Original Article

The potential association of polybrominated diphenyl ether concentrations in serum to thyroid function in patients with abnormal thyroids: a pilot study

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Background: To explore possible associations between polybrominated diphenyl ether (PBDE) exposure and patients with abnormal thyroid hormone levels whose thyroid function parameters are above normal ranges.

Methods: The serum of 40 patients with thyroid hormone abnormalities was collected in Kunming. triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were detected in serum using chemiluminescence. The PBDE homologs in the patients' serum were quantitatively analyzed by gas chromatography-mass spectrometry. If the detection frequency of the compound exceeded 50%, it was included in the analysis. Spearman's rank correlation coefficient and multiple linear regression were used to evaluate the correlation between PBDE homologs and five thyroid function parameters.

Results: A total of 33 PBDE homologs were detected, 7 of which had a more than 50% detection rate. BDE-47 was the main homolog detected. Spearman's correlation showed that no relationship was found between PBDE homologs and thyroid hormones. Multiple linear regression showed that BDE-153 was positively correlated with T4, negatively correlated with T3, while BDE-47 was negatively correlated with FT4 ($P<0.05$). The correlation between other PBDE homologs and thyroid function parameters was weak ($P>0.05$). The β coefficient showed that the increase in the logarithmic unit of $\sum_7$PBDEs was related to an increase in FT4 and T4 levels and decreased TSH, T3, and FT3 levels.

Conclusions: There is a significant correlation between exposure to PBDE and thyroid dysfunction. The increase of total PBDEs was significantly correlated with the increase of FT4 and T4 levels and decreased TSH, T3, and FT3 levels.

Keywords: Polybrominated diphenyl ethers (PBDEs); thyroid-stimulating hormone (TSH); free triiodothyronine (FT3); free thyroxine (FT4); thyroid dysfunction

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Introduction

Polybrominated diphenyl ethers (PBDEs) are a group of flame retardant chemicals that have been widely used in consumer products such as home electronics (televisions, computers), textiles (carpeting, drapery), and furniture to ensure they meet fire safety standards (1). PBDEs have three commercial formulations: a mixture of congeners, c-pentaBDE, c-octaBDE, and c-decaBDE in this study (2).

PBDEs have been widely used worldwide, but they are lipophilic, persist in the environment, bio-accumulate in wildlife, and have been reported in human serum, breast milk, hair, and tissue (2-7). Over recent years, many studies on human exposure to PBDEs have originated from North America and Europe (8-15). Several studies on PBDEs in human serum from China have mostly focused on key cities such as Shanghai, Hangzhou, and Dalian (16-20). Previous studies using experimental animals have concluded that PBDEs may have a wide range of adverse health effects, including interfering with metabolic processes, sexual dimorphism, and interference with the function of thyroid hormones (21-25). The associations between PBDEs and thyroid function have also been widely reported in animals, and these findings have raised more concerns about the influence of human exposure to PBDEs. At present, although the associations between PBDEs and thyroid function has been partially verified in animal experiments (23,24), large-scale population studies still lack. This study is based on the population to explore the relationship between the two.

The thyroid regulates basic metabolism and growth, especially in the healthy brain development of young children. Five parameters are used to examine the level of thyroid function: triiodothyronine (T3), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and thyroxine (T4). For example, TSH and T4 would influence language ability, memory, and executive processing skills (26). Due to the structural similarities between PBDEs and the two major thyroid hormones, T4 and T3, some concerns have been expressed about PBDEs potentially interfering with thyroid function (27). The pituitary gland produces TSH in response to low T4 levels, which stimulates the thyroid to secrete more T4. A previous study by (13) demonstrated that PBDEs may disrupt this action and that TSH can be down-regulated when T4 levels are high. In addition to interfering with thyroid hormone transport, it was suggested that PDBEs might bind to transthyretin, leading to decreased FT4 concentrations in serum (28). However, epidemiological evidence is presently unclear, with studies showing positive, negative, and no associations between PBDE exposure and thyroid function (28-33).

Previous studies have demonstrated that PBDEs cause a decrease in both T4 levels and the metabolically active unbound free form of T4 and an increase in rat, mouse, or rodent TSH levels (22,34-36). Some studies have also shown that PBDE exposure in humans was associated with changes to thyroid hormone concentrations in adults, pregnant women, and young children (26,28,29,37-39). Makey *et al.* [2016] concluded that a significant decrease in T4 levels occurred alongside an increase in BDE-47 exposure (28). Stapleton *et al.* (31) reported a positive association between PBDE exposure and T4 and FT4 levels in women after 34 weeks of gestation. However, limited studies on the association between PBDEs and thyroid function have been carried out in China. Only two studies have been reported by Liu *et al.* and Zheng *et al.* (40,41). Liu *et al.* investigated the association of PBDEs in serum with thyroid function in thyroid cancer patients (41), and suggested that OH-PBDEs and PBDEs would result in reduced levels of FT4 and elevated TSH concentrations. Zheng *et al.* (40) collected serum samples from e-waste workers to observe any associations with PBDE concentrations and thyroid function. They concluded that T3 and T4 were significantly and positively correlated with low PBDE concentrations, including BDE-47, BDE-66, and BDE-85.

This study aimed to examine possible associations between PBDE exposure and patients with abnormal thyroid hormone levels whose thyroid function parameters were above normal ranges. The data could then be explored to investigate the profile of PBDE congeners in patients' serum and to discuss any correlations between PBDE congeners and five thyroid hormone parameters, including T4, T3, FT4, FT3 and TSH.

Located in the Southwest of China, Kunming, was selected as the study city. It borders Guangxi, Guizhou, and Sichuan Provinces, and Vietnam, Laos, and Myanmar. Yunnan is one of China's major production bases of copper, lead, zinc, tin, and aluminum. The main reason for this is the long-term cable production history of Kunming. Kunming Cable Group Co., Ltd., built-in 1936, is the first wire and cable manufacturer in China and is the birthplace of China's first wire (Kunming Cable Group Co., Ltd.). There are also commercial PBDE products manufactured in Kunming to added to cables. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1697).

Methods

Sampling

In this study, 40 serum samples were collected from patients at the Disease Control Centre in Kunming who suffered from abnormal thyroid hormone levels. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Kunming Center for Disease Control and Prevention and informed consent was obtained from all volunteers. Concerning thyroid hormone parameters, there are normal ranges for healthy people as defined by the hospital. Any one of the parameters found outside of these normal ranges indicates the patient would be assessed as having abnormal thyroid function. For example, if FT3 and FT4 increased, clinical symptoms would manifest as hyperthyroidism, and conversely, FT3 and FT4 are decreased when hypothyroidism is diagnosed. Increased TSH levels can be seen in patients with primary hypothyroidism, and T3 and T4 are the specific diagnostic indicators of chronic lymphatic thyroiditis. All volunteers included in this study had these five thyroid hormone parameters measured at the hospital and two or three factors outside normal ranges. Thyroid hormone levels were measured by the Kunming Municipal Hospital of Traditional Chinese Medicine's Chemiluminescence Enzyme Immunoassay. Five thyroid parameters, including T3, T4, FT3, FT4, and TSH, were recorded. The normal range of T3 is 1.34–2.73 nmol/L, T4 is 78.4–157.4 nmol/L, FT3 is 2.77–6.31 pmol/L, FT4 is 10.44–24.38 pmol/L, and TSH is 0.34–5.6 mIU/L. Forty human serum samples were collected, 28 from female patients with an age range of 16 to 83, and 12 samples from males ranging from 19 to 82. The samples had reported ranges for T3, T4, FT3, FT4, and TSH of 1.3–16.99 nmol/L, 78–353.4 nmol/L, 0.691–37.72 pmol/L, 10.812–74.266 pmol/L, and 0.005–5.641 mIU/L, respectively. The distribution of characteristics is shown in *Table 1*. Supporting materials include some basic information about the volunteers and their clinical diagnoses.

All blood samples were collected from the participants at the Disease Control and Prevention Centre of Kunming in July 2016. All patients included in this study were informed as volunteers and gave written consent. These samples were collected on the same date, in the same clinical room, and used the same preservation method. Fasting blood was required, and 5 mL of blood from the cubital vein was collected into a sterile serum tube without anticoagulants, and the serum was separated by centrifugation at 4,000 rpm for 5 min using a high-speed centrifuge (Thermo Fisher Scientific, Waltham, MA), then transferred to a new tube. All the serum samples were kept at –20 ℃ until further analysis. A questionnaire for each volunteer was completed, including gender, age, family history of thyroid function, other diseases, height, and weight. The details are listed in the supporting information.

Standards

A standard mixture of 39 PBDEs (including BDEs 7, 11, 8, 12, 15, 32, 30, 17, 25, 33, 28, 35, 37, 75, 49, 47, 66, 100, 119, 99, 116, 118, 155, 85, 126, 154, 153, 138, 166, 183, 181, 190) and BDE-209 were produced by AccuStandard, Inc. (New Haven, CT, USA). The ^{13}C labeled PCB-208, ^{13}C-PCB-141 and ^{13}C-BDE-77 were purchased from Cambridge Isotope Laboratories (Andover, MA, USA) as recovery standards and internal standards, respectively.

Acetone, dichloromethane (DCM), and N-hexane were obtained from Fisher Chemical (MA, USA). Anhydrous sodium sulfate, which was baked at 660 ℃ for 6 hours, was sourced from Puhui Chemical Co., Ltd., Hangzhou, China). Silica gel and alumina were activated at 550 ℃ for 6 hours and 660 ℃ for 6 hours, respectively.

Sample extraction

^{13}C-BDE-77 and ^{13}C-PCB-141 were added to a 1 mL serum sample in a 15 mL centrifuge tube that had been cleaned with acetone and hexane. Samples were placed in an ultrasonic bath for 10 minutes and allowed to equilibrate overnight. After equilibrium, 2 mL of formic acid and acetonitrile (2:1, v/v) and 5 mL of ultra-pure water were placed in an ultrasonic bath for 10 minutes to achieve denaturation and dilution. The samples were extracted using an Oasis HLB cartridge. Before extraction, the cartridge was cleaned with 3 mL of DCM and conditioned with 3 mL of MeOH and 3 mL of ultra-pure water. The samples were then eluted with 4 mL of isopropanol and water (1:19, v/v); 200 μL of sulfuric acid was added to remove lipids and other contaminants and diluted with ultra-pure water until the pH value of the solution was neutral. This was further cleaned using 2 mL of MeOH and water (9:1, v/v). The cartridge was then dried. After being dried, the cartridge was eluted with 4mL of DCM to collect the target compounds. After N_2 reduction, the extract was transferred to 100μL of hexane. The standard internal

Table 1 Basic characteristics of the 40 volunteers

Characteristics	Number
Sex	
Female	28 (70%)
Male	12 (30%)
Age (years)	
<20	4 (10%)
20–39	16 (40%)
40–59	9 (23%)
60–85	11 (27%)
BMI (kg/m^2)	
Normal weight (<24)	17 (42%)
Overweight or obese (≥24)	23 (58%)
Thyroid hormone parameters	
T3 NR: 1.34–2.73 nmol/L	In the NR: 21 (52%)
	Not in the NR: 19 (48%)
T4 NR: 78.4–157.4 nmol/L	In the NR: 12 (30%)
	Not in the NR: 28 (70%)
FT3 NR: 2.77–6.31 pmol/L	In the NR: 20 (50%)
	Not in the NR: 20 (50%)
FT4 NR: 10.44–24.38 pmol/L	In the NR: 24 (60%)
	Not in the NR: 16 (40%)
TSH NR: 0.34–5.6 mIU/L	In the NR: 22 (55%)
	Not in the NR: 18 (45%)

NR, normal range; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

^{13}C-PCB-208 was added, and quantification was carried out using gas chromatography-mass spectrometry (GC-MS). The samples were all prepared and analyzed at the Institute of Urban Environment, Chinese Academy of Sciences, Xiamen, China.

Specific analysis

The samples were analyzed with an Agilent 7890A gas chromatograph with negative chemical ionization using the selected ion monitoring (SIM) mode. BDE-209 was quantified using 486.6 and 488.6 m/z, while ^{13}C-PCB-141 was monitored through 371.9 and 373.9 m/z, ^{13}C-PCB-208 was monitored through 473.8 and 475.8 m/z, and ^{13}C-BDE-77 was monitored through 471.8 and 473.8 m/z. Bromide ions of 79 and 81 m/z quantified the other congeners. Helium (purity >99.999%) was used as the carrier gas at a flow rate of 1 mL/min, and methane (purity >99.99%) was used as a chemical ionization moderating gas. Gas chromatography was performed on a DB-XLB 15 m × 250 μm × 0.1 m with the following oven program: from 110 ℃ held for 0.5 min to 200 ℃ at 60 ℃/min, then to 280 ℃ at 5 ℃/min (held for 0.5 min), and to 310 ℃ at 60 ℃/min (held for 8 min). The total operation time was 28 minutes.

Quality assurance/control

PBDE measurements below the Method detect limit MDL were assigned a value of MDL/2. Statistical analysis was implemented when detection frequencies of compounds were over 50%. Quality control was performed by regular analysis of procedural blanks, random injection of standards, and solvent blanks. The average recovery of target compounds was above 90%, with a relative standard deviation of 0.56–8.57%. No PBDEs were detected in the procedure or instrument blanks. The limit of detection (LOD) was defined as three times signal to noise, and the limit of quantification (LOQ) was defined as ten times signal to noise. The limits of LODs from low PBDE congeners ranged from 0.002–0.016 ng/mL.

Statistical analyses

The normality test (Shapiro-Wilk test) and Student's *t*-test were both utilized. If the data showed normal logarithmic distribution, the data was log transformed before being analyzed. Spearman's test was used to evaluate the correlation between parameters and total PBDEs. Multiple linear regressions were conducted to explore the associations between PBDE concentrations and thyroid hormone levels after adjusting for known socio-demographic characteristics, such as age, sex, body mass index (BMI), lipids, etc. Statistical analyses were carried out using the SPSS Statistics 23.0 software (IBM Co., Armonk, NY, USA). The levels of significance were $P<0.05$.

Results

Sociodemographic characteristics of the participants

Table 1 presents the sociodemographic characteristics of

the 40 participants. The study population consisted of 28 females and 12 males classified by four age groups; 42% of the participants had a lower BMI (<24 kg/m^2). Five thyroid hormone parameters were measured for each participant, then classified separately into two groups, those within the normal range or over it.

Total PBDE concentrations in human serum

The concentration of PBDEs was expressed using the wet weight basis (ng/mL serum) and adjusted to a lipid weight basis (ng/g lipid), with a lipid weight basis being used for subsequent analysis. In the same hospital, total cholesterol (CHOL) and triglycerides (TG) were determined enzymatically in a separate aliquot of serum along with the thyroid hormone parameters. Total lipids (TL) were calculated by the following formula: TL (g/L) =2.27 × CHOL + TG + 62.3 (26).

In this study, 33 PBDE congeners were detected, but only those with detection frequencies over 50% will be discussed. BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, and BDE-183 were detected in approximately 79%, 100%, 98%, 83%, 65%, 89%, and 82% levels, respectively. *Table 2* and *Figure 1* contain serum and lipid-adjusted values, detection frequencies, ranges, median values and geometric mean (GM). $\sum_7$PBDE (including BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE154, and BDE183) concentrations ranged from 2.23–18.71 ng/g lipid, and the median value was 7.50 ng/g lipid. BDE-47 was found to have the highest median concentration in serum, with 3.63 ng/g lipid and a range of 0.56–11.01 ng/g lipid, followed by BDE-99, with the second-highest of 1.20 ng/g lipid. BDE-183 had 0.87 ng/g lipid and BDE-153 showed 0.55 ng/g lipid. For the profile of congeners measured in human serum, *Figure 2* shows the percentage contribution of each PBDE congener in the serum from the 40 samples. BDE-47 was the predominant serum congener and accounted for 43.04%, followed by BDE-99 and BDE-183 with 16.61% and 15.75%, respectively. The levels of thyroid function parameters from the 40 participants can be found in Table S1. Correlation between the PBDE concentration of 7 PBDE congeners and gender is shown in Figure S1. The results showed that there was no difference in the total PBDE concentration between males and females.

Spearman's correlation between total PBDE concentration and thyroid function parameters

Correlations between basic characteristics, the five thyroid function factors, and concentrations of $\sum_7$PBDE were evaluated using Spearman's test. *Table 3* shows correlations between PBDE concentration, age, BMI, lipid, and thyroid hormone parameters (T3, T4, FT3, FT4, and TSH) in 40 human serum samples. In this study, lipid contents positively correlated with each PBDE congener and $\sum_7$PBDE at the P<0.05 level, but not for the thyroid function parameters. BDE-28, BDE-47, BDE-99, BDE-100, and $\sum_7$PBDE were significant and positive correlated (r=0.2–0.8, P<0.01), whereas slightly weaker correlations were found with BDE-154 and BDE-153 (r=0.3, P<0.05). However, BDE-154 and BDE-153 were shown to positively correlate with each other (r=0.44, P<0.01). For the five thyroid function parameters, there were strong positive correlations among TSH, T4, T3, FT3, and FT4 (r=0.4–0.8, P<0.01), which could be explained by T3 being the more metabolically active hormone produced by T4. T4 is deiodinated by three deiodinase enzymes and produces the more active T3 (42). Nevertheless, no correlations were observed between concentrations of total PBDEs to age or BMI (P>0.05).

Correlation between PBDE and thyroid function parameters after log-transformation by multiple linear regressions

Based on Spearman's correlations in *Table 3*, no significant correlations were observed between PBDE congeners and thyroid hormones. To examine significant associations, multiple linear regressions were needed after adjusting for sociodemographic characteristics. Since T4, TSH, FT4, FT3, T3, and PBDE congener concentrations were not normally distributed, the data was log-transformed before regression analysis.

Table 4 shows the associations between the major PBDE congeners and the five thyroid function parameters analyzed by multiple linear regressions after log-transformation. The regression results suggest that BDE-153 had a significant positive correlation with T4 (P<0.05), and a negative correlation with T3 (P<0.05), while BDE-47 had a negative correlation with FT4 (P<0.05). However, other PBDE congeners had weak and non-statistical correlations with

Table 2 Statistical parameters of age, BMI, lipid, PBDEs, thyroid function parameters and lipid-adjusted PBDEs in 40 participants

Items	Minimum	Maximum	Median	GM	R (%)
Age (years)	1	83	40	40	
BMI (kg/m^2)	16.65	30.86	23.77	23.02	
Lipid (g/L)	5.5	12.5	9.05	8.62	
$\sum_7$PBDE concentration (ng/mL serum)					
BDE-28	nd	0.01	nd	nd	79
BDE-47	0.01	0.11	0.03	0.02	100
BDE-99	nd	0.03	nd	0.01	98
BDE-100	nd	0.03	nd	nd	83
BDE-154	nd	0.05	nd	nd	65
BDE-153	nd	0.04	nd	0.01	89
BDE-183	nd	0.04	0.01	0.01	82
$\sum_7$PBDE	0.02	0.17	0.06	0.06	100
Thyroid function					
TSH (mIU/L)	0.01	15.64	0.89	0.31	
T4 (ug/dL)	6.06	27.46	14.45	13.56	
FT4 (pg/mL)	8.32	57.13	16.12	19.54	
T3 (ng/mL)	0.84	11.03	1.65	1.95	
FT3 (pg/mL)	0.45	24.45	3.82	4.65	
$\sum_7$PBDE concentration lipid-adjusted (ng/g lipid)					
BDE-28	nd	0.86	0.28	0.23	79
BDE-47	0.562	11.01	3.63	2.77	100
BDE-99	nd	4.18	1.20	1.00	98
BDE-100	nd	3.14	0.25	0.27	83
BDE-154	nd	5	0.28	0.28	65
BDE-153	nd	4.72	0.55	0.58	89
BDE-183	nd	4.27	0.87	0.9	82
$\sum_7$PBDE	2.232	18.71	7.5	7.27	100

PBDE, polybrominated diphenyl ether; GM, geometric mean; R, detection frequency; nd, not detected; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

thyroid function parameters (P>0.05). The β-coefficients (beta coefficients) could be used and estimated to compare the trend of thyroid function indices. A log-unit increase in $\sum_7$PBDE was associated with an increase of FT4 and T4 and decreased TSH, T3, and FT3.

Discussion

Status of BDE-209 in human serum

In this study, BDE-209 was found to be lower than the LOD (0.1 ng/mL) in all human serum samples. This is

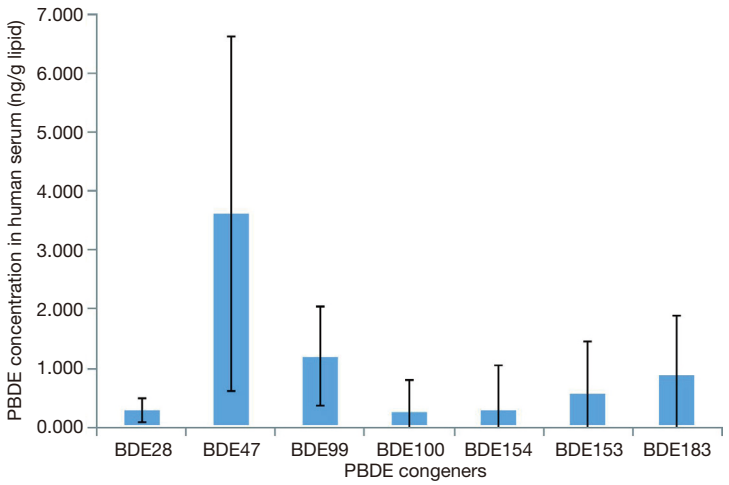

Figure 1 Concentration of 7 PBDE homologues in serum from the 40 volunteers. Error bars were calculated from the standard deviation of 40 serum samples. PBDE, polybrominated diphenyl ether.

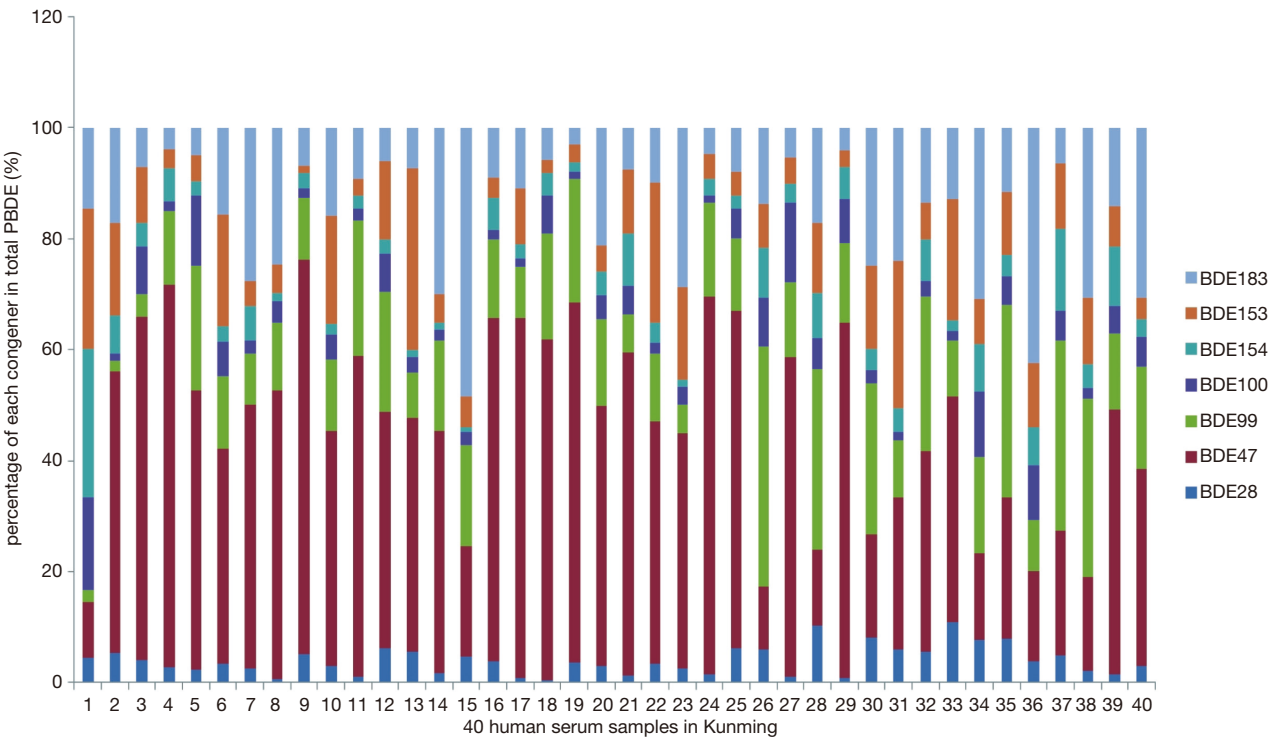

Figure 2 Percentage of each PBDE homologue in the 40 serum samples. PBDE, polybrominated diphenyl ether.

likely due to its short half-life of 15 days in humans (43), higher detection limits (44), and being less accumulated in nature because of its large molecular size and high octanol-water partition coefficient (45,46). The US Environmental Protection Agency suggests that BDE-209 has a rapid half-life of under 10 days in human serum (EPA/600/R-08/086F). The estimated half-life of BDE-47 averages 3 years, with a range of 1.9–4.2 years, and BDE-99 also has a long half-life of 5 years, with a range of 3.5–7.2 years (EPA/600/R-08/086F). However, BDE-209 is seen to have

Table 3 Spearman's correlations between PBDEs and thyroid function parameters in the 40 serum samples

Items	Age	TSH (mIU/L)	T4 (ug/dL)	FT4 (pg/mL)	T3 (ng/mL)	FT3 (pg/mL)	Lipid	BDE28	BDE47	BDE99	BDE100	BDE154	BDE153	BDE183	$\sum_7$PBDE
Age	1														
TSH (mIU/L)	0.05	1													
T4 (ug/dL)	−0.26	−0.474**	1												
FT4 (pg/mL)	−0.213	−0.692**	0.634**	1											
T3 (ng/mL)	−0.153	−0.467**	0.790**	0.577**	1										
FT3 (pg/mL)	−0.259	−0.630**	0.714**	0.890**	0.746**	1									
Lipid	−0.019	−0.045	−0.292	0.054	−0.183	−0.062	1								
BDE-28	0.08	0.049	−0.051	−0.168	−0.099	−0.156	0.226	1							
BDE-47	−0.059	−0.064	−0.032	0.001	0.104	0.013	0.191	0.437**	1						
BDE-99	−0.028	0.042	0.08	0.084	0.098	0.125	0.234	0.364**	0.399**	1					
BDE-100	0.006	0.039	−0.103	0.044	−0.12	0.039	0.357*	0.369**	0.221**	0.453**	1				
BDE-154	0.064	−0.1	0.064	0.096	−0.143	−0.024	0.489**	0.203*	0.306*	0.201*	0.154*	1			
BDE-153	−0.208	−0.135	0.167	0.103	0.109	0.064	0.339*	0.141*	0.286*	0.243*	0.156*	0.444**	1		
BDE-183	−0.145	−0.054	−0.042	−0.028	−0.097	−0.053	0.470**	0.855**	0.457**	0.568**	0.525**	0.462**	0.468**	1	
Total PBDE	−0.038	−0.083	−0.041	0.005	−0.112	−0.042	0.317*	0.496**	0.823**	0.501**	0.585**	0.781**	0.533**	0.645**	1
BMI	0.059	0.219	−0.053	−0.095	−0.164	−0.097	0.224	0.06	−0.189	−0.327*	−0.027	−0.053	−0.044	0.036	−0.147

**, presents Correlation is significant at the 0.01 level. *, presents Correlation is significant at the 0.05 level. PBDE, polybrominated diphenyl ether; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; BMI, body mass index.

Table 4 Multiple linear regressions with thyroid function parameters, individual PBDE congeners and total PBDE concentrations after log-transformation

β (95% CI)	logTSH β (95% CI)	logFT4 β (95% CI)	logT3 β (95% CI)	logFT3 β (95% CI)	logT4 β (95% CI)
log BDE-28	−0.11 (−0.29, 0.07)	0.69 (−0.42, 1.81)	−0.14 (−0.92, 0.63)	−0.43 (−1.24, 0.38)	−0.93 (−2.07, 0.20)
logBDE-47	−0.05 (−0.26, 0.16)	−0.37 (−1.69. 0.95)*	−0.23 (−1.14, 0.68)	0.01 (−0.96, 0.96)	0.56 (−0.78, 1.89)
logBDE-99	−0.05 (−0.20, 0.11)	0.47 (−0.50, 1.45)	0.29 (−0.38, 0.97)	−0.37 (−1.01, 0.34)	−0.50 (−1.49, 0.48)
logBDE-100	0.10 (−0.10, 0.30)	0.13 (−1.13, 1.34)	−0.05 (−0.92. 0.82)	0.35 (−0.56, 1.26)	−0.16 (−1.43, 1.11)
logBDE-153	−0.05 (−0.22, 0.13)	0.05 (−1.06, 1.16)	−0.97 (−1.74, −0.20)*	0.05 (−0.76, 0.85)	1.11 (−0.1, 2.23)*
logBDE-154	0.08 (−0.11, 0.28)	−0.10 (−1.32, 1.12)	−0.56 (−1.40, 0.29)	0.51 (−0.38, 1.4)	0.22 (−1.02, 1.46)
logBDE-183	−0.06 (−0.23, 0.11)	0.56 (−0.50, 1.62)	0.13 (−0.60, 0.86)	−0.71 (−1.49, 0.06)	0.47 (−0.60, 1.55)
log$\sum^{7}$PBDE	−0.04 (−0.16, 0.09)	−0.06 (−0.75, 0.88)	−0.17 (−0.74, 0.40)	−0.12 (−0.72, 0.48)	0.21 (−0.62, 1.04)

*, represents P<0.05. PBDE, polybrominated diphenyl ether.

an approximate half-life only of 15 days, with a range of 11–18 days in human blood (47,48). Thuresson *et al.* (47) suggested that the apparent half-lives of decaBDE to pentaBDE in serum increased in correlation to a decrease in the number of bromine substituents.

The results from this study are similar to those reported from other countries and previous studies from China (17,26,28,41,44). BDE-209 was either not detected in these studies, or even if it was measured, the levels were low (around 5 ng/g lipid). Also, these previous studies suggested that debromination and metabolism of highly brominated congeners to lower brominated congeners had occurred, resulting in increased concentrations of BDE-47, BDE-28, and BDE-99.

Previous studies have also shown that BDE-209 is the dominant congener in human serum, but these studies were conducted at production sites or e-waste processing areas (18,40,44,49,50). An explanation for this was provided by Zheng *et al.* (40), and was related to the high concentrations of BDE-209 detected in worker's serum, which was a result of the widespread application of commercial decaBDE mixtures from obsolete electronics in e-waste areas. Other studies conducted in China, such as at e-waste processing sites in Guiyu, China (50) and electrical appliance factories site in Wenzhou, China (18) have suggested that the BDE-209 measured in worker's serum was due to the high concentration of BDE-209 in air, lake or food samples, and to be continuously exposed to high levels of BDE-209.

Some human epidemiological studies have focused on the associations between the presence of higher brominated PBDEs and thyroid function (26,32,41,51). DecaBDE, which contains ten bromine atoms, is thought to have limited ability to bind non-covalently with thyroid hormone transport proteins compared to triBDE and pentaBDE congeners, which are more structurally similar to T3 and T4. In addition, Liu *et al.* (41) also suggested that the larger molecular mass and shape of decaBDE had difficulty interacting directly with the thyroid hormone receptors (41).

Comparisons of concentrations and congener profiles of total PBDEs in human serum from China and the rest of the world

The mean concentration of $\sum_{7}$PBDE across all samples in this present study was 7.5 ng/g lipid. This result was similar to those reported in blood samples in other cities in China, such as in Dalian, where 5.56 ng/g lipid was recorded (17), from thyroid papillary cancer patients in Dalian, with 4.46 ng/g lipid (41). While in Hong Kong, 5.36 ng/g lipid was seen (52), but much lower was evidenced in worker serum samples from electrical appliance factories in Liushi and Wenzhou, with 1.69 ng/mL serum (0.061 ng/g serum in the present study) (18). Serum samples from Laizhou Bay, which is one of the main brominated flame retardant (BFRs) production areas in China, 613 ng/g lipid (48), and from e-waste recycling workers in southern China, 724 ng/g lipid (40). Compared to other countries, the concentrations in human serum samples in the present study are lower than serum samples from the USA, which ranged from 22–40 ng/g lipid (28,44,53) but similar to the UK and European samples, which ranged from 2.4–5.6 ng/g lipid (54-57). However, the samples in the present study were from patients with abnormal thyroid hormone function, including groups

with hyperthyroidism and hypothyroidism, while the samples from other countries were from thyroid cancer patients or special e -waste workers.

In this study, BDE-47 comprised about 50% of the total serum concentration, followed by BDE-99 and BDE-153, with 16.61% and 15.75%, respectively. This result is similar to those of other countries, including the USA and European countries, and other studies conducted in China (17,18,44,57,58). The situation for BDE-209, with low detection rates or low concentrations being observed in several previous studies from different countries. It suggests that PBDE composition profiles in human serum are similar worldwide because low PBDEs (such as pentaBDE and HexaBDE) have a long half-life in humans (17,26,56).

Associations between PBDEs, thyroid hormones, and human characteristics

In this study, no significant correlations were observed between concentrations of PBDEs to age, gender, or BMI, which is consistent with some previous studies (17,18,59,60), although several studies had differing results (8,48). Jin *et al.* (48) reported that female groups had higher PBDE concentrations than compared to males in Shandong, China, although they did not provide an explanation for this finding. Although Harrad and Porter *et al.* (8) reported PBDE concentrations in male serum were higher than in females in Wellington, New Zealand, a *t*-test revealed the difference to be statistically insignificant (P>0.1). Jacobson *et al.* (26) found that PBDE concentrations in serum from children were higher than those in adults, which could be explained by the transformation processes in adults being more efficient than in children.

The regression analysis results after logarithmic transformation showed that BDE-153 was positively correlated with T4 and negatively with T3, while BDE-47 was negatively correlated with FT4. The same result was reported by Makey *et al.* (28), with samples from the USA, which also noted that BDE-153 had an inverse association with T3 (β=–0.27, P<0.01), and a positive correlation to FT4 (β=0.03, P<0.01). Other previous studies showed similar results on the effect of PBDEs on thyroid function. Liu *et al.* (41) suggested that high concentrations of OH-PBDEs (hydroxylated PBDE metabolites) and PBDEs would reduce FT4 levels and elevated TSH values in the serum of thyroid cancer patients. Zheng *et al.* (40) observed that T3 and T4 are significantly and positively correlated with low PBDE concentrations including, BDE-47, BDE-66, and BDE-85 from e-waste workers' serum samples in China. Jacobson *et al.* (26) suggested that higher total PBDE concentrations (including BDE-47, BDE-99, BDE-100, and BDE-153) correlated with lower T4 levels but higher FT3 and higher TSH levels. Zota *et al.* (32) also found a similar result, which showed a positive association between TSH levels and low brominated PBDE concentrations in pregnant women from California. However, conflicting results have also been reported, with serum PBDE concentrations significantly correlated to T4 and FT4 levels but inversely to TSH (37). Shy *et al.* (51) reported that cord blood levels of FT3 were negatively correlated with BDE-183, but FT4 had a positive association with BDE-197 and BDE-207.

In this study, lipid content had a significantly positive correlation with PBDE congener concentrations. As PBDEs accumulate in lipid and serum, PBDEs were expressed on a lipid basis (ng/g lipid), and the concentration of PBDEs was adjusted for lipids before being compared (4,61).

Limitations

This study collected only 40 samples from patients with hyperthyroidism and hypothyroidism and measured the samples in one short column. It was the first study to focus on hyperthyroidism and hypothyroidism patients. Previous studies paid more attention to e-waste workers, the general public, or thyroid cancer patients. Up to now, the number of patients with hyperthyroidism and hypothyroidism has increased yearly since home chemical decorations began being used, accompanied by unhealthy living habits and lifestyle pressures. These two groups of patients are not treated as seriously as e-waste workers or cancer patients but still occupy a significant portion of the general public. Compared to results from previous studies, the conclusions of this study have advanced the progress made in this area of inquiry and have also conceived of extraction and analysis methods for patients with abnormal thyroid function. However, the limitation of this study was the lack of a control group of data relating to PBDE concentrations in human serum samples with normal thyroid hormone factor ranges in Kunming to allow for a comparison between the two groups (normal ranges and abnormal ones). Thus, in future work, three more tests should be conducted. The first test will explore the relationship between an indoor environment, such as indoor dust, to hyperthyroidism and hypothyroidism groups. The second research inquiry would be to use an increased sample size of patients. The final additional test would be to compare a normal control group

to hyperthyroidism and hypothyroidism groups and evaluate the PBDEs concentration levels in human serum. PBDEs pollution is serious in China. It is found that PBDEs are mainly BDE-47, BDE-99 and BDE-209 in the industrial zone and the Pearl River Delta region, which are mainly caused by the use of decabromo and pentabromo diphenyl ether (62). Leung *et al.* found that the concentration of PBDEs was as high as 33,000–97,400 ng/g dry weight in the burning residues of plastic chips and cables collected from residential areas, when detecting PBDEs in surface soil and burning residues in Guiyu area (63). The concentration of PBDEs reached of 2,720–4,250 ng/g dry weight in the soil of the acid leaching of electronic products, and 593–2,890 ng/g dry weight in the soil where the printer cartridge was stacked (63). In order to alleviate the harm of PBDEs to the population in the lowest possible level, first of all, public awareness of this pollutant should be raised. Secondly, pregnant women and infants need to be provided with qualified safe commodities. Thirdly, it is necessary to develop environmentally friendly flame retardant materials to replace PBDEs.

Conclusions

In this study, serum samples taken from patients with abnormal thyroid hormone levels in Kunming were evaluated for PBDE concentrations to assess levels of exposure and possible interactions. The results identified BDE-47 as the main congener present in human serum. The concentrations of $\sum_7$PBDE were similar to those from previous studies for general population groups, including adults and children, at the same order of magnitude as found in European data but lower than in data from the USA. Multiple linear regressions were used to examine the associations between PBDE congeners and the five thyroid hormone parameters. BDE-153 had a significant positive correlation to T4, and negative correlation to T3, whilst BDE-47 was negatively correlated with FT4. The β-coefficients also suggested that a log-unit increase in $\sum_7$PBDE was associated with an increase of FT4 and T4 levels and a decrease of TSH, T3, and FT3. Further research is required, preferably using an increased sample size of patients with abnormal thyroid function, to investigate this possible relationship further.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This research was approved by the Ethics Committee of the Kunming Center for Disease Control and Prevention, and informed consent was obtained from all volunteers.

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Table S1 The levels of thyroid function parameters in the 40 participants

Order#	Gender	Age	TSH (mIU/L)	T4 (nmol/L)	FT4 (pmol/L)	T3 (nmol/L)	FT3 (pmol/L)
1	Female	27	0.019	187.9	25.61	1.95	6.36
2	Female	19	15.641	184.04	29.47	2.1	7.25
3	Male	19	1.933	169.88	21.49	1.98	5.39
4	Female	54	8.23	172.46	16.09	1.97	3.9
5	Male	39	0.001	238.1	72.72	6.67	30.72
6	Female	28	1.408	171.17	10.81	2.1	3
7	Female	62	3.385	205.92	13.51	2.2	0.69
8	Female	26	1.061	157.01	11.46	2.12	3.56
9	Female	34	1.626	162.16	14.42	1.69	3.69
10	Female	40	0.004	169.88	36.68	3.61	12.18
11	Female	62	0.063	153.15	18.15	1.47	3.53
12	Female	29	1.605	166.02	12.36	2.4	3.27
13	Female	53	0.002	334.62	74.27	8.59	30.72
14	Female	38	0.34	157.01	18.15	1.95	4.67
15	Male	49	0.005	189.4	48.28	3.77	13.49
16	Female	45	0.72	192.6	21.24	2.52	5.4
17	Female	19	1.89	204.6	19.28	2.8	4.4
18	Female	47	0.01	221.9	34.94	4.17	11.14
19	Male	75	0.005	213.1	41.92	2.92	8
20	Male	24	0.01	188.4	64.54	5.02	20.37
21	Female	24	0.93	222.3	30.51	3.28	10.14
22	Male	54	0.005	249.7	37.47	3.16	8.69
23	Female	22	0.01	204.9	18.2	3.8	12.21
24	Male	27	0.01	234.7	73.6	5	20.6
25	Female	33	0.005	245.2	56.72	5.85	19.96
26	Female	16	5.4	194.7	20.21	3.63	13.21
27	Male	32	0.002	244.2	52.83	6.12	22.2
28	Female	37	0.005	348.3	56.26	5.27	18.41
29	Female	48	0.12	353.4	70.64	16.99	37.72
30	Male	75	2.096	226.4	14.33	13.46	6.94
31	Male	82	1.55	80	14.82	4.46	3.91
32	Female	23	2.56	131.8	20.66	2.21	5.16
33	Female	66	1.24	93.4	16.56	1.36	3.41
34	Female	83	0.7	95.1	18.41	1.65	4.25
35	Female	70	1.18	78	16.14	1.48	4.12
36	Female	47	1.15	161.8	21.69	2.55	4.13
37	Male	37	0.84	110	22	1.3	6.64
38	Female	64	2.58	102.2	16	1.66	4.05
39	Male	68	2.49	112.7	16.1	1.98	4.47
40	Female	66	2.75	112.4	16.99	2.03	4.59

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Figure S1 Correlation between total PBDE concentrations and gender.

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