Elevated Serum Polybrominated Diphenyl Ethers and Alteration of Thyroid Hormones in Children from Guiyu, China

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Abstract

Informal electronic waste (e-waste) recycling results in serious environmental pollution of polybrominated diphenyl ethers (PBDEs) and heavy metals. This study explored whether there is an association between PBDEs, heavy metal and key growth- and development-related hormones in children from Guiyu, an e-waste area in southern China. We quantified eight PBDE congeners using gas chromatographic mass spectrometry, lead and cadmium utilizing graphite furnace atomic absorption spectrometry, three thyroids with radioimmunoassay and two types of growth hormones by an enzyme-linked immune-sorbent assay (ELISA) in 162 children, 4 to 6 years old, from Guiyu. In blood, median total PBDE was 189.99 ng/g lipid. Lead and cadmium concentrations in blood averaged 14.53 ± 4.85 µg L⁻¹ and 0.77 ± 0.35 µg L⁻¹, respectively. Spearman partial correlation analysis illustrated that lead was positively correlated with BDE153 and BDE183. Thyroid-stimulating hormone (TSH) was positively correlated with almost all PBDE congeners and negatively correlated with insulin-like growth factor binding protein-3 (IGFBP-3), whereas free triiodothyronine (FT3) and free thyroxine (FT4) were negatively correlated with BDE154. However, no correlation between the hormones and blood lead or cadmium levels was found in this study. Adjusted multiple linear regression analysis showed that total PBDEs was negatively associated with FT3 and positively associated with TSH. Notably, FT4 was positively correlated with FT3, house functions as a workshop, and father’s work involved in e-waste recycling and negatively correlated with vitamin consumptions. TSH was negatively related with FT4, paternal residence time in Guiyu, working hours of mother, and child bean products intake. IGFBP-3 was positively correlated...
with IGF-1 and house close to an e-waste dump. These results suggest that elevated PBDEs and heavy metals related to e-waste in Guiyu may be important risk factors for hormone alterations in children.

Introduction

Electronic waste (e-waste) is an emerging environmental health issue because of the explosive growth of electronic products and its rapid update rate and accumulation worldwide, as well as inadequate recycling technology and informal recycling activities [1]. Guiyu, a town with a total area of 52 km² and a population of 139,000 (2010) located in Shantou, China, is one of the largest e-waste destinations in the world. More than 6,000 small-scale family-run workshops and nearly 160,000 workers (including approximately 100,000 migrant farmer laborers) are involved in the business of e-waste dismantling and recycling with crude and uncontrolled methods that extensively introduce environmental pollutants into the community [2–5].

Polybrominated diphenyl ethers (PBDEs) are one of the most common used materials among the organic contaminants in electronic equipment, which are a large group of brominated compounds widely utilized as flame retardant additives in the products of commodity such as automobiles, airplanes and furniture [6]. Compared with other sites from Nigeria or China, higher levels of PBDE are found in soil, air, sediment, as well as freshwater fish collected from Guiyu [7, 8]. PBDE concentrations in umbilical cord blood are also higher than those from nearby reference areas without e-waste recycling activities [4, 9]. The metabolites and environmental derivatives of PBDE have a similar chemical structure as thyroid hormones (TH), especially for thyroxine (T4) [10, 11]. A study shows that PBDEs may mimic or compete with TH to disrupt the function of target organs [12]. In addition, epidemiological studies suggest that occupational and environmental exposure to persistent organic pollutants (POPs) might alter insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) levels or their gene expression, which are involved in the insulin-like growth factor (IGF) axis when impact on growth and development [4, 13–15].

Guiyu is a well-known e-waste disassembling town mainly polluted by metal chemicals and persistent organic pollutants (POPs). Our previous studies found that heavy metals, such as lead and cadmium, in Guiyu children are much higher than that in nearby regions Chendian and Chaonian, which are also located in Shantou, China. It is notable that distance from Guiyu to Chendian or Chaoan is less than 40 kilometers. Inhabitants who live in the three regions mentioned above have similar life-styles except that people living in Guiyu are engaged in activities related to e-waste recycling. The percentages of blood lead concentration exceeding 10 μg/dL in Guiyu children were 81.83% (2004), 70.8% (2006), 69.9%
(2008), and 88.02% (2010), from 2004 to 2010, respectively [2, 16, 17]. Cadmium levels in human and environmental samples from Guiyu are also higher than those in other places without e-waste recycling [7, 18–21]. Similar to the case of PBDEs, lead and cadmium may also relate to hormone alteration. In adolescents, long-term low-level lead exposure may reduce FT4 levels [22]; while a decrease in TSH levels was correlated with blood lead levels in women [23]. In addition, animal studies show that exposure to 25 or 50 mg/L cadmium chloride (CdCl₂) can increase median TSH levels in rats [24]. Kortenkamp et al. reported that cadmium, and some other heavy metals should be regarded as estrogen mimics [25]. This endocrine-disruption of thyroid function might have significant impact on growth and development during the rapid growth stages of the central nervous system of children, as children are the most vulnerable to the harmful effects of environmental insults [26, 27].

However, few epidemiology studies have reported an association among PBDEs and heavy metal (lead and cadmium) co-exposure with thyroid and growth hormones in children, especially from an e-waste recycling area. This study was designed to evaluate the relationships between these co-exposures and hormone levels among children living in Guiyu.

Materials and Methods
Participants
Children greater than 6- or less than 4-years old was precluded before blood collection. According to the exclusion principle, 167 children, 4-to-6-years of age, were recruited from a kindergarten of Guiyu in October, 2010. The study protocol was approved by the Human Ethics Committee of Shantou University Medical College. Parents or guardians received detailed explanations of the study and potential consequences prior to enrollment and gave their written informed consent. They were interviewed by well-trained research staff using questionnaires involving information covering the dwellings (residence close to an e-waste dismantling site, passive smoking), child behavior (frequency of hand-to-mouth contact), diet and nutritional conditions, parent education, occupation, and social status. Parent education was classified by their relationship to e-waste recycling activities (e.g. unrelated, transporting e-waste, sorting e-waste, splitting e-waste, acid baths, and burning to recover metals). In addition, child physical growth and development indices, such as body height, weight, and head and chest circumferences were measured at the time of blood sample collection.

Blood sample collection
The children were required to fast after dinner until the blood samples were collected on the following morning. For each child, 0.5 mL whole blood with heparin and 5 mL blood without anticoagulant were obtained by trained nurses. After coagulation, serum samples were instantly separated into 2 mL and 0.5 mL
acetone-washed clean glass containers, numbered, immediately transported to the laboratory, and stored at −80°C. In addition, whole blood was stored at −20°C as soon as possible.

Data collection

PBDE analysis
PBDE concentrations of 145 children in 167 were measured due to the limited volume of blood samples. PBDE congeners such as BDE28, 47, 99, 100, 153, 154, 183, and 209 were identified. The standard mixture containing eight congeners was purchased from Cambridge Isotope Laboratories (CIL). Serum PBDE concentrations were analyzed based on a previously published method, with minor modifications [28]. The serum sample was first extracted with formic acid and acetonitrile, and equilibrated in an ultrasonic bath, then loaded on the solid-phase extraction cartridge (Plexa) and washed with water (Milli-Q), dried and subsequently eluted with dichloromethane. The eluate of PBDE was concentrated under a gentle stream of nitrogen to 1 mL, then applied to a silica gel/sulfuric acid column, and eluted with dichloromethane. After that, the eluate was concentrated to 50 μL and transferred to glass inserts in amber GC vials for gas chromatography/mass spectrometry (GC/MS) analysis. The final samples were analyzed with an Agilent 7890A-5975C GC/MS (Agilent Technologies, America), with electro-ionization used in the selected ion monitoring mode. Concentrations of PBDEs in individual samples were reported as ng/g lipid weight. Total cholesterol (CHOL) and triglycerides (TG) were determined enzymatically in a separate aliquot of serum by a clinical laboratory. Total lipid (TL) was calculated according to the following formula: TL (g/L) = 1.12 × CHOL + 1.33 × TG + 1.48 [29].

Thyroid hormone analysis
Serum free T3 (FT3) and free T4 (FT4) concentrations were quantified in duplicate by radioimmunoassay, using human serum T3 and T4 standard substance, respectively (Chemclin, Biotechnology Corp., Beijing, China). The sensitivities of the assays of FT3 and FT4 were 0.5 pmol/L. Serum thyroid-stimulating hormone (TSH) concentrations were measured by ultrasensitive third-generation immunochemiluminometric assay (Advia Centaur CP, Siemens, German), and the limit of detection of TSH was 0.01 μIU/mL.

Growth hormone levels
Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) in serum were examined by enzyme-linked immune-sorbent assay (ELISA).

Lead and cadmium levels
Lead and cadmium in whole blood were determined by graphite furnace atomic absorption spectrometry (GFAAS, ZEEnit 650, Germany) using an auto sampler.
(MPE60) with an injection volume set at 10 µL. The detection methods were based on previously published papers [21].

Statistical analysis
Normality was assessed by quantile-quantile plots and Kolmogorov-Smirnov tests for all continuous variables. The two independent sample t-tests were utilized to compare two sets of normally distributed data. The Mann–Whitney U test was applied to the two sampling site comparison because of the non-normal distribution. The One-Way ANOVA was available to the comparison of multiple sets of data normally distributed. The Pearson Chi-square test was used as a comparison between two or more groups between ranked characters or subjects. PBDE levels below the detection limit were defined as zero [30,31]. Covariates, such as gender, age, and BMI that have been reported for associations with thyroid hormones elsewhere [32], were adjusted in multivariate models. Spearman rank correlation analysis and multiple stepwise regression analysis were used to examine relationships between PBDEs, lead, cadmium, TSH, FT3, FT4, IGF-1, IGFBP-3 and factors in the questionnaire. All statistical tests were two-sided with a significance level of 0.05. Statistical analyses were conducted using SPSS version 13.0 (SPSS Inc., Chicago, IL, 2004).

Results
PBDE levels in children
Concentrations of PBDE were expressed on a serum lipid basis. The frequencies of detection of each PBDE were all greater than 95% except for BDE209, which was 71.72%. The levels and distribution for the eight PBDE congeners and their sums are shown in Table 1 and Table 2. First, the geometric mean (95% CI) of the total PBDE was 162.98 (141.25–186.21) ng/g lipid. Besides, total PBDE concentration was 582.35 ng/g lipid in this study. In addition, the concentration of total PBDE exceeded 100 ng/g lipid for 79% of the children (115/145) recruited from Guiyu. The highest concentrations of PBDE congener were BDE209, which ranged from undetectable to 470.29 ng/g lipid, with a geometric mean value of 184.19 ng/g lipid. In particular, BDE209 contributed to 70% of the total PBDE burden. The second most abundant PBDE congener was BDE153, with concentrations varying from undetectable to 94.39 ng/g lipid. BDE153 accounted for approximately 20% of the total PBDE burden and ranked only second to BDE209. In addition, we found high concentrations of BDE47 and BDE28, which represent 9% and 8% of the total PBDE burden excluding BDE209, respectively. It is worth mentioning that BDE153 increased with age (r = 0.214; P<0.05), while BDE154 decreased with BMI (r = −0.169; P<0.05). No significant difference in any of the eight PBDEs or the total PBDE was found between boys and girls (P>0.05). In addition, the other PBDE congener and total PBDE concentrations was not altered by age (all P>0.05).
Blood lead and cadmium levels

Table 1 show the blood lead and cadmium levels of children from Guiyu. The mean concentrations of lead and cadmium were 14.53 ± 4.85 μg/dL, and 0.77 ± 0.35 μg/L, respectively. Among children from Guiyu in this study, all of them could be identified with elevated blood lead levels (> 5 μg/dL) according to the U.S. CDC, 2012 reference criterion [33]. The proportion of children with blood lead levels greater than 10 μg/dL was 88.0%, with 10.2% (147/167) having blood lead levels higher than 20.0 μg/dL. In addition, the blood cadmium levels observed in this study exceeded the current range of normal values (≥0.2 μg/L) [34, 35]. However, no different of blood lead and cadmium were found between male and female.
Thyroid hormones and growth hormones

Average serum concentrations of FT3 and FT4 were $6.28 \pm 1.44$ pmol/L and $17.78 \pm 4.87$ pmol/L, respectively. The mean concentrations of TSH, IGF-1, and IGFBP-3 were $2.85 \pm 1.09$ μIU/mL, $510.79 \pm 254.84$ ng/mL, and $60.97 \pm 29.20$ ng/mL, respectively (Table 1). Among them, one participant had low FT3 ($<3.2$ pmol/L) and another one had low FT4 ($<8.56$ pmol/L), whereas none had low TSH ($<0.35$ μIU/mL). In addition, two children had high FT3 ($>9.3$ pmol/L), 7 other children had high FT4 ($>25.8$ pmol/L), and two had elevated TSH concentrations ($>5.5$ μIU/mL) based on reference ranges. Moreover, FT3 had a positive association with BMI ($P<0.05$), whereas IGFBP-3 had a negative association with age in a linear fashion ($P<0.05$). Furthermore, there is no association between FT3, FT4, TSH, IGF-1 and age in this study. Compared with girls, boys had higher levels of FT4.

Association between PBDEs and related factors in children

Relationship between PBDEs and related factors were analyzed with the spearman rank correlation analysis (Table 3 and Table S1). Dietary choosiness had a positive correlation with BDE28. Frequency of eating dairy and frequency of calcium

| Congener | Detection Frequency (%) | GM | 95% CI | Min | Max | Percentile |
|----------|-------------------------|----|--------|-----|-----|------------|
| BDE28    | 97.93                   | 7.10 | 6.03–8.32 | ND  | 96.02 | 2.51  | 3.02  | 4.71  | 17.02  | 34.63  |
| BDE47    | 90.34                   | 7.92 | 6.46–9.77 | ND  | 97.56 | 1.51  | 2.48  | 4.93  | 21.37  | 50.07  |
| BDE99    | 97.24                   | 5.22 | 4.47–6.17 | ND  | 63.09 | 1.67  | 2.22  | 4.27  | 9.88   | 19.70  |
| BDE100   | 100.00                  | 3.33 | 3.02–3.63 | 1.36 | 45.17 | 1.85  | 2.16  | 2.85  | 4.38   | 6.63   |
| BDE153   | 97.93                   | 13.17 | 11.75–14.79 | ND | 94.39 | 4.72  | 7.60  | 12.28 | 21.78  | 37.42  |
| BDE154   | 100.00                  | 4.66 | 4.27–5.13 | 1.81 | 54.60 | 2.48  | 3.00  | 3.99  | 6.48   | 10.54  |
| BDE183   | 100.00                  | 6.88 | 6.17–7.67 | 2.53 | 70.89 | 3.33  | 4.37  | 6.04  | 9.59   | 15.34  |
| BDE209   | 71.72                   | 18.41 | 17.39–199.53 | ND | 470.02 | 1.59  | 2.12  | 2.64  | 3.43   | 4.64   |

Table 2. PBDEs (ng/g lipids), Thyroid Hormone and Growth Hormone in Serum of Children, Guiyu, China, 2010.

Abbreviations: CI, confidence interval; BDE, brominated diphenyl ether; FT3, free triiodothyronine; FT4, free thyroxine; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; ND, not detectable; TSH, thyroid-stimulating hormone.

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consumption had a positive correlation with BDE47. Frequency of calcium consumption also had a positive correlation with BDE99. Residence of the child had a positive correlation with BDE100. Age and residence of child had a positive correlation with BDE153, whereas frequency of eating dairy had a negative correlation with BDE153. BMI, dietary choosiness, and residence of child had a positive correlation with BDE154, while frequency of eating dairy had a negative correlation with BDE154. Extent of passive smoking and house close to an e-waste recycling site had positive correlations with BDE183. There was no correlation between BDE209, total PBDE and related factors found in this study. Multiple stepwise regression analysis was used to evaluate factors related to each congener of PBDEs in children from Guiyu. TSH was positively correlated with BDE28, BDE47, BDE99, BDE209, and total PBDE. FT3 was negatively correlated with BDE99, BDE209, and total PBDE. IGFBP-3 was negatively correlated with BDE47. Biting fingers was positively correlated with BDE28 and BDE47. Eating dairy was negatively correlated with BDE154 and BDE209. Bean products intake was negatively correlated with BDE28 and BDE100. Blood lead positively correlated with BDE153.

Association between heavy metals and related factors in children

Relationship between heavy metals and related factors were analyzed with the spearman rank correlation analysis (Table 4). Gender as male and working hours of the mother had a positive correlation with blood lead. Weight had a negative correlation with blood lead. Head circumference and chest circumference had a positive correlation with blood cadmium. Children suffered from any disease and mother’s education levels had a negative correlation with blood cadmium.

Associations between hormones and related factors in children

Relationship between hormones and risk factors were analyzed with the spearman rank correlation analysis (Table 5). BMI was negatively correlated with FT3. Gender as female, vitamin consumption, suffered from any diseases, drinking well water, working hours of mother, and house functions as a workshop were negatively correlated with FT4. Biting fingers, frequency of bean products intake, and paternal dwelling time in Guiyu were negatively correlated with TSH. Age was negatively correlated with IGFBP-3. Multiple stepwise regression analysis was used to evaluate factors related to each hormone in children from Guiyu (Table 6). FT4 was positively associated with FT3, while fever was negatively associated with FT3. Vitamin consumption, suffered from any disease, duration of outdoor play, and house functions as a workshop were negatively associated with FT4. Father’s work involved in e-waste recycling activities was positively associated with FT4. Eating bean products, suffered from any disease, paternal dwelling time in Guiyu, and working hours of the mother were negatively associated with TSH. Residence of child was positively associated with TSH. IGFBP-3 and fevers were positively
associated with IGF-1. House close to an e-waste site was positively associated with IGFBP-3.

Multiple stepwise regression analysis was also used to evaluate factors related to blood lead and cadmium in children from Guiyu (Table 6). Age, residence of mother, and house close to an e-waste recycling site were positively associated with blood lead. Head circumference was positively associated with blood cadmium. FT3, mother’s education level, and children suffered from any disease had a negative association with blood cadmium.

**Discussion**

We demonstrate that serum total PBDEs geometric mean (GM) was 162.98 ng/g lipid and ranged from 16.56 to 582.35 ng/g lipid in children residing in Guiyu. Before this work, a small study compared PBDE levels in children from another e-waste recycling area and a reference site in Taizhou, Zhejiang province, China [36]. The sum of PBDEs reported here in Guiyu children was much higher than that in Taizhou except BDE209, which may indirectly reflect more serious environmental pollution resulting from disassembling of electronic devices in

| Related Factors                      | BDE28 | BDE47 | BDE100 | BDE99 | BDE154 | BDE153 | BDE183 | BDE209 | ΣPBDE |
|--------------------------------------|-------|-------|--------|-------|--------|--------|--------|--------|-------|
| Age (years)                          | −0.018| −0.102| −0.049 | −0.038| 0.115  | 0.204* | 0.058  | 0.060  | 0.033 |
| BMI                                  | 0.094 | 0.088 | −0.053 | −0.066| 0.169* | −0.139 | −0.120 | −0.098 | 0.016 |
| The frequency of eating dairy        | −0.001| 0.177*| −0.102 | −0.001| −0.218*| −0.177*| −0.154 | 0.120  | −0.039|
| The frequency of taking calcium tablet| 0.104 | 0.203*| 0.125  | 0.174*| 0.066  | 0.047  | 0.017  | −0.060 | −0.034|
| The frequency of passive smoking     | 0.134 | 0.113 | 0.138  | −0.017| 0.147  | 0.144  | 0.187* | 0.069  | 0.091 |
| House close to e-waste               | 0.133 | 0.126 | 0.150  | 0.012 | 0.132  | 0.092  | 0.192* | −0.061 | 0.040 |
| The habit of dietary choiness        | 0.187*| 0.051 | 0.162  | 0.109 | 0.174* | 0.068  | 0.089  | 0.063  | 0.102 |
| Residence of the child               | 0.135 | 0.011 | 0.169* | 0.095 | 0.180* | 0.189* | 0.121  | 0.053  | 0.089 |

Abbreviations: BDE, brominated diphenyl ether; BMI, body mass index.
*P<0.05, **P<0.01.

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Table 4. Spearman correlation coefficients between blood heavy metals and some investigated factors in children, Guiyu, China, 2010.

| Related factors                                    | Lead (n=162) | Cadmium (n=162) |
|----------------------------------------------------|--------------|-----------------|
|                                                    | rs           | p              | rs           | p              |
| Gender                                             | −0.190       | 0.016           | −0.072       | 0.364           |
| Head circumference (cm)                            | 0.153        | 0.054           | 0.268        | 0.001           |
| Chest circumference (cm)                           | 0.126        | 0.111           | 0.233        | 0.003           |
| Birth weight                                       | −0.239       | 0.013           | 0.010        | 0.916           |
| Whether suffered from any disease                  | 0.013        | 0.885           | −0.190       | 0.027           |
| Mother’s education levels                          | −0.073       | 0.399           | −0.170       | 0.046           |
| Working hours of the mother                        | 0.181        | 0.034           | 0.066        | 0.444           |

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Guiyu [37]. Although Guiyu and Taizhou are two famous e-waste destinations in China, the e-waste disassembling method is not the same. Most workshops in Guiyu are small family run, home-based workshops using rudimentary and informal procedures that pose more serious health problems to the environment and humans compared to those in Taizhou. “The Handbook of Environmental Chemistry” identifies Guiyu as the largest and the second most polluted site in the world due to its informal recycling processes (acid extraction for metals, open burning of wires to get copper) [38]. Decreases in PBDE concentrations are observed with increasing distance from workshops in samples linked with acid processing of waste [39]. Similar results are found when family residences serve as workshops. One of our previous studies indicates that the PBDE concentration of surface soil samples in residential areas is much higher than that in agricultural areas in Guiyu, suggesting that leakage of PBDEs into the environment occurs from informal e-waste recycling [5]. Therefore, more attention should be given to the health of people living in Guiyu, especially for children residing near workshops or house used as a workshop.

In this study, BDE209 is the predominant congener among the eight BDEs tested, with a range from ND to 470.29 ng/g lipid, in spite of the detection frequency is 71.72%, which may be attributed to its large molecular weight, resulting in relatively rapid excretion after biotransformation [40]. Another study conducted among female e-waste recycling workers in Guiyu found that BDE209 can be as high as 1640 ng/g lipid, with a median of 83.5 ng/g lipid [41]. The half-life of BDE209 is only 15 days in human [42], and BDE209 concentration in child serum show high values, on one hand indicating that PBDEs exposure in Guiyu is high and continuous, and also suggesting a broad use of BDE209 in industry [43]. On the other hand implying the degradation rate of BDE209 in the human body is slower than its intake rate [44]. A top-level predator tends to have a high uptake and accumulation of higher bromine compounds [45]. BDE209 is rich in plasma

| Table 5. Spearman correlation coefficients between hormones and some investigated factors in children, Guiyu, China, 2010. |
|---------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Related factors                  | FT3(n=162)| FT4(n=162)| TSH(n=162)| IGF-1(n=162)| IGFBP-3(n=162)|
|---------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Gender                          | rs        | p         | rs        | p         | rs        | p         |
| Age (years)                     | −0.034    | 0.709     | −0.025    | 0.787     | 0.012     | 0.899     | 0.003     | 0.976     | 0.016     | 0.358     |
| BMI                             | 0.170     | 0.033     | −0.019    | 0.809     | 0.121     | 0.130     | −0.067    | 0.401     | −0.028    | 0.725     |
| The habit of biting fingers     | −0.057    | 0.507     | −0.078    | 0.365     | −0.207    | 0.015     | −0.011    | 0.894     | 0.011     | 0.903     |
| The frequency of eating bean products | −0.026    | 0.759     | −0.034    | 0.697     | −0.182    | 0.033     | 0.030     | 0.727     | −0.101    | 0.238     |
| The frequency of taking vitamin | 0.014     | 0.871     | −0.219    | 0.010     | 0.141     | 0.100     | −0.132    | 0.126     | −0.008    | 0.923     |
| Whether suffered from any disease | −0.074    | 0.390     | −0.188    | 0.028     | −0.146    | 0.089     | 0.104     | 0.227     | 0.025     | 0.769     |
| Household drinking water sources| −0.049    | 0.569     | −0.181    | 0.035     | 0.024     | 0.782     | −0.019    | 0.829     | 0.008     | 0.927     |
| Residence of the father         | −0.037    | 0.668     | −0.088    | 0.305     | −0.196    | 0.022     | −0.100    | 0.246     | −0.029    | 0.736     |
| Working hours of the mother     | −0.086    | 0.318     | −0.188    | 0.028     | −0.148    | 0.085     | 0.006     | 0.949     | 0.117     | 0.173     |
| House functioned as workshop     | −0.068    | 0.430     | −0.217    | 0.011     | 0.096     | 0.262     | −0.068    | 0.431     | −0.020    | 0.813     |

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Table 6. Multiple stepwise regression analysis between PBDEs, Lead, Cadmium, FT3, FT4, TSH, IGP-1, IGPBP-3 and related factors in children, Guiyu, China, 2010.

| Related factors | B   | β  | Partial correlation | $R^2$ | Adjusted $R^2$ | F   | p   | 95% CI for β |
|-----------------|-----|----|---------------------|-------|----------------|-----|-----|--------------|
| **BDE28 Models** |     |    |                     |       |                |     |     |              |
| TSH             | 3.776 | 0.260 | 0.258               | 0.125 | 0.106          | 6.355 | 0.003 | 1.349–6.203  |
| The habit of biting fingers | 3.623 | 0.179 | 0.181               | 0.036 | 0.240–7.006    |     |     |              |
| The frequency of eating bean products | −4.624 | −0.202 | −0.218             | 0.017 | −8.413–0.835   |     |     |              |
| **BDE47 Models** |     |    |                     |       |                |     |     |              |
| TSH             | 4.698 | 0.217 | 0.220               | 0.127 | 0.100          | 4.781 | 0.011 | 1.106–8.289  |
| IGFBP-3         | −0.131 | −0.165 | −0.174             | 0.045 | −0.258–0.003   |     |     |              |
| The habit of biting fingers | 5.657 | 0.187 | 0.191               | 0.027 | 0.660–10.654   |     |     |              |
| Father’s education levels | 6.164 | 0.196 | 0.204               | 0.018 | 1.079–11.250   |     |     |              |
| **BDE100 Models** |     |    |                     |       |                |     |     |              |
| The frequency of eating bean products | −1.549 | −0.187 | −0.187             | 0.035 | 0.028          | 4.884 | 0.029 | −2.935–0.163 |
| **BDE99 Models** |     |    |                     |       |                |     |     |              |
| TSH             | 2.429 | 0.236 | 0.252               | 0.181 | 0.150          | 5.804 | 0.003 | 0.814–4.044  |
| FT3             | −1.776 | −0.243 | −0.251             | 0.004 | −2.957–0.594   |     |     |              |
| Gender          | −4.252 | −0.196 | −0.208             | 0.016 | −7.706–0.797   |     |     |              |
| Fever           | −1.648 | −0.175 | −0.184             | 0.034 | −3.170–0.125   |     |     |              |
| Whether decorate house | −3.573 | −0.165 | −0.176             | 0.042 | −7.023–0.123   |     |     |              |
| **BDE154 Models** |     |    |                     |       |                |     |     |              |
| The frequency of eating dairy | −1.705 | −0.264 | −0.268             | 0.037 | 0.030          | 5.168 | 0.026 | −2.753–0.657 |
| The habit of dietary choosiness | 2.251 | 0.185 | 0.191               | 0.008 | 6.536–43.671   |     |     |              |
| **BDE153 Models** |     |    |                     |       |                |     |     |              |
| Lead            | 0.512 | 0.192 | 0.192               | 0.102 | 0.081          | 5.012 | 0.025 | 0.067–0.958  |
| **BDE209 Models** |     |    |                     |       |                |     |     |              |
| TSH             | 18.432 | 0.185 | 0.191               | 0.126 | 0.106          | 6.400 | 0.001 | 13.002–50.425|
| FT3             | −13.054 | −0.184 | −0.190             | 0.151 | 0.129          | 6.380 | 0.001 | 5.050–27.325 |
| The frequency of eating dairy | 25.104 | 0.221 | 0.226               | 0.019 | −29.262–2.709  |     |     |              |
| **Cadmium Models** |     |    |                     |       |                |     |     |              |
| FT3             | −0.032 | −0.167 | −0.180             | 0.038 | −0.063–0.002   |     |     |              |
| Head circumference | 0.050 | 0.254 | 0.268               | 0.002 | 0.019–0.081    |     |     |              |
| Mother’s education levels | −0.080 | −0.219 | −0.230             | 0.008 | −0.138–0.022   |     |     |              |
| Whether suffered from any disease | −0.224 | −0.221 | −0.231             | 0.007 | −0.387–0.061   |     |     |              |
| **FT3 Models**  |     |    |                     |       |                |     |     |              |
| FT3             | 0.101 | 0.331 | 0.339               | 0.162 | 0.150          | 12.982 | 0.000 | 0.053–0.148  |
| Fever           | −0.266 | −0.206 | −0.219             | 0.296 | 0.263          | 9.097  | 0.010 | −0.468–0.064 |
| FT4             | 0.019 | 0.254 | 0.268               | 0.002 | 0.019–0.081    |     |     |              |
| Whether suffered from any disease | −0.224 | −0.221 | −0.231             | 0.007 | −0.387–0.061   |     |     |              |
| **FT4 Models**  |     |    |                     |       |                |     |     |              |
| FT3             | 0.101 | 0.331 | 0.339               | 0.296 | 0.263          | 9.097  | 0.010 | −0.468–0.064 |
| Fever           | −0.266 | −0.206 | −0.219             | 0.296 | 0.263          | 9.097  | 0.010 | −0.468–0.064 |
and blood-rich tissues due to the high plasma protein-binding properties of deca-BDE [46]. Consistent with our previous study, prior investigations find that BDE209 is present in high concentrations in the environmental matrix of Guiyu, including air, road and farmland soil, and e-waste dumpsite soil [5,7,47,48]. In spite of BDE209 being the major PBDE in children, it does not indicate that BDE209 is the most influential on thyroid function [49]. In this study, BDE209 is weakly associated with TSH and IGFBP-3. Further studies are suggested.

When compared with children from around the world, PBDE concentrations in the present study were higher than those in newborns and 4-year-old children from Menorca Island [50], 0–11-year-old children from Dalian, China [51], 6–13-year-old children from Mexico [52], newborns from Indiana, USA [53], 0–15-year-old children from Australia [54], and 7-year-old children from Faroe Island [55], and comparable with those in California Mexican-American children, USA [56], but lower than those in the children residing in Berkeley, California USA [57]. All together, these results are in concordance with those reported in other studies, where people in Asia are exposed to comparable or lower levels than people living in North American and much higher than people in Europe. In addition, several studies showed that PBDE concentrations in children were higher than those of the mothers [54,56,58].

To our knowledge, this is thus far the first study to include lead and cadmium as co-exposures when investigating associations between PBDEs and key growth- and development-related hormones in children from an e-waste area. One prior study investigated the relationship between metals in blood and urine, and thyroid function among adults in the United States, and the authors found blood cadmium

| Table 6  |
|----------|
| FT3      |
| 1.140    |
| 0.347    |
| 0.378    |
| 0.000    |
| 0.655–1.624 |

| Whether suffered from any disease |
|----------------------------------|
| −3.184                           |
| −0.185                           |
| −0.212                           |
| 0.015                            |
| −5.736–0.632                     |

| The frequency of taking vitamin |
|---------------------------------|
| −1.613                           |
| −0.274                           |
| −0.303                           |
| 0.000                            |
| −2.494–0.732                     |

| The length of outdoor play       |
|---------------------------------|
| −0.833                           |
| −0.150                           |
| −0.173                           |
| 0.048                            |
| −1.658–0.008                     |

| Father’s work involved in e-waste recycling |
|---------------------------------------------|
| 3.121                                        |
| 0.231                                        |
| 0.250                                        |
| 0.004                                        |
| 1.024–5.219                                  |

| House functions as workshop              |
|------------------------------------------|
| −2.268                                    |
| −0.232                                    |
| −0.255                                    |
| 0.003                                     |
| −3.763–0.774                              |

| TSH Models                               |
|------------------------------------------|
| 0.267                                    |
| 0.233                                    |
| 7.898                                    |

| FT4                                      |
|------------------------------------------|
| −0.054                                   |
| −0.251                                   |
| −0.269                                   |
| 0.022                                    |
| 1.023–1.334                              |

| The frequency of eating bean products    |
|------------------------------------------|
| −0.308                                   |
| −0.196                                   |
| −0.222                                   |
| 0.017                                    |
| 1.019–1.212                              |

| Whether suffered from any disease        |
|------------------------------------------|
| −0.780                                   |
| −0.209                                   |
| −0.232                                   |
| 0.030                                    |
| 0.002–0.724                              |

| Residence of the father                 |
|------------------------------------------|
| −0.539                                   |
| −0.373                                   |
| −0.354                                   |
| 0.023                                    |
| 0.688–0.972                              |

| Residence of the child                  |
|------------------------------------------|
| 0.347                                    |
| 0.244                                    |
| 0.240                                    |
| 0.023                                    |
| 1.043–1.743                              |

| Working hours of the mother             |
|------------------------------------------|
| −0.198                                   |
| −0.249                                   |
| −0.264                                   |
| 0.000                                    |
| 1.280–2.271                              |

| IGF-1 Models                            |
|------------------------------------------|
| 0.115                                    |
| 0.102                                    |
| 8.699                                    |

| IGFBP-3                                 |
|------------------------------------------|
| 1.803                                    |
| 0.199                                    |
| 0.205                                    |
| 0.017                                    |
| 0.331–3.276                              |

| Fever                                   |
|------------------------------------------|
| 56.353                                   |
| 0.248                                    |
| 0.252                                    |
| 0.003                                    |
| 19.445–93.261                            |

| IGFBP-3 Models                          |
|------------------------------------------|
| 0.087                                    |
| 0.073                                    |
| 6.349                                    |

| IGF-1                                   |
|------------------------------------------|
| 0.028                                    |
| 0.250                                    |
| 0.252                                    |
| 0.003                                    |
| 0.010–0.046                              |

| House close to an e-waste site          |
|------------------------------------------|
| 10.329                                   |
| 0.179                                    |
| 0.184                                    |
| 0.032                                    |
| 0.882–19.777                             |

Note: All values are presented as mean ± standard deviation (SD).
levels to be inversely related with the logarithm of TSH, and blood lead levels was correlated with decreased T4 [59]. However, no relationships are observed between lead, cadmium and thyroid or growth-related hormones among children in this study. We suggest further study should be performed on the relationships and mechanisms between heavy metals and thyroid and growth hormones.

This study finds out that when the house functions as an e-waste recycling workshop negatively associate with FT4 of children, suggests that living in an e-waste dismantling area or in a family-run informal e-waste workshop might cause changes in thyroid hormones, a conclusion differing from prior studies. Exposure to brominated flame retardants released from informal e-waste handling might result in changes in THs and TSH levels [60], whereas in that study, the TSH levels in the e-waste recycling occupational-exposed groups were lower than that in the non-occupational-exposed group. These results are consistent with several studies that found PBDEs were negatively associated with TSH [61–63]. However, the TSH was positively correlated with both BDE154 and total PBDE in this study. According to the study conducted by Han, who also found PBDEs were negatively associated with TSH during low concentration range (<3 μIU/mL), whereas positively associated with TSH within high concentration range (≥3 μIU/mL) [64]. Exhilaratingly, the TSH levels (Mean ± SD, 2.85 ± 1.09) in this study generally fall in the high concentration range, which is consistent with the result from Han [64]. The studies show a negative association between PBDEs and TSH all with low concentration of TSH [62, 65]. This may be because the PBDE congeners were different, and the participants in our study were all from an e-waste recycling region. Children seemed to be particularly appropriate for a monitoring program, as they are not directly exposed to occupational pollution; thus, children normally reflect present trends of environmental exposure more accurately than adults [66]. In addition, serum TSH concentrations may vary with age, and several epidemiological and animal studies find that association between TSH levels and PBDE exposure maintain inconsistency [67–73]. Therefore, it is difficult to make direct comparisons between occupational-exposed populations or the prenatal-exposed population in the present study. Positive associations between BDE209 and IGFBP-3 are observed in this study. Another study demonstrated that the log IGF-1 level is significantly linked to an increase in the log BDE196 level and a decrease in the log BDE85 level [74]. However, we did not find any associations between IGF-1 and any of the eight PBDE congeners tested or the total PBDE.

One limitation is that we did not obtain other organic pollutant such as polychlorinated biphenyls (PCBs), another important endocrine disruptor, due to insufficient blood. However, the outcomes of our study still strongly suggest that elevated concentrations of PBDEs may cause adverse effects on child hormone function. Thyroid hormones affect the function of nearly all tissues via their effects on cellular metabolism and play an essential role in differentiation and growth. Interference with thyroid hormone homeostasis by environmental compounds has the potential to impact development [75]. Obviously, there are a variety of chemical contaminants in e-waste and we cannot measure all potentially
relevant toxicants, but our results included other potentially relevant chemicals (lead and cadmium) that are present in informal e-waste recycling areas. Another limitation is that the present study was conducted in a cross-sectional design that may raise an issue of validity of causal inferences between exposures and hormone alterations. However, our study can serve as a reference for further studies performed at similar sites and in similar populations, or serve as a foundation for policy makers.

In conclusion, the present study supports the finding that elevated serum PBDEs are associated with thyroid hormone alterations, and that elevated blood lead levels are common in children at an e-waste area. BDE153 is positively correlated with blood lead levels in children from Guiyu. More research is needed to differentiate mechanisms governing TH levels between e-waste recycling sites and non-e-waste-recycling sites. Our findings support efforts of the EU RoHS Directive to restrict the use of PBDEs, lead and other hazardous substances in electronic equipment.

Supporting Information
Table S1. Spearman correlation analysis among PBDEs (ng/g lipids), Heavy Metals, Thyroid Hormone and Growth Hormone in Serum of Children, Guiyu, China, 2010.
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Author Contributions
Conceived and designed the experiments: XH XJX. Performed the experiments: JXL. Analyzed the data: XJX JXL AMC FFL XZ. Wrote the paper: XJX JXL AMC FFL XZ XH.

References
1. Ogunseitan OA, Schoenung JM, Saphores JD, Shapiro AA (2009) Science and regulation. The electronics revolution: from e-wonderland to e-wasteland. Science 326: 670–671.
2. Huo X, Peng L, Xu X, Zheng L, Qiu B, et al. (2007) Elevated blood lead levels of children in Guiyu, an electronic waste recycling town in China. Environ Health Perspect 115: 1113–1117.
3. Zheng G, Xu X, Li B, Wu K, Yekeen TA, et al. (2013) Association between lung function in school children and exposure to three transition metals from an e-waste recycling area. J Expo Sci Environ Epidemiol 23: 67–72.
4. Xu X, Yekeen TA, Xiao Q, Wang Y, Lu F, et al. (2013) Placental IGF-1 and IGFBP-3 expression correlate with umbilical cord blood PAH and PBDE levels from prenatal exposure to electronic waste. Environ Pollut 182C: 63–69.
5. Zhang S, Xu X, Wu Y, Ge J, Li W, et al. (2014) Polybrominated diphenyl ethers in residential and agricultural soils from an electronic waste polluted region in South China: distribution, compositional profile, and sources. Chemosphere 102: 55–60.

6. Harley KG, Chevrier J, Aguilar SR, Sjodin A, Bradman A, et al. (2011) Association of prenatal exposure to polybrominated diphenyl ethers and infant birth weight. Am J Epidemiol 174: 885–892.

7. Alabi OA, Bakare AA, Xu X, Li B, Zhang Y, et al. (2012) Comparative evaluation of environmental contamination and DNA damage induced by electronic-waste in Nigeria and China. Sci Total Environ 423: 62–72.

8. Wu K, Xu X, Liu J, Guo Y, Li Y, et al. (2010) Polybrominated diphenyl ethers in umbilical cord blood and relevant factors in neonates from Guiyu, China. Environ Sci Technol 44: 813–819.

9. Luo Q, Wong M, Cai Z (2007) Determination of polybrominated diphenyl ethers in freshwater fishes from a river polluted by e-wastes. Talanta 72: 1644–1649.

10. McDonald TA (2002) A perspective on the potential health risks of PBDEs. Chemosphere 46: 745–755.

11. Hooper K, McDonald TA (2000) The PBDEs: an emerging environmental challenge and another reason for breast-milk monitoring programs. Environ Health Perspect 108: 387–392.

12. Kim UJ, Kim MY, Hong YH, Lee DH, Oh JE (2012) Assessment of impact of internal exposure to PBDEs on human thyroid function – comparison between congenital hypothyroidism and normal paired blood. Environ Sci Technol 46: 6261–6268.

13. Boada LD, Lara PC, Alvarez-Leon EE, Losada A, Zumbado ML, et al. (2007) Serum levels of insulin-like growth factor-I in relation to organochlorine pesticides exposure. Growth Horm IGF Res 17: 506–511.

14. Johnsen SP, Sorensen HT, Thomsen JL, Gronbaek H, Flyvbjerg A, et al. (2004) Markers of fetal growth and serum levels of insulin-like growth factor (IGF) I, -II and IGF binding protein 3 in adults. Eur J Epidemiol 19: 41–47.

15. Lagiòu P, Samoli E, Hsieh CC, Lagiòu A, Xu B, et al. (2014) Maternal and cord blood hormones in relation to birth size. Eur J Epidemiol 29: 343–351.

16. Zheng L, Wu K, Li Y, Qi Z, Han D, et al. (2008) Blood lead and cadmium levels and relevant factors among children from an e-waste recycling town in China. Environ Res 108: 15–20.

17. Liu J, Xu X, Wu K, Piao Z, Huang J, et al. (2011) Association between lead exposure from electronic waste recycling and child temperament alterations. Neurotoxicology 32: 458–464.

18. Guo Y, Huo X, Li Y, Wu K, Liu J, et al. (2010) Monitoring of lead, cadmium, chromium and nickel in placenta from an e-waste recycling town in China. Sci Total Environ 408: 3113–3117.

19. Li Y, Huo X, Liu J, Peng L, Li W, et al. (2011) Assessment of cadmium exposure for neonates in Guiyu, an electronic waste pollution site of China. Environ Monit Assess 177: 343–351.

20. Zhang Q, Zhou T, Xu X, Guo Y, Zhao Z, et al. (2011) Downregulation of placental S100P is associated with cadmium exposure in Guiyu, an e-waste recycling town in China. Sci Total Environ 410–411: 53–58.

21. Yang H, Huo X, Yekeen TA, Zheng Q, Zheng M, et al. (2013) Effects of lead and cadmium exposure from electronic waste on child physical growth. Environ Sci Pollut Res Int 20: 4441–4447.

22. Dundar B, Oktем F, Arslan MK, Delibas N, Baykal B, et al. (2006) The effect of long-term low-dose lead exposure on thyroid function in adolescents. Environ Res 101: 140–145.

23. Abdelouahab N, Mergler D, Takser L, Vanier C, St-Jean M, et al. (2008) Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada). Environ Res 107: 380–392.

24. Caride A, Fernandez-Perez B, Cabaleiro T, Tarasco M, Esquifino Al, et al. (2010) Cadmium chronotoxicity at pituitary level: effects on plasma ACTH, GH, and TSH daily pattern. J Physiol Biochem 66: 213–220.

25. Kortenkamp A (2011) Are cadmium and other heavy metal compounds acting as endocrine disrupters? Met Ions Life Sci 8: 305–317.

26. Leith SJ, Carpenter DO (2012) Special vulnerability of children to environmental exposures. Rev Environ Health 27: 151–157.
27. Zhai W, Huang Z, Chen L, Feng C, Li B, et al. (2014) Thyroid endocrine disruption in zebrafish larvae after exposure to mono-(2-ethylhexyl) phthalate (MEHP). PLoS One 9: e92465.

28. Ramos JJ, Gomara B, Fernandez MA, Gonzalez MJ (2007) A simple and fast method for the simultaneous determination of polychlorinated biphenyls and polybrominated diphenyl ethers in small volumes of human serum. J Chromatogr A 1152: 124–129.

29. Covaci A, Voorspoels S (2005) Optimization of the determination of polybrominated diphenyl ethers in human serum using solid-phase extraction and gas chromatography-electron capture negative ionization mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 827: 216–223.

30. Wu N, Herrmann T, Paepeke O, Tiekcer J, Hale R, et al. (2007) Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. Environ Sci Technol 41: 1584–1589.

31. Zhao Y, Ruan X, Li Y, Yan M, Qin Z (2013) Polybrominated diphenyl ethers (PBDEs) in aborted human fetuses and placental transfer during the first trimester of pregnancy. Environ Sci Technol 47: 5939–5946.

32. Franklin RC, Carpenter LM, O’Grady CM (1985) Neonatal thyroid function: influence of perinatal factors. Arch Dis Child 60: 141–144.

33. Betts KS (2012) CDC updates guidelines for children’s lead exposure. Environ Health Perspect 120: a268.

34. Cao Y, Chen A, Radcliffe J, Dietrich KN, Jones RL, et al. (2009) Postnatal cadmium exposure, neurodevelopment, and blood pressure in children at 2, 5, and 7 years of age. Environ Health Perspect 117: 1580–1586.

35. Chen A, Dietrich KN, Huo X, Ho SM (2011) Developmental neurotoxicants in e-waste: an emerging health concern. Environ Health Persp 119: 431–438.

36. Shen H, Ding G, Han G, Wang X, Xu X, et al. (2010) Distribution of PCDD/Fs, PCBs, PBDEs and organochlorine residues in children’s blood from Zhejiang, China. Chemosphere 80: 170–175.

37. Li LX, Chen L, Meng XZ, Chen BH, Chen SQ, et al. (2013) Exposure levels of environmental endocrine disruptors in mother-newborn pairs in China and their placental transfer characteristics. PLoS One 8: e62526.

38. Suciu N, Capri E, Trevisan M, Tanaka T, Tien P, Brigden K (2013) Levels and distribution of polybrominated diphenyl ethers in soil, sediment and dust samples collected from various electronic waste recycling sites within Guiyu town, southern China. Environ Sci: Processes Impacts 15: 503–511.

39. Eljarrat E, de la Cal A, Raldua D, Duran C, Barcelo D (2004) Occurrence and bioavailability of polybrominated diphenyl ethers and hexabromocyclododecane in sediment and fish from the Cinca River, a tributary of the Ebro River (Spain). Environ Sci Technol 38: 2603–2608.

40. Qu W, Bi X, Sheng G, Lu S, Fu J, et al. (2007) Exposure to polybrominated diphenyl ethers among workers at an electronic waste dismantling region in Guangdong, China. Environ Int 33: 1029–1034.

41. Thuresson K, Högland P, Hagmar L, Sjödin A, Bergman A, et al. (2006) Apparent half-lives of hepta- to decabrominated diphenyl ethers in human serum as determined in occupationally exposed workers. Environ Health Perspect 114: 176–181.

42. Inoue K, Harada K, Takenaka K, Uehara S, Kono M, et al. (2006) Levels and concentration ratios of polychlorinated biphenyls and polybrominated diphenyl ethers in serum and breast milk in Japanese mothers. Environ Health Perspect 114: 1179–1185.

43. Jin J, Wang Y, Yang C, Hu J, Liu W, et al. (2009) Polybrominated diphenyl ethers in the serum and breast milk of the resident population from production area, China. Environ Int 35: 1048–1052.

44. Lindberg P, Sellstroem U, Hagberg L, de Wit CA (2004) Higher brominated diphenyl ethers and hexabromocyclododecane found in eggs of peregrine falcons (Falco peregrinus) breeding in Sweden. Environ Sci Technol 38: 93–96.

45. Morck A, Hakk H, Orn U, Klasson WE (2003) Decabromodiphenyl ether in the rat: absorption, distribution, metabolism, and excretion. Drug Metab Dispos 31: 900–907.
47. Chen LG, Mai BX, Bi XH, Chen SJ, Wang XM, et al. (2006) Concentration levels, compositional profiles, and gas-particle partitioning of polybrominated diphenyl ethers in the atmosphere of an urban city in South China. Environ Sci Technol 40: 1190–1196.

48. Luo Y, Luo XJ, Lin Z, Chen SJ, Liu J, et al. (2009) Polybrominated diphenyl ethers in road and farmland soils from an e-waste recycling region in Southern China: concentrations, source profiles, and potential dispersion and deposition. Sci Total Environ 407: 1105–1113.

49. Rice DC, Reeve EA, Herlihy A, Zoeller RT, Thompson WD, et al. (2007) Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. Neurotoxicol Teratol 29: 511–520.

50. Carrizo D, Grimalt JO, Ribas-Fito N, Sunyer J, Torrent M (2007) Influence of breastfeeding in the accumulation of polybromodiphenyl ethers during the first years of child growth. Environ Sci Technol 41: 4907–4912.

51. Chen C, Chen J, Zhao H, Xie Q, Yin Z, et al. (2010) Levels and patterns of polybrominated diphenyl ethers in children’s plasma from Dalian, China. Environ Int 36: 163–167.

52. Perez-Maldonado IN, Ramirez-Jimenez MR, Martinez-Arevalo LP, Lopez-Guzman OD, Athanassiadis I, et al. (2009) Exposure assessment of polybrominated diphenyl ethers (PBDEs) in Mexican children. Chemosphere 75: 1215–1220.

53. Mazdai A, Dodder NG, Abernathy MP, Hites RA, Bigsby RM (2003) Polybrominated diphenyl ethers in maternal and fetal blood samples. Environ Health Perspect 111: 1249–1252.

54. Toms LM, Harden F, Paepeke O, Hobson P, Ryan JJ, et al. (2008) Higher accumulation of polybrominated diphenyl ethers in infants than in adults. Environ Sci Technol 42: 7510–7515.

55. Fangstrom B, Hovander L, Bignert A, Athanassiadis I, Linderholm L, et al. (2005) Concentrations of polybrominated diphenyl ethers, polychlorinated biphenyls, and polychlorobiphenylols in serum from pregnant Faroese women and their children 7 years later. Environ Sci Technol 39: 9457–9463.

56. Eskenazi B, Fenster L, Castorina R, Marks AR, Sjodin A, et al. (2011) A comparison of PBDE serum concentrations in Mexican and Mexican-American children living in California. Environ Health Perspect 119: 1442–1448.

57. Fischer D, Hooper K, Athanasiadou M, Athanassiadis I, Bergman A (2006) Children show highest levels of polybrominated diphenyl ethers in a California family of four: a case study. Environ Health Perspect 114: 1581–1584.

58. Lunder S, Hovander L, Athanassiads I, Bergman A (2010) Significantly higher polybrominated diphenyl ether levels in young U.S. children than in their mothers. Environ Sci Technol 44: 7510–7515.

59. Yorita CK (2013) Metals in blood and urine, and thyroid function among adults in the United States 2007–2008. Int J Hyg Environ Health 216: 624–632.

60. Wang H, Zhang Y, Liu Q, Wang F, Nie J, et al. (2010) Examining the relationship between brominated flame retardants (BFR) exposure and changes of thyroid hormone levels around e-waste dismantling sites. Int J Hyg Environ Health 213: 369–380.

61. Ste-Marie N, Venners S, Webster G (2012) Effects of polybrominated diphenyl ethers on thyroid hormones in pregnant women and newborn children. Am J Epidemiol 176: 180.

62. Chevrier J, Harley KG, Bradman A, Gharbi M, Sjodin A, et al. (2010) Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. Environ Health Perspect 118: 1444–1449.

63. Xu P, Lou X, Ding G, Shen H, Wu L, et al. (2014) Association of PCB, PBDE and PCDD/F body burdens with hormone levels for children in an e-waste dismantling area of Zhejiang Province, China. Sci Total Environ 499: 55–61.

64. Han G, Ding G, Lou X, Wang X, Han J, et al. (2011) Correlations of PCBs, DIOXIN, and PBDE with TSH in children’s blood in areas of computer E-waste recycling. Biomed Environ Sci 24: 112–116.

65. Herbstman JB, Sjodin A, Apelberg BJ, Witter FR, Halden RU, et al. (2008) Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polybrominated diphenyl ether (PBDE) and neonatal thyroid hormone levels. Environ Health Perspect 116: 1376–1382.

66. Link B, Gabrio T, Zoellner I, Piechotowski I, Paepeke O, et al. (2005) Biomonitoring of persistent organochlorine pesticides, PCDD/PCDFs and dioxin-like PCBs in blood of children from South West Germany (Baden-Wuerttemberg) from 1993 to 2003. Chemosphere 58: 1185–1201.
67. Penny R, Spencer CA, Frasier SD, Nicoloff JT (1983) Thyroid-stimulating hormone and thyroglobulin levels decrease with chronological age in children and adolescents. J Clin Endocrinol Metab 56: 177–180.

68. Hallgren S, Sinjari T, Hakansson H, Darnerud PO (2001) Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. Arch Toxicol 75: 200–208.

69. Zhou T, Ross DG, DeVito MJ, Crofton KM (2001) Effects of short-term in vivo exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. Toxicol Sci 61: 76–82.

70. Hallgren S, Darnerud PO (2002) Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats-testing interactions and mechanisms for thyroid hormone effects. Toxicology 177: 227–243.

71. Turyk ME, Persky VW, Imm P, Knobeloch L, Chatterton R, et al. (2008) Hormone disruption by PBDEs in adult male sport fish consumers. Environ Health Perspect 116: 1635–1641.

72. Zhang J, Jiang Y, Zhou J, Wu B, Liang Y, et al. (2010) Elevated body burdens of PBDEs, dioxins, and PCBs on thyroid hormone homeostasis at an electronic waste recycling site in China. Environ Sci Technol 44: 3956–3962.

73. Zota AR, Park JS, Wang Y, Petreas M, Zoeller RT, et al. (2011) Polybrominated diphenyl ethers, hydroxylated polybrominated diphenyl ethers, and measures of thyroid function in second trimester pregnant women in California. Environ Sci Technol 45: 7896–7905.

74. Shy CG, Huang HL, Chao HR, Chang-Chien GP (2012) Cord blood levels of thyroid hormones and IGF-1 weakly correlate with breast milk levels of PBDEs in Taiwan. Int J Hyg Environ Health 215: 345–351.

75. Talsness CE (2008) Overview of toxicological aspects of polybrominated diphenyl ethers: a flame-retardant additive in several consumer products. Environ Res 108: 158–167.