



Impact of Brominated POPs on the Neurodevelopment and Thyroid Hormones of Young Children in an Indoor Environment—A Review

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ABSTRACT

The goal of this report is to evaluate brominated persistent organic pollutants (POPs) in the indoor air and dust to further assess their health effects on thyroid hormones and neurodevelopment in infants, toddlers, and young children. This category of brominated POPs includes polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDs), polybrominated biphenyls (PBBs), and polybrominated dibenzo-*p*-dioxins (PBDD/DFs). These organobromines are lipophilic compounds which resist physical and chemical degradation in the environment and biota, and so easily bioaccumulate in adipose tissue. Brominated POPs, particularly in brominated fire retardants (BFRs) such as PBDEs, HBCDs, and PBBs, are ubiquitous in indoor environments due to their inadvertent release from certain consumer products. Some of these organobromines have been recognized in some *in-vitro* and *in-vivo* studies to be neurotoxins and disrupt thyroid hormones, although the evidence from actual epidemiological studies is contradicted and inconsistent, especially for infants, toddlers, and young children, who are particularly vulnerable to these substances as they spend most of their time in the home. This report focuses on exposure to PBDEs, HBCDs, PBBs, and PBDD/DFs in the indoor dust and on the indoor aerosol, to explore their association with human health, particularly the disruption of thyroid hormones and neurodevelopment in early childhood.

Keywords: Brominated persistent organic pollutants; Dust; Aerosol; Thyroid hormones; Neurodevelopment.

INTRODUCTION

Organobromine compounds, including brominated fire retardants (BFRs) and polybrominated dibenzo-*p*-dioxins/furans (PBDD/DFs) have emerged as globally persistent organic pollutants (POPs) in the recent years. These brominated POPs have an unusually high resistance to chemical, physical, and biological degradation and are ubiquitous in the environment and they are also easily bioaccumulated at the biota (de Boer *et al.*, 1998; Darnerud *et al.*, 2001; de Wit, 2002). BFRs are included in polybrominated diphenyl ethers (PBDEs), polybrominated biphenyls (PBBs), and hexabromocyclododecanes (HBCDs). Besides the commercial PBDE mixtures, combustion sources have been recognized an important atmospheric

PBDE sources (Wang *et al.*, 2010a, b, 2011). BDE-209 is the indicatory congener of important combustion sources (Wang *et al.*, 2010a, c). A recent study has showed that for indoor and workplace air, their BDE-209 could be from the evaporative releases of products containing deca-BDE mixture, and the ventilation with outdoor ambient air (Wang *et al.*, 2011). Many reports are also indicated that indoor air may be one of significant sources for the contamination of PBDEs and HBCDs into outdoor air through ventilation system or naturally dispersion (Abdallah *et al.*, 2008; Besis and Samara, 2012; Björklund *et al.*, 2012; Thuresson *et al.*, 2012). Furthermore, boilers fueled with woods also emit PBDEs through their stack flue gases (Wang *et al.*, 2010a), therefore, stoves and fireplaces that fuelled with woods could be a potential PBDE sources to the indoor environment. PBDEs are widely used in a number of commercial products, such as upholstered furniture, textiles, and household electronic equipment, as they improve their resistance to fire (de Wit, 2002). Several studies indicated that brominated POP levels, particularly for PBDEs, in indoor dust were associated with POP levels in breast milk and

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hormone levels (i.e., thyroid and sex hormones) in male adults (Wu *et al.*, 2007; Meeker *et al.*, 2009; Johnson *et al.*, 2013).

The manufacture of pentaBDEs and octaBDEs has been banned in Europe and voluntarily phased out in USA since 2004 (Costa and Giordano, 2007), but as of 2012, decaBDE is still produced and widely used in most countries outside of Europe. PBBs and certain PBDEs, such as tetra-, penta-, hexa-, and heptaBDEs have been added to the list of POPs at the Stockholm Convention- Annex A (Stockholm Convention, 2012). Despite the bans of PBDE use in many industrialized countries, including European countries and the United States, PBDEs will be continue to be released from exiting products for many years to come (Frederiksen *et al.*, 2009). Owing to current legislative restrictions on PBDEs, the demands for HBCDs have recently increased. Many studies have reported the global bioaccumulation of HBCD in wild animals and humans (de Wit, 2002, Marvin *et al.*, 2011). Recently, HBCDs have been considered to the list at the Stockholm Convention on POPs (Marvin *et al.*, 2011). Little is known about the effects on people with casual as opposed to occupational exposure to PBDD/DFs and their associated health effects, particularly on infants and toddlers. PBDD/DFs are unintentionally released from various combustion processes of textiles, plastics, building materials, and consumer products containing BFRs, and are also present as impurities in technical mixtures of BFRs, particularly in technical mixtures of pentaBDEs, octaBDEs, and decaBDEs (Hanari *et al.*, 2006). PBDD/DFs and BFRs are globally emerging issues in the field of environmental pollution because they are persistent, bioaccumulative, and toxic.

The chemicals in BFRs have long been recognized as lipophilic endocrine disruptors (Legler and Brouwer, 2003) with a potential for bioaccumulation and biomagnification in the food chain (de Boer *et al.*, 1998; Chen *et al.*, 2012). A very important report has revealed that levels of PCDD/Fs, PCBs, and DDTs in breast milk significantly decreased in most developed countries during the last two decades of 20th Century (1980s–1990s) after governmental regulations have been enacted to reduce their emissions (Noren and Meironyte, 2000). In contrast, levels of PBDEs in human specimens, including breast milk and blood, have dramatically increased in the same period (Noren and Meironyte, 2000; Kalantzi *et al.*, 2004). Recently, an Australian study shows no temporal trend in breast milk levels of HBCD between 1993 and 2009, but PBDE levels in Australian breast milk samples have peak between 2002 and 2004 after which they begin to decline in 2007–2008 (Tomes *et al.*, 2012). In Taiwan, a slight decline of PBDEs in Taiwanese breast milk was found between 2000–2001 and 2007–2008 in our previous study (Koh *et al.*, 2009; Chao *et al.*, 2010a). A declining trend of PBDEs in breast milk may be related to the involuntary phase-out of the use of penta- and octaBDE mixtures since 2005. To date, temporal trends or changes of PBDEs in breast milk have been evaluated and found to be inconsistent with the results in a few studies made after the ban or restriction of the use of PBDEs (Hoopmann *et al.*, 2012; Tomes *et al.*, 2012). In addition, few reports examine the internal doses of PBDD/DFs to explore whether

PBDD/DFs act as endocrine disruptors. Scientific concerns regarding contamination of the environment by PBDD/DFs have been raised because these brominated dioxins are considered to be a byproduct of consumer products containing BFRs during the thermal processes (Sakai *et al.*, 2001).

Infants, toddlers, and children are the most vulnerable population. Prenatal and postnatal exposure to BFRs and PBDD/DFs may cause physiological, developmental, or neurobehavioral damage. In recent years, concerns about the adverse health effects on infants, toddlers, and children after they are exposed to brominated POPs have steadily increased. The indoor environment is likely to be an essential exposure route through dust ingestion, hand-to-mouth behaviour, and respiration inhalation, which leads to accumulate PBDEs in human bodies (Stapleton *et al.*, 2012). Toddlers, infants, and children, unlike adults, are likely to spend almost all their time indoors, and due to their behaviour, are likely to ingest even more of these harmful substances, and as they are in a developmental stage, the overall effects are likely to be more serious and long-lasting (Jones-Otazo *et al.*, 2005; Stapleton *et al.*, 2012). Unfortunately, little is known about the specific health effects on infants, toddlers, and children prenatally or postnatally exposed to PBDD/DFs and HBCD. Only a few epidemiological studies have been conducted on the connection between HBCD and breast milk. Currently our greatest concern is that PBDE exposure may cause alterations in thyroid hormone homeostasis and developmental neurotoxicity during these formative years (Chao *et al.*, 2011; Lin *et al.*, 2011; Shy *et al.*, 2011; Shy *et al.*, 2012), but it is still unknown whether higher levels of HBCDs and PBDD/DFs in infants or toddlers may induce adverse health effects, particularly in the disruption of thyroid hormones or interference with neurodevelopment and neurobehavioral development.

BROMINATED POPS IN INDOOR AEROSOL AND DUST

The ubiquitous existence of BFRs in indoor environments is mainly due to the persistent and the widespread use of certain consumer products, such as furniture, building materials, electronics (e.g., TV sets), electrical wiring, and textile applications. In Table 1, several recent studies have shown that concentrations of brominated POPs, including PBDEs and HBCDs, can be detected in indoor dust and air samples (de Wit *et al.*, 2012; Dirtu *et al.*, 2012; Thuresson *et al.*, 2012). In Sweden, Thuresson *et al.* (2012) indicates that PBDEs can be detected in indoor air and dust from houses, apartments, day care centers, offices, and cars; while HBCDs have been detected in most samples of dust but in only a few indoor air samples. BDE-209 has been found to clearly be the predominant compound among PBDE and HBCD congeners in indoor dust and air, according to most articles published on the topic (de Wit *et al.*, 2012; Dirtu *et al.*, 2012; Thuresson *et al.*, 2012). The Swedish research team also found significant associations between levels of certain PBDEs and HBCDs in indoor air and/or dust (Thuresson *et al.*, 2012). They are confident that it is probably due to certain goods or conditions, including but not limited

Table 1. Current concentrations of PBDEs and HBCDs in the indoor environment.

Countries	Sampling period	Indoor type	Σ PBDEs (ng/g or pg/m ³) ^a	Σ HBCDs (ng/g or pg/m ³) ^a	References
Japan Hokkaido (2 houses)	2006	Indoor air and dust	Concentration: 17–39 (air) and 730 (dust) in House A; 33–55 (air) and 240 (dust) for the sum of BDE-28, 47, 66, 99, 100, 153, 154, 209 Median: 1200 (dust, n = 8) for the sum of BDE-3, 7, 15, 17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 138, 153, 154, 156, 183, 184, 191, 196, 197, 206, 207, 209, NC ^b (air, n = 2)	Concentration: 160–280 (air) and 13000 (dust) in House A; 6.7–10 (air) and 140 (dust) in House B Median: 740 (dust, n = 8), NC (air, n = 2)	Tagigami et al. (2009a)
Japan Osaka (a hotel)	2006–2007	Indoor air and dust	Median: 510 (House, n = 10), 1400 (Apartment, n = 34), 1200 (Office, n = 10), 1200 (Day care, n = 10), 1400 (Car, n = 4) for BDE-28, 47, 99, 153, 183, 197, 206, 207, 208, 209 Median: 330 (House, n = 10), 58 (Apartment, n = 44), 4000 (Office, n = 10), 1400 (Day care, n = 10), 510 (Car, n = 24) for BDE-28, 47, 99, 153, 183, 197, 206, 207, 208, 209	Median: 100 (House, n = 10), 45 (Apartment, n = 34), 300 (Office, n = 10), 340 (Day care, n = 10), 50 (Car, n = 4) Median: 2.0 (House, n = 10), <1.6 (Apartment, n = 44), <1.6 (Office, n = 10), <1.6 (Day care, n = 10), <1.6 (Car, n = 24)	Tagigami et al. (2009b)
Sweden Stockholm (n = 68)	2006	Indoor dust	Median: 203000 (cabin), 2860 (trunk) for the sum of BDE-47, 85, 99, 100, 153, 154, 183, 196, 197, 202, 203, 206, 207, 208, 209	Median: 9200 (cabin), 1300 (trunk) for the sum of α , β , γ -HBCD	Thuresson et al. (2012)
Sweden Stockholm (n = 98)	2006	Indoor air	Geometric mean: 434 for the sum of BDE-17, 28, 47, 66, 85, 99, 100, 153, 154, 183, 209	NA ^c	Thuresson et al. (2012)
United Kingdom West Midlands (n = 14)	2009	Indoor dust in car	Median: 8 for the sum of BDE-28, 47, 99, 100, 153, 154, 183; 275 for BDE-209	Median: 250 for the sum of α , β , γ -HBCD	Diru et al. (2012)
United States North Carolina (n = 81)	2009–2010	House dust	Median: 645 (floor dust), 3180 (electronic dust) for the sum of BDE-7, 15, 17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 138, 139, 140, 153, 154, 183, 184, 191, 196, 197, 203, 206, 207, 208, 209	NA	Stapleton et al. (2012)
Romania Iasi (n = 47)	2010	House dust			
Taiwan Southern Area (n = 18)	2011–2012	indoor dust			Chao et al. (2013)

^a The units in the indoor dust and indoor air are ng/g and pg/m³, respectively.^b Not calculated.^c Not analyzed.

to the presence of electronic consumer products; foam furniture; PUF mattresses or synthetic bed pillows; and floor area; and the construction year of the microenvironment (de Wit *et al.*, 2012). House dust is the main source of infant exposure to endocrine disrupting chemicals, pesticides, PBDEs, and lead (Roberts *et al.*, 2009). Indoor environment or microenvironment is a likely exposure route for children through dust ingestion as a result of hand-to-mouth behaviour and respiration inhalation leading to the bioaccumulation of PBDEs in their bodies (Jones-Otazo *et al.* 2005; Stapleton *et al.*, 2012). As a result, toddlers are estimated to have higher internal levels of PBDEs and HBCDs from dust ingestion when compared with adults (de Wit *et al.*, 2012). Jones-Otazo *et al.* (2005) assert that inadvertent ingestion of house dust contributes most to the exposure of people from when they are toddlers to when they are adults, but breast milk is still the largest contributor to infants' exposure. In a study done in Greater Boston, a statistically significant and positive correlation was discovered between PBDE concentrations in house dust and in breast milk (Wu *et al.*, 2007). A recent study of family members with non-occupational exposure to PBDEs suggests that toddlers and children have a higher risk of PBDE exposure and face higher risks of PBDE-related health effects than their parents (Fischer *et al.*, 2006). Toms *et al.* (2009) investigates concentrations of PBDEs in matched samples of breast milk, dust, and indoor air to determine if levels are based on congener profiles, as the level of bromination increased the contribution of intake decreased via breast milk and increased via dust and the contribution of inhalation to total PBDE intake was minor. The estimated Σ PBDE daily intake from dust for children (49.3 ng/kg b.w./day) during the period from 1–5 years old is six time higher than for adults (7.7 ng/kg b.w./day) because of children's lower body weight and higher dust intake (Lorber, 2008). Toms *et al.* (2009) calculates that the Σ PBDE daily intake from dust in children ranges between 33 and 118 ng/day but for adults is only from 2.5 to 59 ng/day.

PBDES AND HUMAN HEALTH EFFECTS

PBDEs have been shown to cause reproductive disorders, have neurotoxic and developmental effects, and cause endocrine disruption and thyroid gland dysfunction in animal models (Costa and Giordano, 2007; Tseng *et al.*, 2008; Tseng *et al.*, 2011; Liu *et al.*, 2012). Several epidemiological studies in the general population have strengthened the notion that PBDE exposure can induce adverse health effects (Mazdai *et al.*, 2003; Chao *et al.*, 2007; Main *et al.*, 2007; Herbstman *et al.*, 2008; Lim *et al.*, 2008; Turyk *et al.*, 2008; Turyk *et al.*, 2009; Chao *et al.*, 2010b, 2011; Gascon *et al.*, 2012; Shy *et al.*, 2012). There was a non-significant association of Σ PBDEs with diabetes in three studies (Lim *et al.*, 2008; Turyk *et al.*, 2009; Lee *et al.*, 2011), while Lim *et al.* (2008) found that BDE-153 shows an inverted U-shaped association with metabolic syndrome. Lee *et al.* (2012) reports that serum BDE-47 in the elderly is not related to abdominal obesity. However, an earlier report in Taiwan (n = 20) (Wang *et al.*, 2008) (i.e., BDE-47 and 183) and a large-scale

study (n = 1367) by Lim *et al.* (2008) (i.e., BDE-153) both demonstrate a negative correlation between levels of PBDEs and body mass index (BMI). A study for the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) reveals a negative association between serum PBDE levels and child BMI collected from 7-year old Mexican-American children living in an agriculture community in California (n = 272) (Bradman *et al.*, 2012). In addition, two studies, one from Spain (Vizcaino *et al.*, 2010) and one of ours (Shy *et al.*, 2011) have revealed no significant association between maternal education level and cord blood levels of PBDEs. We collected breast milk samples (n = 46) from the same population as the report of Shy *et al.* (2011) and found that higher breast milk Σ PBDEs are present in older women, those with a higher education level, and those who have had occupational exposure (Chao *et al.*, 2010a). For the CHAMACOS cohort, several factors positively correlate with high levels of PBDEs in 7-year old Mexican-American children, for examples: higher PBDE levels in maternal serum during pregnancy, longer duration of lactation for exclusively breastfed infants, and having no safe places to play in their neighbourhood (Bradman *et al.*, 2012).

PBDEs and Reproduction

Our previous study shows that background breast milk levels of BDE-47, 99, 100, and 209 in 20 mothers possibly had a significant association with low birth weight and small birth length for newborns (Chao *et al.*, 2007). A report from the CHAMACOS study (n = 286, pregnant mothers) states that elevated serum levels of BDE-47, 99, and 100 during pregnancy is related to lower birth weight (Harley *et al.*, 2011). For female reproductive toxicity, increased levels of BDE-47, 99, 100, 153, and Σ_4 PBDEs in women's serum are related to women spending more time to conceive, but is not associated with changes in the menstrual cycle (Harley *et al.*, 2010). In our previous study, age-adjusted odds ratios (ORs) of BDE-153, 183, 207, 208, and Σ PBDEs were significantly higher in women with menstrual cycles of average length (i.e., >32 days) compared to the control; while women whose menstruation periods still came irregularly when they were 18 years old had higher age-adjusted ORs of BDE-207, 208, 209, and Σ PBDEs than those whose periods came regularly at the same age (Chao *et al.*, 2010b). Prof. Chen and his team members analyzed the National Health and Nutrition Examination Survey's (NHANES) 2003–2004 data to explore associations between female adolescents' exposure to PBDEs and age at menarche to determine if their current serum PBDE levels are linked to menarche occurring at an earlier age in American female adolescents (Chen *et al.*, 2011). With regard to toxicity for male reproduction, Main *et al.* (2007) found significantly higher Σ PBDEs concentrations in the breast milk of nursing mothers of boys with cryptorchidism than in the nursing mothers of boys not affected by the disorder, and they also found that Σ PBDEs in breast milk associates positively with the serum of luteinizing hormone. Serum BDE-153 in male adults (n = 10) is inversely correlated with semen quality and testes size (Akutsu *et al.*, 2008). In an American study in Massachusetts (Meeker *et al.*, 2009), a study recruited

24 nonsmoking men age 18–54 to investigate house dust PBDE concentrations. Serum hormones revealed that dust PBDE concentrations had negative correlations with the free androgen index, luteinizing hormone (LH) and follicle stimulating hormone (FSH), and positive correlations with inhibin B and sex hormone binding globulin (SHBG). However, epidemiological evidence in PBDEs-induced impacts on reproductive functions remains limited, so it is still unknown whether certain PBDE congeners are able to affect reproduction in males or females. Therefore, longitudinally epidemiological studies to evaluate PBDEs' effects on reproduction are needed.

PBDES AND THYROID HORMONES

Several reports have demonstrated that PBDEs exposure may disrupt thyroid hormone functions, the elimination of thyroid hormones (i.e., thyroxin), bind with thyroid hormone receptors and transporter proteins (i.e., transthyretin), and interfere *in-vivo* and *in-vitro* with thyroid homeostasis (Meerts *et al.*, 2000; Legler and Brouwer, 2003; Costa and Giordano, 2007; Yu *et al.*, 2010; Ernest *et al.*, 2012). Many epidemiological studies that evaluate associations of PBDEs exposure and thyroid hormones in adults and newborns have been published previously, but their results are not consistent (Hagmar *et al.*, 2001; Mazdai *et al.*, 2003; Herbstman *et al.*, 2008; Turyk *et al.*, 2008; Dallaire *et al.*, 2009; Kim *et al.*, 2009; Roze *et al.*, 2009; Chevrier *et al.*, 2010; Zhang *et al.*, 2010; Chevrier *et al.*, 2011; Eggesbø *et al.*, 2011; Gascon *et al.*, 2011; Lin *et al.*, 2011). A few studies report the negative impact of cord blood PBDEs on levels of human thyroid hormones after *in utero* exposure (Herbstman *et al.*, 2008; Lin *et al.*, 2011), but most studies conducted in humans have found no correlations. Recent studies in humans have not consistently concluded that PBDEs exposure disrupts thyroid functions. We listed current reports for associations between human in the early age with exposure to PBDEs and thyroid hormones in Table 2.

Our previous report shows that higher cord blood levels of BDE-153, -154, or -183 are significantly associated with lower cord blood levels of T3 and FT3, whereas increased BDE-100 are positively correlated with a higher T4/T3 ratio (Lin *et al.*, 2011). Similar to the findings of our previous study (Lin *et al.*, 2011), in a cohort study of infants born in the US indicates negative associations between cord blood levels of BDE-100 and BDE-153 and cord blood values of total T4 and FT3 (Herbstman *et al.*, 2008). In contrast, several human studies that assess the associations between PBDEs and thyroid hormones in cord blood find no significant relation (Mazdai *et al.*, 2003; Kim *et al.*, 2009; Zhang *et al.*, 2010; Chevrier *et al.*, 2011; Gascon *et al.*, 2011; Kim *et al.*, 2011). Specifically, Kim *et al.* (2009) finds no apparent relationship between fetal T4 and cord-blood PBDEs in 108 Korean infants. Zhang *et al.* (2010) discovers non-significant correlations between PBDEs and levels of total T3 (TT3), TT4, and TSH in 50 cord blood samples from Chinese infants near an electronic waste recycling site in southeast China. Mazdai *et al.* (2003) finds no apparent correlations between ΣPBDEs and TT4 and

FT4 in 12 sample pairs of maternal and cord blood taken from subjects in the United States. A Spanish cohort study also finds that serum PBDEs had no effect on serum levels of TSH, total T3, and FT4 in 4-year-old children (Gascon *et al.*, 2011). A CHAMACOS cohort study shows the negative significant correlation between neonatal TSH and PBDEs in maternal blood during pregnancy and delivery (Chevrier *et al.*, 2011). Kim *et al.* (2011) discovers no significant associations between thyroid hormones and cord blood PBDEs, but FT4 was negatively and positively correlated with BDE-28 and 153, respectively. Contrary to the above findings, a Dutch study finds that cord blood T3 level have significantly positive correlation with maternal serum levels of BDE-47, BDE-99, and BDE-100 in the 35th week of pregnancy (Roze *et al.*, 2009). Most current epidemiological studies, including our previous study, have not found any relationship between prenatal exposure to PBDEs and cord blood TSH level (Herbstman *et al.*, 2008; Kim *et al.*, 2009; Roze *et al.*, 2009; Zhang *et al.*, 2010; Chevrier *et al.*, 2011; Lin *et al.*, 2011).

In our recently published study (Shy *et al.*, 2012), breast milk levels of certain PBDEs are significantly correlated with cord blood levels of T3, T4, FT4, IGF-1, and FT4/T3, but not TSH. We also find a positive significant association of higher log BDE-154 level with log T4 and log FT4 levels (Shy *et al.*, 2012). An increased log BDE-196 level is significantly and positively linked to the log IGF-1 level. Log FT4 and log IGF-1 has negative significant associations with higher log BDE-99 and log BDE-85 levels, respectively (Shy *et al.*, 2012). A Norwegian Human milk Study (HUMIS) finds no significant association between BDE-47, 99, 153, 154, and 209 in breast milk and TSH in neonates (Eggesbø *et al.*, 2011). In contrast, a higher serum PBDE level is correlated with lower serum TSH values in epidemiological studies in adult men and women, including 270 pregnant American women around their 27th week of gestation (Chevrier *et al.*, 2010), and 308 male Great Lakes sport fish consumers (Turyk *et al.*, 2009), and 110 males consuming Baltic Sea fish (Hagmar *et al.*, 2001). Levels of BDE-28 and 207 in 25 breast milk samples have a significantly positive and negative correlation, respectively, with TSH (Zota *et al.*, 2011). There is still a lack of reliable and consistent epidemiological data to support these findings or to make conjectures based on information extrapolated from *in vivo* data that PBDEs disrupt thyroid hormone homeostasis (Jugan *et al.*, 2010).

PBDES AND NEURODEVELOPMENT OR NEURO-BEHAVIORAL DEVELOPMENT

PBDEs have been linked to irregularities in neurodevelopment and neurobehavioral development in animals and humans. Previous *in vivo* studies have documented that neonatal exposure to PBDEs can cause persistent neurobehavioral defects, including changes in locomotor activity, cognitive effects, spontaneous behavior, and cholinergic susceptibility (Costa and Giordano, 2007). Currently, only eight recent human studies show that *in utero* or postnatal exposure to PBDEs is related with delay

Table 2. Current reports for associations between human in the early age with exposure to PBDEs and thyroid hormones.

Authors	Number	Sampling time	Specimens	Σ PBDEs (ng/g lipid)	Significant findings
Mazdai <i>et al.</i> (2003)	12 pairs	2001	Maternal or cord serum	Median: 37 (maternal serum) and 39 (cord serum) for the sum of BDE-47, 99, 100, 153, 154, 183	No apparent association between serum PBDEs and thyroid hormone concentrations
Herbstman <i>et al.</i> (2008)	289	2004–2005	Cord blood	19.7 (mean) and 18.7 (median) for the sum of BDE-47, 100, 153	BDE-100 was correlated with increased odds of low TT4 in cord blood, increased odds of low cord TT4 and FT4 in relation to BDE-153
Kim <i>et al.</i> (2009)	108	2007	Cord blood	8.23 (median) and 8.38 (mean) for the sum of BDE-28, 47, 99, 100, 153, 154, 183	No apparent associations between cord blood PBDEs and TSH and T4 in maternal and cord blood
Zhang <i>et al.</i> (2010)	50	2007	Cord blood	Median: 23.4 (n = 25; zone A), 16.2 (n = 25; zone B) for the sum of BDE-28, 47, 99, 100, 153, 154	No correlations between cord blood PBDEs and TT3, TT4, and TSH in maternal blood
Chevrier <i>et al.</i> (2011)	289	1999–2000	Mothers' blood at 27th week's gestation and at delivery	Median: 25.4 for the sum of BDE-17, 28, 47, 66, 85, 99, 100, 153, 154, 183	No correlation between PBDEs in maternal blood and TSH in neonatal blood
Gascon <i>et al.</i> (2011)	244	1997–1998	Cord blood (n = 88) and children's blood (n = 244)	Median: 2.86 (cord blood) and 0.36 (children's blood) for the sum of BDE-12-13, 17, 28-33, 32, 47, 66, 71, 85, 99, 100, 116, 119, 126, 138, 153, 154, 155, 183, 190	No differences in TSH, TT3, and FT4 between PBDE exposed and reference groups
Lin <i>et al.</i> (2011)	54	2007–2008	Cord blood	4.72 (mean) and 3.49 (median) for the sum of BDE-15, 28, 47, 99, 100, 153, 154, 183	Increased BDE-154 was associated with lower T3. Lower FT3 was correlated with increased BE-153 and 183, respectively. In contrast, the increased T4/T3 ratio was related with BDE-100.
Kim <i>et al.</i> (2011)	111	2008–2009	Cord blood (n = 90) breast milk (n = 21)	Mean: 16.3 (cord blood) and 2.65 (breast milk) for the sum of BDE-28, 47, 99, 100, 153, 154, 183	A negative correlation between breast milk BDE-28 and children's FT4.
Shy <i>et al.</i> (2012)	149	2000–2001 2007–2009	Breast milk	3.38 (median) and 5.34 (mean) in 2000–2001, 3.13 (median) and 5.22 (mean) in 2007–2009 for the sum of BDE-28, 47, 49, 85, 99, 100, 153, 154, 183, 196, 197, 206, 207, 209	A slightly positive correlation was between cord blood T4 and breast milk BDE-154. Cord blood FT4 was slightly correlated with increased BDE-99, but weakly correlated with decreased BDE-154.

in the neurodevelopment of infants, toddlers, or young children (Roze *et al.*, 2009; Herbstman *et al.*, 2010; Chao *et al.*, 2011; Gascon *et al.*, 2011; Shy *et al.*, 2011; Gascon *et al.*, 2012; Hoffman *et al.*, 2012; Eskenazi *et al.*, 2013) in Table 3. Although it has been demonstrated that PBDEs exposure delays the neurodevelopment of neonates and adults in animal models, only four epidemiological studies have examined the correlations between infants' or toddlers' neurodevelopment and PBDEs exposure, particularly for octaBDEs, nonaBDEs, and decaBDE (Herbstman *et al.*, 2010; Chao *et al.*, 2011; Shy *et al.*, 2011; Gascon *et al.*, 2012).

Two research teams, Herbstman *et al.* (2010) and Gascon *et al.* (2012), have used the Bayley Scale of Infants and Development, Version II, (BSID-II) to examine whether infants, toddlers, or young children with *in utero* or postnatal exposure to PBDEs experienced neurodevelopmental disorder. Herbstman *et al.* (2010) finds that associations are inversely significant for the 12-month Psychomotor Development Index (PDI) (BDE-47), 24-month Mental Development Index (MDI) (BDE-47, 99, and 100), 36-month MDI (BDE-100), 48-month full-scale and verbal IQ (BDE-47, 99, and 100), and 48-month and 72-month performance IQ (BDE-100) when their subjects were prenatally exposed to PBDEs. A recent Spanish study is explored associations between breast milk PBDEs (BDE-47, 99, 100, 153, 154, 183, and 209) and BSID-II and discovered that only BDE-209 is inversely and significantly correlated with MDI, but this association has only a weak and imprecise margin of significance after adjustments are made for PCBs, HCB, and DDE (Gascon *et al.*, 2012).

In our two previous studies (Chao *et al.*, 2011; Shy *et al.*, 2011), a Bayley-III test (cognition, language, motor, social-emotion, and adaptive behavior) is performed on infants who have been prenatally or perinatal exposed to PBDEs. As compared to the lower PBDEs group (Σ_{11} PBDEs < 4.63 ng/g lipid), the higher PBDEs group (Σ_{11} PBDEs > 4.63 ng/g lipid) has a significantly higher odds ratio (OR) of the cognition score as well as a lower OR of the adaptive behavior score (Shy *et al.*, 2011). For associations between breast milk PBDEs and neurodevelopment (Chao *et al.*, 2011), a significantly inverse association between BDE-209 and the cognitive scale is found after multivariate stepwise linear regression analyses. In contrast, the language scale is positively correlated with BDE-196 in breast milk. Based on our findings, we suggest that prenatal or perinatal PBDEs exposure may affect infant neurodevelopment.

Two European studies are conducted to examine associations between prenatal PBDEs exposure and children's neuropsychological development and behavior (Roze *et al.*, 2009; Gacon *et al.*, 2011). Roze *et al.* (2009) states that prenatal PBDE exposure (maternal blood in 35 weeks of gestation) is probably related to irregular outcomes in the field of cognition (the Wechsler Preschool and Primary Scale of Intelligence, Revised Edition (WPPSI-R)) and behavior (the parents completed the Child Behavior Checklist (CBCL)). For instance, negative associations between PBDE exposure and children's neurodevelopment are shown for fine manipulative abilities (BDE-154), verbal memory (BDE-153), and sustained attention (BDE-47, 99, and 100), and

positive correlations are found for total behavioral outcome (BDE-99 and 100) and internalizing behavior (BDE-47, 99, and 100) in Dutch children aged 5–6 (Roze *et al.*, 2009). Gacon *et al.* (2011) reports that prenatal exposure to PBDEs (BDE-47, 99, and 100) and Σ_3 PBDEs (the sum of BDE-47, 99, and 100) are not significantly correlated with cognitive and motor values (McCarthy Scales of Children's Abilities) or social competence (California Preschool Social Competence Scale). Neither of these European studies shows any association with attention deficit hyperactivity disorders (ADHD) in young people who experienced prenatal PBDEs exposure.

In addition, an American report from the Pregnancy Infection and Nutrition (PIN) and PIN Babies (a cohort of North Carolina pregnant women and their children through 36 months of age) assert that breast milk PBDEs are positively linked to externalized behaviors and specifically activity/impulsivity behaviors for toddlers, but their associations are not statistically significant ($n = 222$) (Hoffman *et al.*, 2012). Toddlers in this PIN cohort study were assessed using the Infant–Toddler Social and Emotional Assessment (ITSEA) test. A new CHAMACOS study has shown an association between prenatal and childhood PBDE exposure and neurodevelopmental problems when the children are 5 ($n = 310$) and 7 ($n = 323$) years old (Eskenazi *et al.*, 2013). Prof. Eskenazi and her team examine the relationships between serum PBDEs and children's neurobehavioral development, including attention, motor functioning, and cognition, to show the negative impact of PBDEs in maternal serum transmitted during the perinatal period on Verbal Comprehension IQ when the children reached 7 years old. They also find an inverse association of PBDEs in children's serum with children's Full-Scale IQ and Processing Speed IQ at the age of 7 (Eskenazi *et al.*, 2013).

Consequently, based on the current findings of these eight scientific reports it cannot be firmly concluded whether PBDEs exposure affects neurological development in the early life of human beings or not. The major reasons for the inconclusiveness of the data are probably due to lack of PBDEs exposure data from octa to decaBDE in most reports, and large variations among various evaluation tools. Larger and longitudinal epidemiological studies to examine whether PBDE exposure causes developmental neurotoxicity in infants, toddlers, and children are required.

RELATION OF HBCDS, PBBS, AND PBDD/DFS TO HUMAN HEALTH

HBCDs and Human Health

HBCDs are a class of brominated aliphatic cyclic hydrocarbons only used as BFRs. The commercial HBCD mixtures usually contain three stereoisomers, such as α -HBCD, β -HBCD, and γ -HBCD. A global phase-out of HBCDs will be reviewed by the Stockholm Convention POPs in 2013 (Stockholm Convention, 2012). HBCDs are on the Taiwanese Environmental Protection Administration's list of chemicals about which they feel "concerned". In spite of a ban on the use of penta- and octa-BDEs and a voluntary phase out of decaBDE in European and North

Table 3. Current reports for associations between human in the early age with exposure to PBDEs/HBCDs and neurological behavior.

Authors	Concentrations (ng/g lipid)	Neurological evaluation	Significant findings
Roze et al. (2009)	n = 62; ΣPBDEs: 3.4 (median) for the sum of BDE-47, 99, 100, 153, 154; ΣHBCDs: 0.8	Preschool age (5–6 yr); Motor: Movement ABC ^a ; Cognitive: WPPSI-R ^b , NEPSY-II ^c , AVLT ^d . The two subtests “Score1” and “Sky Search” of the Test of Everyday Attention for Children; Behavior: CBCL ^e , ADHD ^f questionnaire	Measurements of PBDEs and HBCDs from the maternal blood at the 35th week of pregnancy; BDE-47: negatively correlated with sustained attention; BDE-99: positively correlated with total behavioral outcome and internalizing behavior (CBCL), negatively correlated with sustained attention; BDE-153: negatively correlated with verbal memory; HBCDs: positively correlated with coordination, total intelligence, and verbal intelligence
Herbstman et al. (2010)	n = 96–118; ΣPBDEs: 18.4 (median) for the sum of BDE-47, 85, 99, 100, 153, 154, 183	BSID-II ^g (12th, 24th, and 36th month), WPPSI-R ^b (48th and 72th month)	PBDE measurements in cord blood; 12-month PDI ^h : negatively correlated with BDE-47; 24-month MDI ⁱ : negatively correlated with BDE-47, 99, and 100; 48-month full-scale and performance IQ: negatively correlated with BDE-100 and 153; 48-month verbal IQ: negatively correlated with BDE-100; 72-month full and performance IQ: negatively correlated with BDE-100
Gascon et al. (2011)	n = 88; ΣPBDEs: 2.86 (median) (cord blood); n = 244, ΣPBDEs: 0.36 (median) (children’s blood at 4 yr) for the sum of BDE-47, 99, 100	4 yr; MSCA ^j , CP-SCS ^k ADHD-DSM-IV ^l	PBDE measurements in cord blood and children’s blood at 4 years old; Elevated BDE-47 in children’s blood associated with higher prevalence of hyperactivity symptoms
Shy et al. (2011)	n = 36; ΣPBDEs: 4.36 (median) for the sum of BDE-15, 28, 47, 49, 99, 100, 153, 154, 183, 196, 197	8–12th month; Bayley-III ^m	PBDEs in cord blood; higher levels of ΣPBDEs linked to higher cognition and lower adaptive behavior scores
Chao et al. (2011)	n = 70; ΣPBDEs: 2.92 (median) for the sum of BDE-28, 47, 49, 99, 100, 153, 154, 183, 196, 197, 203, 206, 207, 208, 209	8–12th month; Bayley-III ^m	PBDEs in breast milk within one month after delivery; the inverse correlation between BDE-209 and cognition score, but the positive association of BDE-196 and language score
Gascon et al. (2012)	n = 290; ΣPBDEs: 3.91 (GM ^o), 4.05 (median) for the sum of BDE-47, 99, 100, 153, 154, 183, 209	12–18th month; BSID-II ⁿ	PBDEs in breast milk during the first 48–96 hours postpartum; the negative correlation between BDE-209 and MDI ¹
Hoffman et al. (2012)	n = 222; ΣPBDEs: 89.3 (mean), 47.3 (median) for the sum of BDE-28, 47, 99, 100, 153	24–36 th month; ITSEA ^o	PBDEs in breast milk at 3 months postpartum; higher levels of BDE-47, 99, and 100 associated with increased externalizing behaviors particularly for activity/impulsivity behaviors
Eskenazi et al. (2013)	n = 212–270; Maternal blood: ΣPBDEs: 26.3 (GM), 24.9 (median); Children’s blood: ΣPBDEs: 84.4 (GM), 84.6 (median) for the sum of BDE-47, 99, 100, 153	5 yr: CBCL ^e , K-CPT ^p ; 7yr: CADSD ^q , maternal report, BASC-2 ^r -maternal report, CADS-teacher’s report, BASC-2-teacher’s report	<i>In utero</i> exposure: PBDEs in maternal blood during pregnancy and at delivery; Children’s exposure: PBDEs in children’s blood at 7 yr; Prenatal ΣPBDEs correlated with poorer fine motor coordination, the nondominant hand, at 5 and 7 years of age; prenatal ΣPBDEs negatively correlated with Verbal Comprehension IQ at the age of 7; children’s blood ΣPBDEs inversely related with Full-Scale IQ and Processing Speed IQ at 7 years old

^aA standardized test of motor skills for children 4–12 years of age; ^bThe Wechsler Preschool and Primary Scale of Intelligence, revised; ^cNeuropsychological Assessment, 2nd edition; ^dThe Rey’s Auditory Verbal Learning Test; ^eThe Child Behavior Checklist; ^fAttention deficit/hyperactivity disorder; ^gThe Bayley Scales of Infant Development, 2nd edition; ^hPsychomotor Development Index; ⁱMental Development Index; ^jThe McCarthy Scales of Children’s Abilities; ^kThe California Preschool Social Competence Scale; ^lThe ADHD Criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition; ^mThe Bayley Scales of Infants and Toddlers Development, Third Edition; ⁿGeometric mean; ^oThe Infant–Toddler Social and Emotional Assessment; ^pThe Conners’ Kiddie Continuous Performance Test; ^qConners’ ADHD/DSM-IV Scales; ^rThe Behavior Assessment System for Children, 2nd edition.

American countries, HBCDs use is still unrestricted in most industrialized countries, including Taiwan. The widespread use of HBCD isomers in the environment and biota has been reported (Covaci *et al.*, 2006). Few epidemiological studies consider the internal doses of HBCDs and their associated health effects, either in the United States or in Asia, including Taiwan (Aylward and Hays, 2011). Recently, HBCDs exposure has been raised to the level of a global issue of scientific concern due to their persistence and toxicity. The time trend of HBCDs does not show a significant increase or decrease, according to two studies (Asante *et al.*, 2011; Tomes *et al.*, 2012). Breast milk HBCD levels are positively correlated with the number of stereo and video electronics in a home, and are lower in women who regularly choose organic foods compared to those who do not, according to a series of tests performed on Boston mothers (Carignan *et al.*, 2012). Eggesbø *et al.* (2011) argues that breast milk HBCDs are not related to cord blood TSH. Asante *et al.* (2011) calculates that the Σ HBCDs daily intake for a breastfed infant through breastfeeding is 0.003 $\mu\text{g}/\text{kg}$ b.w./day in Ghana. The daily HBCDs intake for Spanish breastfed infants has been assessed to be 175 ng/kg b.w./day (Eljarrat *et al.*, 2009). Breast milk HBCD levels do not correlate with maternal age and parity in most epidemiological studies (Tanabe and Kunisue, 2007; Malarvannan *et al.*, 2009; Asante *et al.*, 2011; Malarvannan *et al.*, 2012). Human data from numerous biomonitoring studies of HBCDs performed over the past decade reveal that HBCD concentrations in human blood and breast milk are approximately 1 ng/g lipid, and recent risk assessment evaluations from Health Canada and the European Union have identified the levels in those areas as 10 and 20 mg/kg day, respectively (Aylward and Hays, 2011).

Currently, a new Belgian study which focuses on BFRs exposure in adolescents examines the associations between exposure levels and secretion of thyroid hormones and neurobehavioral functions, which are determined using the Neurobehavioral Evaluation System (NES-3) (Kiciński *et al.*, 2012). Serum levels of HBCDs are not found to be associated with changes in TSH, FT4, and FT3, and were not consistently correlated with NES-3. In contrast, an average decrease of FT3 is found to be significantly related to BDE-99 or 100, whereas BDE-47 is positively correlated with changes in TSH. Serum Σ PBDE levels are significantly linked to low scores of NES-3.

PBBs and Human Health

At the present time there are very few reports on PBBs in human tissues. A large-scale American epidemiological study for infant-mother pairs with accidental exposure to PBBs from 1975 to 1997 (birth cohort in 1975–1978, first follow-up in 1978–1993, second follow-up in 1997) in Michigan indicates that increased BB-153 in maternal serum has no relation to period of gestation, but has a negative relation to low birth weight (Givens *et al.*, 2007). In another epidemiological study from the same accident cohort (Terrell *et al.*, 2009), the overall proportion of male offspring to the cohort mothers is 0.542, higher than the national male proportion of 0.514. If both parents fit into the PBBs birth

cohort, there is an increase in the odds of a male birth with the parents in the high PBBs exposure group as compared to the low exposure group. Small *et al.* (2011) assert that the mid-range and high PBB (BB-153) *in utero* exposure increases the odds of spontaneous abortion compared to the lowest exposure group. Time to pregnancy and infertility are not associated with BB-153 *in utero* exposure.

PBDD/DFs and Human Health

To date, few studies have reported on PBDD/DFs in human tissue. The first report on PBDD/DFs in the general population in Asian is Choi's study for Japanese adipose tissue, published in 2003 (Choi *et al.*, 2003). His team collects Japanese human adipose tissue in 1970 and 2000 and finds that three dominant PBDD/DF congeners, 2,3,7,8-TeBDD, 2,3,7,8-TeBDF, and 2,3,4,7,8-PeBDF, are higher in 1970 (median: 5.1 pg/g lipid) than in 2000 (3.4 pg/g lipid). The comparable PBDD/DF values are reported in Swedish adipose tissue collected in 2007 (Ericson Jogsten *et al.*, 2010). In a Swedish breast milk study (Kotz *et al.*, 2005), 2,3,7,8-TeBDD and 2,3,7,8-TeBDF is detected in breast milk at levels of 0.55 and 0.33 pg/g lipid, respectively. There have been no conclusive studies reporting on the relation of PBDD/DFs exposure with adverse health effects in humans, including infants and toddlers.

CONCLUSIONS

There has been a negative impact on human health, including disruption of thyroid hormone secretion, induction of neurotoxic effects, and changes in neurobehavioral development after humans were exposed to brominated POPs, especially in infants, toddlers, and young children. PBDEs have been recognized as an endocrine disrupting chemical which creates irregularities in the secretions of thyroid hormones and further alters neurological behavior in neonates and adults, according to *in-vivo* and epidemiological studies. The results of several animal and epidemiological studies for PBDEs are contradictory based on the current evidence. Recently, many researchers have energetically begun studies on human exposure to HBCDs, but few human studies explore the relation of HBCD exposure with thyroid hormones and neurodevelopment. For PBB and PBDD/DF exposure, few *in-vivo* and human studies have focused on the correlations of health outcomes. Future work is constantly emerging, and there is significant encouragement for longitudinal studies measuring the effects of human exposure to brominated POPs and their associated effects on health.

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DISCLAIMER

The authors declare no conflict of interest.

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