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# Polybrominated diphenyl ethers (PBDEs) and thyroid hormones in cord blood☆

Guodong Ding [a, b, 1], Jing Yu [c, 1], Limei Chen [d], Caifeng Wang [d], Yijun Zhou [d], Yi Hu [d], Rong Shi [d], Yan Zhang [d], Chang Cui [e], Yu Gao [d], Ying Tian [a, d, *], Fang Liu [b, **]

[a] MOE and Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Department of Pediatrics, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China
[c] Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital East Campus Affiliated to Shanghai University of Medicine & Health Sciences, Shanghai, China
[d] Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[e] Research Base of Key Laboratory of Surveillance and Early-warning on Infectious Disease in China CDC, Shanghai Pudong New Area Center for Disease Control and Prevention, Shanghai, China

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ABSTRACT

Human exposure to polybrominated diphenyl ethers (PBDEs) has been increasing over the last three decades in China and around the world. Animal studies suggest that PBDEs could reduce blood levels of thyroid hormones, but it is unclear whether PBDEs disrupt thyroid function in humans. We used data from a prospective birth cohort of 123 pregnant women who were enrolled between September 2010 and March 2011 in Shandong, China. We measured the concentrations of eight PBDE congeners (n = 106) and five thyroid hormones (n = 107) in cord serum samples. We examined the relationship between prenatal exposure to PBDEs and thyroid function (n = 90). Median concentrations of BDEs 47, 99, 100, and 153 (detection frequencies > 75%) were 3.96, 8.27, 3.31, and 1.89 ng/g lipid, respectively. A 10-fold increase in BDE-99 and $\Sigma_4$ PBDEs (the sum of BDEs 47, 99, 100, and 153) concentrations was associated with a 0.41 μg/dL (95% confidence interval [CI]: 0.10 to 0.72) and 0.37 μg/dL (95% CI: 0.06 to 0.68) increase in total thyroxine levels ($TT_4$), respectively. No associations were found between other individual congeners and any of the five thyroid hormones. Our study suggests that prenatal exposure to PBDEs may be associated with higher $TT_4$ in cord blood. Given the inconsistent findings across existing studies, our results need to be confirmed in additional studies.



## 1. Introduction

Polybrominated diphenyl ethers (PBDEs), a family of brominated flame retardants (BFRs), are synthetic chemicals which have been used as flame retardants for several decades in a wide array of consumer products such as electronics, furniture, textiles, and construction materials. Because PBDEs are semivolatile and are not covalently bound to consumer products, they have the propensity to be released into the environment (Darnerud et al., 2001). Furthermore, PBDEs are considered to be a group of persistent organic pollutants (POPs) due to similar properties with polychlorinated biphenyls (PCBs) and DDT in terms of lipophilicity, bioaccumulation, and persistence (Hooper and McDonald, 2000). Consequently, PBDEs are ubiquitous contaminants commonly detected in the environment, animals, and humans throughout the world (Hites, 2004). Human exposure to PBDEs comes primarily from dust and diet, particularly via air and ingestion of indoor dust and through intake of vegetable and animal products (Frederiksen et al., 2009). PBDE concentrations in human serum, adipose tissue, and/or breast milk samples collected in Asia, Europe, and North America have been dramatically increasing in the last three decades (Thomsen et al., 2002; Schecter et al., 2005; Kim et al., 2012; Ni

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* Corresponding author. MOE and Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, 200092 Shanghai, China.
** Corresponding author. Department of Pediatrics, Shanghai East Hospital, Tongji University School of Medicine, 150 Jimo Road, 200120 Shanghai, China..
*E-mail addresses:* tianmiejp@sjtu.edu.cn (Y. Tian), liufangsh30@163.com (F. Liu).
[1] Guodong Ding and Jing Yu are jointly first authors.

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et al., 2013; Linares et al., 2015), suggesting that exposure to PBDEs could be an important public health issue deserving greater attention.

Prenatal or early-life exposure to PBDEs can cause long-lasting behavioral alterations, including changes in spontaneous motor activity characterized by hyperactivity, decreased habituation, and disruption of learning and memory in animal studies (Viberg et al., 2003; Kuriyama et al., 2005; Rice et al., 2007; Costa and Giordano, 2007). In humans, prenatal PBDE levels were found to be associated with lower scores on measures of intelligence and attention (Herbstman et al., 2010; Chen et al., 2014; Ding et al., 2015) and poorer birth outcomes (Wu et al., 2010; Harley et al., 2011; Chen et al., 2015). Thyroid hormones are known to play an essential role in fetal growth and neurological development. Given the structural similarity of PBDEs and their hydroxylated metabolites to thyroid hormones, disruption of thyroid homeostasis has thus been proposed frequently as a critical underlying mechanism that could link PBDE exposures to a number of adverse outcomes (Czerska et al., 2013).

Various animal studies have investigated the association between prenatal or early-life exposure to PBDEs and thyroid hormones, and many of those studies were quite consistent in showing a decrease in T4 levels following exposure to PBDEs (Zhou et al., 2002; Rice et al., 2007; Kim et al., 2009a; Kodavanti et al., 2010), suggesting a hypothyroxinemic or hypothyroid effect. Current hypotheses relate to an enhanced metabolism and excretion of $T_4$ as a result of exposure to PBDEs (Zhou et al., 2002), and/or to an interaction of PBDEs with the thyroid hormone transport system (Richardson et al., 2008). However, several human epidemiological studies examining PBDE exposures in relation to thyroid function have produced inconsistent results, with some revealing positive association (Stapleton et al., 2011; Vuong et al., 2015), some reporting negative relationship (Herbstman et al., 2008; Lin et al., 2011; Abdelouahab et al., 2013), and others showing no apparent correlation (Mazdai et al., 2003; Kim et al., 2009b; Zhang et al., 2010). Further, most of these studies have examined the associations between PBDEs and thyroid hormones among pregnant women during gestation and only a few studies assessed PBDEs and thyroid hormones in cord blood (Mazdai et al., 2003; Herbstman et al., 2008; Kim et al., 2009b; Lin et al., 2011). Measuring PBDEs in cord blood is noninvasive and is probably a direct measure of prenatal exposure.

China is one of the few countries in the world which produces BFRs and has an increasing annual domestic market demand. The nationwide production of BFRs reached 10,000 tons in the year of 2000 and the demand for PBDEs each year has been elevating at a rate of 8%, which would inevitably result in continuous increase of PBDE levels in our environment (Jin et al., 2009; Ding et al., 2015). Up until now, there have been no legal restrictions on the production and use of penta-BDEs, octa-BDEs, and deca-BDEs in mainland China. Given the inconsistent results of studies linking PBDEs and thyroid function and the elevated body burden of PBDEs in Chinese population, we examined the relationship of prenatal exposure to PBDEs and thyroid hormones measured in cord blood from a pregnancy cohort in Shandong, China.

## 2. Methods

### 2.1. Participants

We used data from a birth cohort study which began in 2010 evaluating the association between environmental exposures and the health of pregnant women and their children living in a rural community in the southern coastal area of Laizhou Wan (Bay) of the Bohai Sea in Shandong province, northern China (LW birth cohort). Detailed methods for the LW birth cohort have been published elsewhere (Ding et al., 2013, 2015).

Briefly, pregnant women were recruited at the time of admission for labor and delivery in the only county hospital which provides obstetric service and care in this area. Women were eligible to participate if they had a singleton pregnancy, were $\geq$18 years of age; resided in the area for $\geq$3 years; and had no report of assisted reproduction, pre-existing diabetes mellitus or gestational diabetes, chronic or pregnancy-associated hypertension, HIV infection or AIDS, and illicit drug use (Ding et al., 2013, 2015). From September 2010 to March 2011, a total of 162 women met the eligibility criteria, among whom 145 women agreed to take part in this study (response rate 89.5%). We further restricted the sample to women with complete data for major confounders and PBDEs ($n = 106$) or thyroid hormones measured in cord serum ($n = 107$). The total number that had complete information on major confounders, PBDEs, and thyroid hormones is ninety. Study participants provided written informed consent, and all research activities were approved by the Medical Ethics Committee of Xinhua hospital, Shanghai Jiao Tong University School of Medicine. The cohort study was performed in accordance with the revised version of the Declaration of Helsinki.

### 2.2. Data collection

Specially trained registered nurses interviewed the women shortly after delivery in the hospital using structured questionnaires. The questionnaire included information on social and demographic characteristics as well as on environmental exposure and living habits (Ding et al., 2013, 2015).

Cord blood samples were collected from an umbilical vein immediately post-delivery. Cord serum was separated from clotted blood samples and stored at $-80$ °C until shipment on dry ice to Minzu University of China (Beijing, China). PBDEs extraction and gravimetric lipid determination procedures have been described elsewhere (Hovander et al., 2000). Cord serum samples were analyzed for eight PBDE congeners including BDEs 28, 47, 85, 99, 100, 153, 154, and 183 using a gas chromatography–mass spectrometer (Agilent Technologies, Palo Alto, CA) with negative chemical ionization. PBDE concentrations are expressed on a serum lipid basis (nanograms per gram lipids) to account for their lipophilic property. The limit of detections (LODs) ranged from 0.24 to 0.48 ng/g lipid in serum samples. Details of serum analyses and quality control procedures, including detection limits and use of blanks, are described elsewhere (Cui et al., 2012; Ding et al., 2015).

Thyroid stimulating hormone (TSH), total thyroxine ($TT_4$), free T4 ($FT_4$), total triiodothyronine ($TT_3$), and free $T_3$ ($FT_3$) in cord serum samples were analyzed using the method of chemiluminescence immunoassay (CLIA) by the Clinical Laboratory in the hospital. Commercial kits for TSH, $TT_4$, $FT_4$, $TT_3$, and $FT_3$ were purchased from the Autobio Diagnostics Co., Ltd. (Zhenzhou, Henan provive, China). Determinations and quality control were made following the manufacturer's instruction.

### 2.3. Statistical analysis

Descriptive statistics were used to present the characteristics of the study population, individual PBDE congeners, and thyroid hormones. Correlations between PBDE congeners and thyroid hormones were initially assessed using Spearman rank-order correlation. We further conducted linear regression models to estimate beta coefficients and 95% confidence intervals (CIs) for PBDEs in relation to each thyroid hormone in cord serum.

PBDE congeners which were frequently detected in cord serum (detection frequencies > 75%) were handled as continuous