 model, Roche Diagnostics Ltd., Basel, Switzerland), which was described in our previous study (Chen et al., 2018). By enzymatically measuring the TG and CHOL levels, the serum lipid content was calculated as described by (Covaci et al., 2006).

2.2.2. Serum DBDPE analysis

Serum (0.5 mL) was analyzed at Capital Medical University for DBDPE using established methods (J. Wang et al., 2018; Y. Wang et al., 2018).

All HPLC-grade organic solvents, including hexane and acetone, were obtained from Merck (Darmstadt, Germany). Sulfuric acid (98%), anhydrous Mg_2SO_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). Standard solutions of DBDPE and a ^{13}C-labeled internal standard, $^{13}C_{14}$-DBDPE, were obtained from Wellington Laboratories (Guelph, Ontario, Canada).

Pretreatment of serum was performed using quick, easy, cheap, effective, rugged, and safe (QuEChERS) approach. In detail, serum samples were thawed before analysis, and an internal standard (IS) solution that contained 10 ng of $^{13}C_{14}$-DBDPE was loaded into a clean polypropylene (PP) tube. The solvent (n-hexane) was dried under nitrogen. Subsequently, 0.5 mL each of serum sample and pure water were added, and the contents of the tube were whirl mixed. Two milliliters of acetone/hexane (1:1, *v*/v) was added to extract the analytes by vigorously shaking for 1 min. Next, 400 mg $MgSO_4$ and 100 mg NaCl were added to the PP tube, immediately shaken for 1 min and centrifuged to obtain separation (5 min, 4000 rpm). The upper layer was transferred to another PP tube that contained 50 mg $MgSO_4$ and 100 mg C18. The tube was vigorously shaken for 1 min to remove the lipids and impurities and then centrifuged for separation (5 min, 10,000 rpm, 4 °C). The upper layer was concentrated to dryness and reconstituted in 100 μL n-hexane for instrumental analysis.

Instrumental analysis was performed on a triple-quadrupole mass spectrometer equipped with an atmospheric pressure chemical ionization (APCI) source (Xevo TQ-S, Waters Corporation, Milford, MA, USA) and coupled to a gas chromatograph (7890B, Agilent Technologies, Santa Clara, CA, USA). A DB-5MS capillary column (15 m × 0.25 mm, 0.10 μm film thickness, J&W Scientific, Folsom, CA, USA) was used for chromatographic separation with helium as a carrier gas (3 mL min^{-1}). The transfer line temperature was maintained at 310 °C. The oven temperature of the GC was set at an initial temperature of 100 °C held for 1 min, followed by an increase at 30 °C min^{-1} to 310 °C and holding for 10 min. The GC injection was performed in the pulsed spitless mode, and the pulsed pressure was maintained at 50 psi for 1 min. The injection volume was 1 μL with an injector temperature of 280 °C.

On the Xevo TQS MS, the ion source was carried out in the APCI + mode. Nitrogen was used as the auxiliary and cone gas and maintained at 250 L h^{-1} and 150 L h^{-1}, respectively. Argon was applied as the collision gas with a constant flow of 0.25 mL min^{-1}. The APCI corona pin current was operated in the constant current mode at 3 μA. The cone voltage was set at 30 V and the APCI source temperature was maintained at 150 °C under "dry" conditions to promote charge transfer ionization. The MS was operated in the multiple reaction monitoring (MRM) mode and two MRM transitions were set for each compound. That is, *m/z* 971 → 468 and *m/z* 971 → 485 were set for DBDPE, and *m/z* 983 → 474 and *m/z* 983 → 491 were set for $^{13}C_{14}$-DBDPE. One transition served as the quantification transition, and the other was the qualifier transition.

Study so far indicates that accurate and sensitive analysis of DBDPE is quite difficult. GC–MS is the most commonly used technique for DBDPE analysis. Because DBDPE are thermally unstable, its degradation during GC–MS analysis was inevitable. Thus, it is better to use ^{13}C-DBDPE as internal standard to compensate for the degradation. However, in early used GC-NCI-MS, GC-EI-MS and GC-EI-MS/MS, fragment ions containing carbon atom of DBDPE or ^{13}C-DBDPE showed extremely low signal intensities, and thus, accurate analysis of DBDPE on these techniques is very difficult (Gao et al., 2016). Comparatively, the GC-APCI-MS/MS, as a novel technique and used in our study, can offer highly sensitive analysis of DBDPE (J. Wang et al., 2018; Y. Wang et al., 2018). Because APCI is a soft (low-energy) ionization technique, more abundant molecular or quasi-molecular ions of DBDPE can be formed, resulting in subsequent highly sensitive and selective detection. And more importantly, ^{13}C-DBDPE showed high signal response in APCI-MS/MS, which has helped to increase the accurate quantification of DBDPE. In summary, compared to NCI-MS and EI-MS/MS, much better sensitivity was obtained when using APCI-MS/MS (J. Wang et al., 2018; Y. Wang et al., 2018).

2.2.3. Quality assurance/quality control

Method blank samples were run every 10 samples. In our study, method blank is an analyte-free matrix that is processed in exactly the same manner as the real sample. We used BFR free fetal bovine serum as the method blank. And purpose of the method blank tests is to document contamination resulting from the analytical process and related reagent and glassware. To minimize background contamination, all glassware was baked in a muffle furnace at 400 °C for 5 h before use. No DBDPE was detected in the method blanks. For recovery testing, matrix spiking tests using fetal bovine serum were conducted. The recoveries of the analytes were in the 81% to 117% range with RSDs < 17% ($n = 5$). We did not correct the reported concentrations based on the recovery data. The LOD of DBDPE in serum was 10 pg mL^{-1}.

2.3. Data analysis

Descriptive statistics were used to present the characteristics of the study population, individual DBDPE, thyroid hormones, and thyroid antibodies. We evaluated the correlations among the serum levels of DBDPE, thyroid hormones and thyroid antibodies using Spearman rank-order correlation. A *t*-test was used to identify different characteristics between two groups. We used 10 log transformations (log_{10}) of DBDPE to approximate a normal distribution. Most of the thyroid hormones (TT4, FT4, TT3, and FT3) levels were normally distributed, whereas the distributions of TSH, TG-Ab and TPO-Ab were skewed, and log-transformed values were used for regression analysis.

The concentrations of DBDPE in serum, including the descriptive statistic values by volume (ng mL^{-1}) and on the lipid basis (ng g^{-1} lw) are shown in supplementary Table S1. There was a high correlation ($r^2 = 0.994$, $p < .001$) between the DBDPE concentration by volume (ng mL^{-1}) and on the lipid basis (ng g^{-1} lw) (data not shown). Thus, we could assume that there was no difference between using the weight per unit volume of serum and as lipid-standardized values when modeling the relationships between serum DBDPE and health outcomes. The lipid-standardized value (DBDPE per unit of serum lipids) is a more widely used value than wet weight (DBDPE per unit of serum) in the literature when expressing concentrations of persistent lipophilic chemicals (Schisterman et al., 2005). Thus, the lipid-standardized DBDPE concentration was used in the subsequent regression models.

The associations of thyroid hormones with DBDPE in serum were

Table 2
Serum concentrations of DBDPE (ng g^{-1} lw) by demographic characteristics.

Characteristic	*N* (%)[a,b]	GM (GSE) of DBDPE
Participants sources		
DBDPE manufacturing plant workers	133 (44.0%)	4100 (374)*
Non-occupational exposure residents from a nearby food processing plant	169 (56.0%)	46.0 (5.01)
Gender		
Female	105 (34.8)	337 (78.3)
Male	197 (65.2)	330 (66.9)
Age (years)		
≤30	121 (40.1)	434 (107)
30–40	114 (37.7)	228 (54.2)
≥40	67 (22.2)	391(143)
BMI		
< 18.5	6 (2.0)	799 (594)
18.5–24	145 (48.0)	397 (85.6)
24–28	109 (36.1)	319 (87.4)
≥28	42 (13.9)	177 (74.3)
Length of employment at the factory (years)		
< 5	133 (44.0)	570 (125)
5–10	80 (26.5)	522 (153)
≥10	89 (29.5)	99.1 (27.4)*
Smoking status		
No	151 (50.0)	289 (59.3)
Environmental tobacco smoke	57 (18.9)	378 (140)
Active	94 (31.1)	387 (111)
Alcohol consumption		
Never	133 (44.0)	363 (74.3)
< 1 alcohol drink per week	150 (49.7)	248 (54.3)
> 1 alcohol drink per week	19 (6.3)	1870 (1260)*
Education		
Primary school or less	122 (40.4)	361 (95.7)
High school	132 (43.7)	281 (58.9)
Bachelor's or more	48 (15.9)	428 (176)
Seafood intake		
< 3 times seafood intake per week	103 (34.1)	70.2 (14.0)
> 3 times seafood intake per week	199 (65.9)	744 (132)**
Iodized salt intake		
No	21 (7.0)	999.4 (573.8)*
Yes	281 (93.0)	306.3 (47.0)
Child-bearing status of females		
No	8 (7.6)	462.6 (482.9)
Yes	94 (89.5)	317.2 (79.4)
Children per female		
0	8 (8.0)	462.6 (491.3)*
1	71 (71.0)	475.9 (133.5)*
2	21 (21.0)	77.9 (41.6)
Lipid (g L^{-1})	4.78 (0.07)[b]	332 (51.0)
TG-Ab abnormal participants[c]	11 (3.64)	500.0 (356.7)
TPO-Ab abnormal participants[c]	20 (6.62)	678.4 (376.3)
TSH (μIU mL^{-1})	1.76 (0.05)[d]	332 (51.0)
TT4 (nmol L^{-1})	99.9 (0.98)[b]	332 (51.0)
TT3 (nmol L^{-1})	1.93 (0.02)[b]	332 (51.0)
FT4 (pmol L^{-1})	16.7 (0.11)[b]	332 (51.0)
FT3 (pmol L^{-1})	5.53 (0.04)[b]	332 (51.0)

Abbreviations: GM, geometric mean; GSE, geometric standard error. SE, standard error.

* $p < .05$.

** $p < .001$ (two-sided *p*-values using analysis of variance).

[a] Frequencies may not add to the total number of participants because of missing values. Percentages may not add to 100% because of missing values.

[b] The value shows Mean (SE) for lipid and thyroid hormones.

[c] Participants with value > 115 IU mL^{-1} and > 34 IU mL^{-1} were considered as TG-Ab and TPO-Ab positive, respectively.

[d] The value shows GM (GSE) for TSH.

modeled using multiple linear regression. As most of the thyroid hormone levels were significantly different between genders, separate regression models were used for different genders. The covariates included in final regression models were based on the results of bivariate analyses that examined the relationship of thyroid hormones and thyroid antibodies ($p < .2$). The final regression models included the following covariates (categorized as shown in Table 2): age, body mass index (BMI), gender, education, smoking status, alcohol consumption, and seafood consumption. The female regression models additionally included child-bearing status and child-bearing numbers. The following covariates were also considered but did not meet the criteria for inclusion in the final models ($p > .2$): lipid concentration, and iodized salt intake status. The percent changes in thyroid hormones associated with 10-fold increases in DBDPE were calculated by dividing the regression model coefficient by the mean thyroid hormone contents of serum.

We also estimated dose-response models by linear regression for DBDPE using indicator variables for quartiles 2, 3 and 4, with quartile 1 as the reference category. The median value in each quartile was used when testing the trend for ordinal quartiles (Greenland, 1995). Modeling exposure using quantiles allows for examination of patterns of association across the range of exposure and the potential for non-linear dose response. We also examined the relationship between the serum DBDPE and thyroid antibodies levels using linear regression models. Several participants had clinically significant levels of TG-Ab (> 115 IU mL^{-1}, $n = 11$) or TPO-Ab (> 34 IU mL^{-1}, $n = 20$). Therefore, regression models between tDBDPE and thyroid antibodies only included participants who had detectable and normal TG-Ab or TPO-Ab levels. The DBDPE quartiles (ng g^{-1} lipid weight) were defined as follows: 3.15–27.9 ($n = 75$); 27.9–235 ($n = 76$); 236–3330 ($n = 75$); > 3330 ($n = 76$). All tests of statistical significance were two-sided, and $p < .05$ was considered significant. Statistical analyses were performed using SPSS software version 23 (IBM Inc., Chicago, IL, USA).

3. Results

3.1. DBDPE concentration

The basic sociodemographic characteristics of the population and DBDPE concentrations are shown in Table 2 and Supplementary Table S1, respectively. DBDPE was detected in all serum samples and from 3.15 to 54,400 ng g^{-1} lw, with a geometric mean of 333 ng g^{-1} lw. The 302 participants consisted of 133 DBDPE manufacturing workers and 169 non-occupational exposure residents from a local food processing plant. The DBDPE manufacturing workers had much higher serum levels of DBDPE (geometric mean: 4100 ng g^{-1} lw) than the non-occupational exposure residents (geometric mean: 46.0 ng g^{-1} lw) ($p < .05$). The ages of the participants varied from 18 to 59 yrs, with an average age of 33.4 yrs (data not shown). The concentrations of DBDPE were higher among participants who had higher frequencies of alcohol consumption and seafood consumption. Participants who did not eat iodized salt also seemed to have higher DBDPE levels. Most females had a child-bearing history (89.5%), and females who had two children had much lower serum DBDPE levels (77.9 ng g^{-1} lw) than childless females (463 ng g^{-1} lw) or females with one child (476 ng g^{-1} lw). None of the participants reported a personal or familial history with thyroid problems.

3.2. Thyroid hormone and thyroid antibody levels

The levels of thyroid hormones and thyroid antibodies in the population are presented in Table 3. The thyroid hormone levels were predominantly within normal ranges (Quinn et al., 2009), but the TT4 and TT3 levels in the DBDPE manufacturing workers were higher than those in the non-occupational exposure residents (Table 3). The bodily burden of DBDPE in males is comparable with that in females, but most of thyroid hormone levels (including TSH, TT3, FT4, and FT3) were significantly different (Supplementary Table S2). Although no statistical significance was observed, the DBDPE manufacturing workers presented a higher prevalence of positive TPO antibodies than non-occupational exposure residents (9.77% vs 4.14%, $T = 3.82$, $p = .052$). The prevalence of positive thyroid antibodies in females was higher

Table 3
Concentrations of DBDPE and levels of thyroid hormones and thyroid antibodies in serum.

	All adults (n = 302)	DBDPE occupationally exposed workers (n = 133)	Non-DBDPE occupationally exposed residents (n = 169)	t-Test[b]
	Mean (SE)[a]	Mean (SE)[a]	Mean (SE)[a]	T
TSH (μIU mL^{-1})	1.76 (0.05)	1.85 (0.07)	1.70 (0.06)	1.61
tT4 (nmol L^{-1})	99.9 (0.98)	108 (1.28)	93.4 (1.30)	8.01**
tT3 (nmol L^{-1})	1.93 (0.02)	2.01 (0.02)	1.87 (0.02)	4.08**
fT4 (pmol L^{-1})	16.7 (0.11)	17.0 (0.15)	16.5 (0.16)	1.85
fT3 (pmol L^{-1})	5.53 (0.04)	5.38 (0.06)	5.33 (0.05)	0.680
TG-Ab abnormal[c] No./Total (%)	11/302 (3.64%)[d]	6/133 (4.51%)[d]	5/169 (2.96%)[d]	0.511[e]
TPO-Ab abnormal[c] No./Total (%)	20/302 (6.62%)[d]	13/133 (9.77%)[d]	7/169 (4.14%)[d]	3.82[e]

** $p < .01$.
[a] Geometric mean value is for TSH, and arithmetic mean values are for tT4, fT4, tT3, and fT3. SE means standard error.
[b] t-Test was used to identify difference between two groups. The value of TSH was $\log_{10}$ changed to a normal distribution.
[c] Participants with value > 115 IU mL^{-1} and > 34 IU mL^{-1} were considered as TG-Ab and TPO-Ab positive, respectively.
[d] The value shows No./Total (%) for thyroid antibodies.
[e] The value was from Chi-square test.

than that in males (Supplementary Table S2).

3.3. Associations between the serum DBDPE concentration and thyroid hormone levels

The DBDPE concentration was significantly and positively associated with several thyroid hormones, including TT4 and TT3, despite a small coefficient of determination (R^2) (Table 4). A 10-fold increase in the serum DBDPE concentration was associated with an elevated TT4 level (4.73 nmol L^{-1}) [95% confidence interval (CI): 2.75–6.71], corresponding to an increase of 4.73% (95% CI: 2.75%–6.71%). Additionally, a 10-fold increase in the serum DBDPE concentration was associated with an elevated TT3 level (0.046 nmol L^{-1}) [95% CI: 0.012–0.081], corresponding to an increase of approximately 2.38% (95% CI: 0.62%–4.20%). We also found positive associations between the DBDPE concentration and thyroid antibodies.

The associations between DBDPE and thyroid hormones in males were similar with those in the collective population of adults, but some associations changed in females (Table S3). In females, the association between DBDPE exposure and the TT4 increase seemed stronger as a 10-fold increase in DBDPE concentration was associated with a TT4 increase of 6.76%. A 10-fold increase in DBDPE concentration was also associated with a 2.41% higher concentrations of FT4 (β = 0.402 pmol L^{-1}). However, a significant association between DBDPE and TT3 was found in males but not in females.

All models adjusted for genders, age, BMI, length of employment at the factory, education, smoking status, alcohol consumption, and seafood intake. p-Value for trend was obtained by using the median value in each quartile as a continuous variable in the linear regression models. Quarter DBDPE quarters (ng g^{-1} lw) were defined as follows: DBDPE, 3.15–27.9 (n = 75), 27.9–235 (n = 76), 236–3330 (n = 75), > 3330 (n = 76). The participants that had detectable and normal TG-Ab or TPO-Ab were included.

Fig. 1 shows the dose-response models for quartiles of DBDPE. We observed a significant linear trend between the quartiles of DBDPE and TT3 (p trend = 0.009). A significant linear trend was also observed with DBDPE and TT4 (p trend < 0.001); however, the pattern suggests a nonmonotonic relationship with FT4, which was not significantly associated in the continuous analysis but was significantly positively associated with the DBDPE quartiles (p trend = 0.049). FT3 was not significantly correlated in the continuous analysis, but the highest DBDPE quartile presented a trend of elevated free T3 (p trend = 0.436). On the other hand, TSH was not significantly associated with DBDPE in the ordinal dose-response models (p trend = 0.407). We also saw strong dose response models for TPO antibodies (p trend < 0.001) and TG antibodies (p trend = 0.011), especially higher level DBDPE quartiles.

4. Discussion

This is the first report indicating that exposure to DBDPE is associated with thyroid hormone levels in humans. We found that serum DBDPE concentrations were associated with increased serum levels of total T4 and T3 in adults from a DBDPE manufacturing area in China. A 10-fold increase in serum DBDPE concentration was associated with a 4.73 nmol L^{-1} increase in TT4 and a 0.046 nmol L^{-1} in TT3, corresponding to increases of 4.73% and 2.38%, respectively.

Table 4
Multiple linear regression models of thyroid hormone levels with serum DBDPE concentrations[a].

	Number	DBDPE (ng g^{-1} lw)		DBDPE (ng g^{-1} lw)	
		Unadjusted β (95% CI)	R^2	Adjusted β (95% CI)[b]	R^2
Log_{10} TSH (μIU mL^{-1})	302	0.009 (−0.012, 0.029)	0.002	0.009 (−0.015, 0.032)	0.077
TT4 (nmol L^{-1})	302	5.19 (3.50, 6.89)**	0.108	4.73 (2.75, 6.71)**	0.149
TT3 (nmol L^{-1})	302	0.051 (0.020, 0.081)**	0.035	0.046 (0.012, 0.081)**	0.145
FT4 (pmol L^{-1})	302	0.212 (0.011, 0.412)*	0.014	0.179 (−0.036, 0.394)	0.211
FT3 (pmol L^{-1})	302	0.036 (−0.030, 0.103)	0.004	0.029 (−0.035, 0.092)	0.353
Log_{10} TG-Ab	241	0.029 (0.009, 0.050)**	0.033	0.031 (0.008, 0.054)**	0.115
Log_{10} TPO-Ab	282	0.044 (0.027, 0.061)**	0.086	0.038 (0.019, 0.058)**	0.135

* $p < .05$.
** $p < .01$.
[a] The concentration of DBDPE was $\log_{10}$ transformed.
[b] All models were adjusted for genders, age, BMI, length of employment at the factory, education, smoking status, alcohol consumption, and seafood intake.

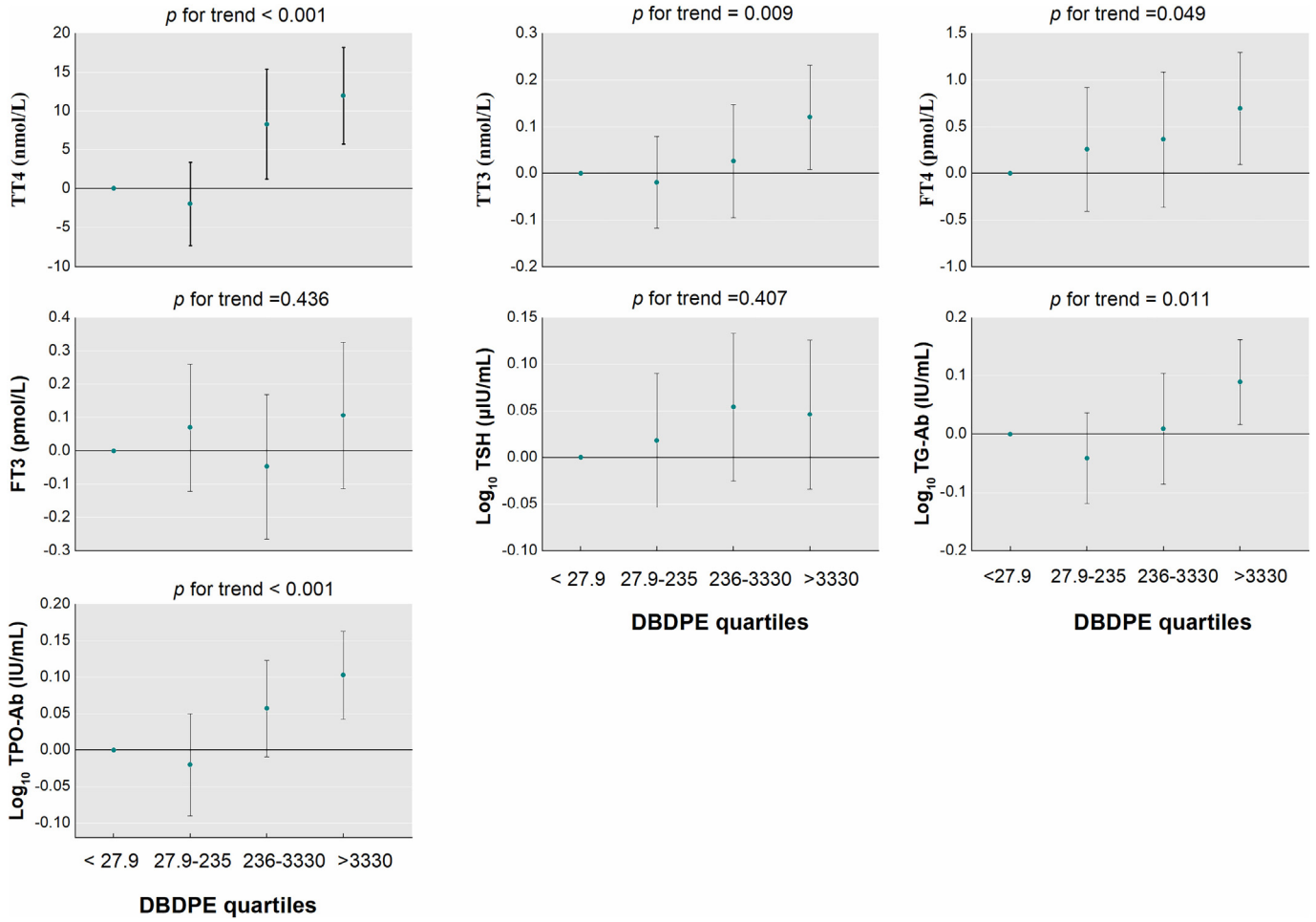

Fig. 1. β-Coefficient and 95% confidence intervals (Cis) for regression models for association of individual DBDPE quarters with thyroid hormones and thyroid antibodies.

It was not surprising that the results showed DBDPE manufacturing workers had extremely high levels of bodily burden from DBDPE, which was at levels > 50-fold higher than those in e-waste workers from e-waste recycle areas in Southeastern China (Liang et al., 2016). The environmental matrix can be contaminated by chemical production. Therefore, residents living in DBDPE production areas have a higher level of DBDPE than the general population from other areas in China (Zhu et al., 2009). The bodily burden of DBDPE in these residents was comparable with that from the e-waste contaminated area located in Guangzhou, China (Qiao et al., 2018). In a review of the currently available data on the DBDPE levels in indoor dust, Hsu et al. (2018) observed that the DBDPE levels in indoor samples in China, even influenced by human activities and geographical distribution, were higher than those in other countries. DBDPE has become the dominant BFR in China, suggesting that DBDPE has been used and released in large quantities in China. Furthermore, the contamination levels of DBDPE in other Asian countries (Khan et al., 2016), the U.S. (Brown et al., 2014; Schreder and La Guardia, 2014) and Europe (Kuang et al., 2016) also show an increasing trend in indoor dust. We hypothesize that the increasing pool of DBDPE-treated consumer items will continue to cause increasing concentrations of DBDPE in environmental metrics and the human body.

To our knowledge, an epidemiological study on the effects of DBDPE on thyroid hormone in humans has not been performed. Limited laboratory animal studies have reported that DBDPE could disturb thyroid hormones homeostasis, but the results were inconsistent. A rat model showed that oral DBDPE exposure at 100 mg kg^{-1} bw day^{-1} significantly increased the level of TT3 in rats after a 90-day exposure (F. Wang et al., 2010; J. Wang et al., 2010), which was consistent with our human study. However, Sun et al. reported that 200 mg kg^{-1} bw day^{-1} exposure of DBDPE significantly decreased TT3 and FT3 and increased TSH in mice after a 30-day oral exposure, which might have been be caused by the induction of metabolizing enzymes, including phase I cytochrome P450 monooxygenase (CYP) enzymes and phase II conjugation enzymes [e.g., uridine diphosphate-glucuronosyltransferase (UDPGT)] (Sun et al., 2014; Sun et al., 2018). Our team also explored the thyroid disruption induced by DBDPE in rats (Wang et al., 2019). However, we found that the direction of thyroid hormone disruption caused by DBDPE in rats was opposite to that observed in this study in adults from DBDPE manufacturing areas. In our rat study, significantly decreased FT3 and increased TSH were observed in the high dosage group (500 mg kg^{-1} bw day^{-1} orally exposed to DBDPE). Decreased, but not significantly, TT4, TT3, and FT4 levels in serum were also observed in DBDPE exposure rats. This phenomenon of conflicting reports between studies had also been observed in PBDE studies (Dallaire et al., 2009; Makey et al., 2016; Turyk et al., 2008), but the mechanism is still unclear. According to the study by Zhao et al., the relationships among PBDEs and thyroid hormones follow U-shaped patterns, suggesting that dosage is an important parameter that affects the direction of correlations. In the dose-response model (Fig. 1), the patterns of TT4, FT3 and TSH might suggest a nonmonotonic relationship. The conflicting reports between human studies and animal studies might stem from physiological differences across species, such as differences in serum transporters (e.g., the dominant binding protein

in rats is transthyretin but in humans it is thyroid binding globulin) and the percentage of T3 production by the thyroid gland (rats vs. humans: 40% vs. 20%). Because the present study was only a cross-sectional study that reported the associations between thyroid hormone levels and DBDPE concentrations, more epidemiologic studies, especially of certain cohorts, are needed to clarify the causal relations and dose-effect relations.

The potential mechanisms of thyroid hormone disruption by DBDPE exposure have been explored in literature. As the liver is the major target organ of DBDPE for accumulation and metabolism, DBDPE could cause an increase in hepatic detoxification enzyme activity, including CYPs and UDPGT, leading to metabolism of DBDPE and increased glucuronidation of T4 (Sun et al., 2014; Sun et al., 2018). Another potential mechanism of thyroid hormone disruption by DBDPE exposure could be through interference with deiodinase activity. One study showed that DBDPE exposure could cause strong inhibition of both outer and inner ring deiodination in human in vitro liver microsomes (Smythe et al., 2017).

Our study found that the prevalence of positive TPO antibodies in DBDPE manufacturing workers was higher than that in non-occupational exposure residents (9.77% vs 4.14%, $p = .052$). Females tended to have a higher prevalence of positive TG-Ab and TPO-Ab than males (7.62% vs 1.52%, $p = .009$; 10.5% vs 4.57%, $p = .049$, respectively). However, we could not conclude that females were more likely to contract thyroid autoimmune disease after DBDPE exposure than males because the prevalence of thyroid autoimmune disease was higher in women than in men over the whole population (Quinn et al., 2009). We found strong dose response relationships between DBDPE and TPO antibodies (p trend < 0.001) and TG antibodies (p trend $= 0.011$), which suggested that DBDPE exposure might cause damage to the thyroid gland. In our previous animal study, exposure to DBDPE caused significant changes in the histological structure and ultrastructure of the thyroid gland in rats (Wang et al., 2019). Although there is no other evidence supporting DBDPE triggering human thyroid autoimmune disease, several human studies have indicated that some other POPs, such as PBDEs, which have a similar structure to DBDPE, are associated with increased thyroid antibodies (Freire et al., 2013; Turyk et al., 2008).

Because of the similar structure to BDE-209, some studies have suggested that DBDPE might present a similar toxicity as BDE-209 (McKinney et al., 2011; Sun et al., 2018). In our previous study that studied thyroid function disruption by BDE-209 in occupational workers, we observed that a 10-fold increase in BDE-209 was associated with an increase in TT4 (8.63 nmol L^{-1}) and TT3 (0.106 nmol L^{-1}), corresponding to increases of 7.8% and 5.4%, respectively (Chen et al., 2018). The directions of the associations between DBDPE and thyroid hormones in this study were similar with those observed in the BDE-209 study, but the effects of the associations were much weaker: a 10-fold increase in DBDPE was associated with elevated TT4 (4.73 nmol L^{-1}) and TT3 (0.046 nmol L^{-1}) levels, corresponding to a 4.73% and 2.38% increase, respectively. This result was also consistent with our animal study, which showed that DBDPE induced less thyrotoxicosis than BDE-209 in rats (Wang et al., 2019). However, some studies have also reported that metabolic mechanisms and biological responses were different between DBDPE and BDE-209 (F. Wang et al., 2010; J. Wang et al., 2010; Zheng et al., 2014). Although DBDPE showed less bioaccumulation and lower maternal transfer ratios than BDE-209 (Feng et al., 2013), DBDPE was highly resistant to metabolism in the biota (Zheng et al., 2014). In a study by Zheng et al. (2014), hens and paired eggs from an electronic waste recycling area in Southern China were collected and tested, and research showed that DBDPE was difficult to metabolize by hens but could be easily transferred from hen to eggs. Thus, more attention should be paid to the selective accumulation and biotransformation of DBDPE in the early development stage of life, which might increase the exposure risk to new life.

5. Conclusion

Our results demonstrated that exposure to DBDPE was associated with changes in thyroid activity in adults with high DBDPE exposure. However, the changes in the thyroid hormone concentrations were in the subclinical range, and the potential impact is unclear. Furthermore, there was evidence to suggest a relationship between DBDPE and thyroid hormone antibodies in human blood. The levels of DBDPE in human serum were much higher in occupationally exposed workers and residents in DBDPE contaminated areas than in the general population in other regions in China. This study provided new evidence of a possible adverse effect on thyroid function caused by long term exposure to DBDPE in humans. More attention should be paid to this emerging contaminant, which might be a new endocrine disrupter.

Declaration of competing interest

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.2019.105179.

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