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

Tian Chen[a], Dong Yu[b], Luping Yang[c], Shaofeng Sui[c], Shibo Lv[c], Yi Bai[a], Wen Sun[c], Yuwei Wang[a], Li Chen[a], Zhiwei Sun[a], Lin Tian[a], Dejun Wang[c,*], Piye Niu[a,*], Zhixiong Shi[a,*]

[a] S fP bi H a a B iji K Lab /a / fE i/ a T i , Ca ia M ia U i /si , B iji 100069, C i a
[b] S a A a fO ai a H a a' O ai a M ii , Ji a 250062, S a , C i a
[c] S a C /f /Dis as C / a P/ i , Ji a 250014, S a , C i a

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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

Corresponding authors at: Shandong Center for Disease Control and Prevention, Jinan 250014, Shandong, China (D. Wang). School of Public Health, Capital Medical University, Beijing 100069, China (P. Niu and Z. Shi).
E- ai a /ss s: wdjsd@126.com (D. Wang), niupiye@ccmu.edu.cn (P. Niu), szx0127@ccmu.edu.cn (Z. Shi).

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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

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 ℃ 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. S / DBDPE a a sis

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).

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 (< .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 (> .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}, = 11) or TPO-Ab (> 34 IU mL^{-1}, = 23). 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 (= 75); 27.9–235 (= 76); 236–3330 (= 75); > 3330 (= 76). All tests of statistical significance were two-sided, and < .05 was considered significant. Statistical analyses were performed using SPSS software version 23 (IBM Inc., Chicago, IL, USA).

3. Results

3.1. DBDPE /a i

The basic sociodemographic characteristics of the population and DBDPE concentrations are shown in Table 2DBand anfromevels. Theanto.3(23nd

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

	All adults (= 302)	DBDPE occupationally exposed workers (= 133)	Non-DBDPE occupationally exposed residents (= 169)	-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]

< .01.
[a] Geometric mean value is for TSH, and arithmetic mean values are for tT4, fT4, tT3, and fT3. SE means standard error.
[b] -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. A ia i b / DBDPE /a i a / i

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. -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 (= 75), 27.9–235 (= 76), 236–3330 (= 75), > 3330 (= 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 (trend = 0.009). A significant linear trend was also observed with DBDPE and TT4 (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 (trend = 0.049). FT3 was not significantly correlated in the continuous analysis, but the highest DBDPE quartile presented a trend of elevated free T3 (trend = 0.436). On the other hand, TSH was not significantly associated with DBDPE in the ordinal dose-response models (trend = 0.407). We also saw strong dose response models for TPO antibodies (trend < 0.001) and TG antibodies (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

< .05.
< .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.

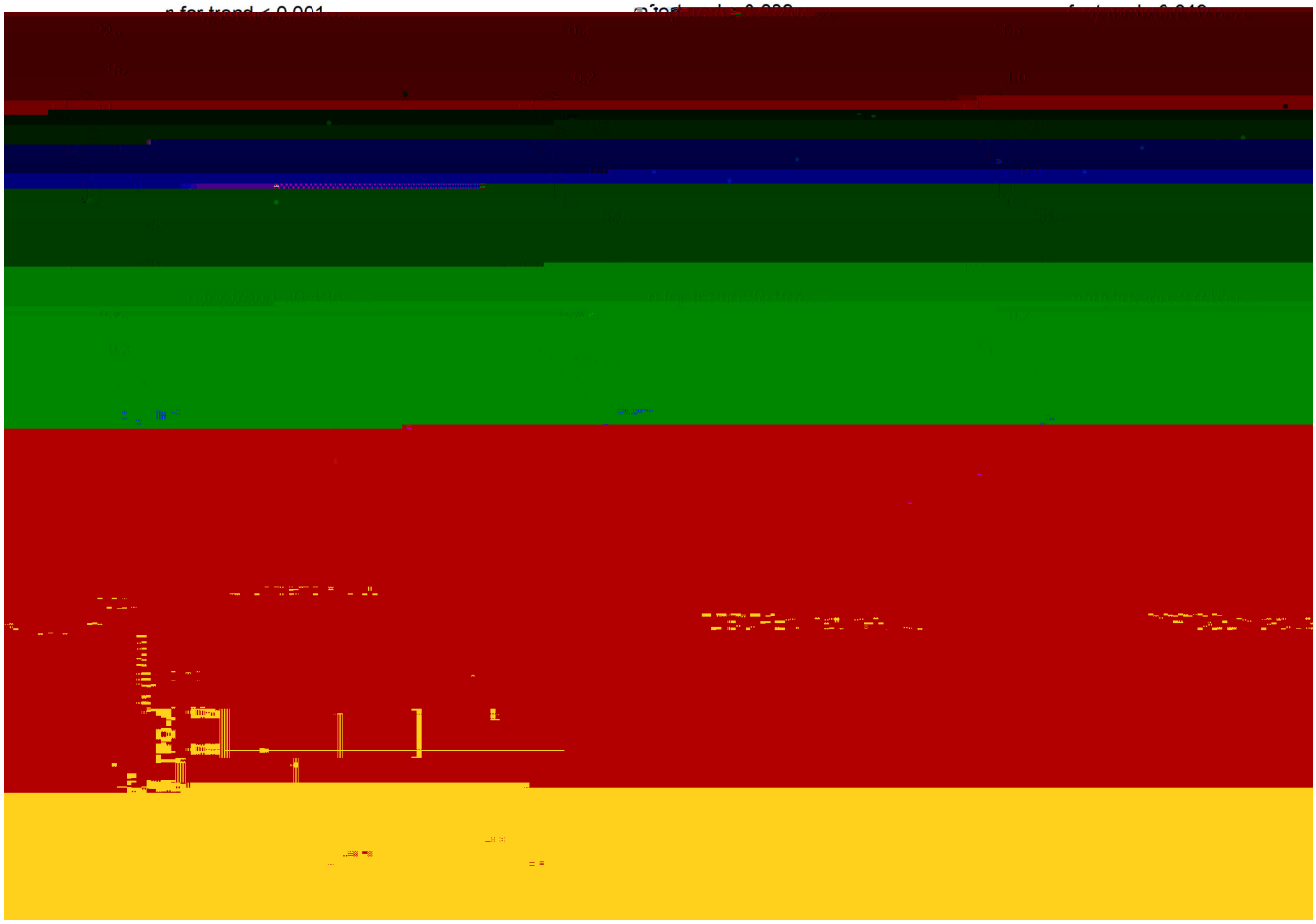

Fig. 1. β-Coefficient and 95% confidence intervals (Cis) for regression models for association of individual DBDPE quarters with thyroid hormones and thyroid antibodies.

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%, = .052). Females tended

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