Chapter 14
Brominated Flame Retardants (BFRs)

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Abstract Evidence for adverse effects of brominated flame retardants (BFRs) in humans is reviewed, with a focus on polybrominated diphenyl ethers (PBDEs). BFRs may easily leach out during manufacture or the use of consumer products, and enter the environment. Food consumption or ingestion of contaminated dust is among the major pathways of human exposure to BFRs. Epidemiological and experimental reports suggest that exposure to BFRs may induce adverse neurodevelopmental, metabolic, and reproductive effects.

The sex hormone-related effects of BRFs include those related to birth outcomes, growth, and reproductive system. Moreover, several other health consequences such as neurodevelopmental and behavioral disorders, thyroid hormone system, and obesity were identified as endocrine effects of BRFs. Some studies reported conflicting observations; however, their thyroid hormone disruption and neurodevelopmental toxicities have been demonstrated frequently. The use of certain BFRs is banned worldwide, however, BFRs are persistent in the ecosystem and are accumulating in human because of their lipophilicity. Thus, active epidemiological and mechanistic studies, especially on the susceptible populations, are warranted.

Keywords Flame retardants · PBDEs · Birth outcomes · Congenital malformation Neurodevelopmental toxicity · Reproductive toxicity · Thyroid hormone disruption Obesity · Diabetes

14.1 Background

Brominated flame retardants (BFRs) are a group of brominated chemicals that have been used as flame retardant. When heated, BFRs release free bromine atoms and respond to free radicals generated during burning, and thus delay the combustion

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process. Because of this property, this group of compounds have been widely used in various consumer products such as electronics, furnishing, textiles, building materials, and polyurethane foams, to enhance ignition resistance. The use of BFRs has led to frequent detection of several major BRFs, such as tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs), polybrominated biphenyls (PBBs), and hexabromocyclododecanes (HBCDs), in the environmental matrices and humans [1].

PBDEs are an important group of BFRs which have been used in a huge amount worldwide. The total production of PBDE commercial mixtures from 1970 to 2005 is estimated between 1.29 and 1.47 million tonnes worldwide [2]. PBDEs can be classified by the degree of bromination, and depending on the degree and location of bromination, a total of 209 congeners are possible. Among them, the most commonly used commercial PBDE mixtures are in forms of penta-, octa-, and deca-BDE. The most abundant PBDE congeners detected in biota and environment are BDE-47, -99, -100, -153, and -209 (Fig. 14.1).

Because of their structural similarity to T4, it is hypothesized that PBDEs might interfere with thyroid hormone transport and metabolism [3, 4]. Animal experimental studies support the thyroid disrupting effects of PBDEs [5]. As a possible consequence of thyroid disruption, their neurodevelopmental toxicity has been also suggested in both experimental organisms and humans [6]. Owing to the health concerns and their persistent nature, some PBDEs such as hexabromodiphenyl ether and heptabromodiphenyl ether (hexa- and hepta-BDE), tetrabromodiphenyl ether, penta-bromodiphenyl ether (tetra- and penta-BDE), and most recently, deca-BDE were listed in Annex A of the Stockholm Convention as persistent organic pollutants (POPs). Therefore, global efforts have been implemented to eliminate the production and the use of PBDEs. However, given the widespread use of this group of compounds and their persistent nature, PBDEs in the environment and biota are expected to be a lingering public health threat for decades to come.

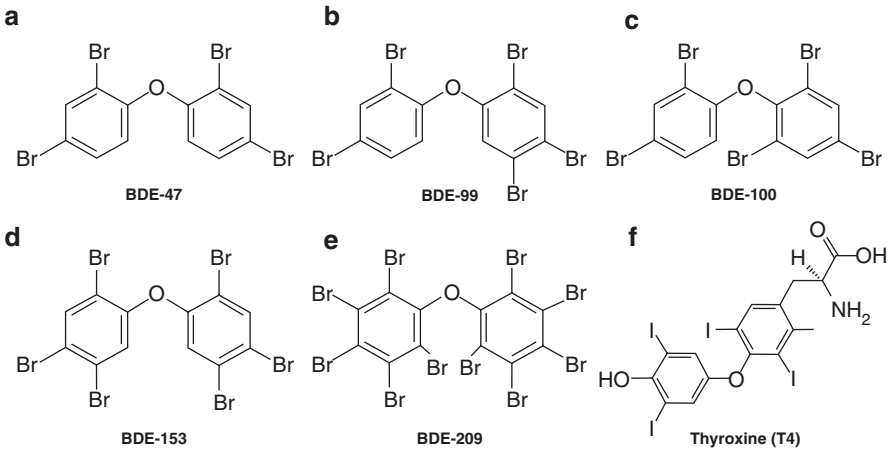

Fig. 14.1 Chemical structures of some major PBDE congeners and thyroxine

Unlike reactive flame retardants (FRs) such as TBBPA, which are covalently bonded into the polymer matrix, PBDEs are additive FRs, which are mixed with the polymer and do not form chemical bonds with the materials [1]. Both additive and reactive FRs can be easily leached out during manufacture or the use of consumer products and subsequently enter the environment. Humans are exposed to PBDEs through ingestion or inhalation of contaminated media. Intake of PBDEs is believed to occur primarily from food consumption, and to a lesser extent through air inhalation and dermal absorption [7–10]. Owing to their bio-accumulative characteristics, PBDEs are expected to be high in seafood, and hence humans with high seafood consumption tend to be exposed more [11]. Dust is another important route of oral exposure [8, 12–15]. In a recent Korean study, it was reported that incidental dust ingestion was major in children while food was more important source of exposure in adults [16].

The developing fetus may be exposed to PBDEs through the placenta [17]. For breastfed infants, breast milk is the most critical source of PBDE exposure [17, 18]. Because many plastic-made toys contain PBDEs, toys may be an important source of exposure to PBDEs in toddlers and young children [19, 20]. Specific behavior patterns of young children, like sucking and crawling, can increase the amount of exposure to PBDEs from the toys [19, 21]. Consequently, several PBDEs were detected at higher concentrations in the serum of toddlers compared to those of adults [22].

14.2 Human Toxicity of Brominated Chemicals

Knowledge about the human toxicity of PBDEs has accumulated in the last two decades. The extent of bromination appears to determine the toxicity of PBDEs, with more brominated congeners being less toxic. Thus, PBDEs found in the environment are likely to be more toxic than the forms which were applied to the products, because debromination occurs when they are released into the environment. Epidemiological evidence suggests an association between endocrine disruption and the developmental effects of PBDEs, even though, often, the observations are not consistent and the underlying etiology is not fully understood. Of particular concern is their association with adverse outcomes in neurobehavioral development among children.

This chapter describes what has been documented as human toxicity for PBDEs in detail, with a focus on endocrine disruption effects. Underlying toxicity mechanisms suggested for these outcomes are also briefly described.

14.2.1 Birth Outcomes

Several epidemiological studies reported the associations between prenatal exposure to PBDEs and birth outcomes [23–32]. Most studies used PBDE levels detected in maternal or cord blood serum to indicate prenatal exposure, and the levels measured in breast milk to represent postnatal exposure.

The associations between PBDE exposure and birth outcomes have been frequently reported worldwide. In many populations, prenatal exposure to PBDEs has been associated with adverse birth outcomes. In a Spanish cohort study, the sum of PBDE concentrations in cord serum was negatively associated with abdominal circumference and the fetal weight estimated at gestational week 12 [23]. In addition, negative associations of maternal serum PBDE concentrations in the first trimester with head circumference and birth weight were reported in the same cohort [23]. Similar observations were reported in China, e.g., negative associations between maternal BDE-28/-100 concentrations and birth length, and BDE-28 concentrations and birth weight [24]. More recently, cord blood concentrations of PBDEs have been shown to be associated with increased head circumference in Chinese prospective birth cohort [25]. In the US general population (N = 234), the association between maternal and paternal PBDE concentrations measured before conception and birth size has been reported. Interestingly, a significant association of both maternal and paternal PBDEs with lower birth weight was found among female infants, whereas paternal concentrations of PBDEs were associated with higher birth weight in boys [26]. In a cohort of pregnant mothers in the USA (N = 286), negative associations were observed between major PBDEs including BDE-47, 99, and 100 and birth weight, even though the significance disappeared when the maternal weight gain was added to the association model [27]. However, in the same study, prenatal exposure to PBDE did not show an association with birth length, head circumference, or gestational duration [27].

Lactational exposure to PBDEs was associated with reduced birth weight, birth length, and chest circumference in a Taiwanese women population [28]. In the USA, weak associations between early-life PBDE exposures via breast milk and anthropometric measurements were shown. However, in this population, weight-to-height z-scores were inversely associated with PBDEs in breast milk among boys; on the contrary, weight-for-height z-scores were positively associated with PBDEs, except for BDE-153, among girls [29]. In a Swedish cohort (1996–2010), maternal breast milk concentrations of PBDEs (sum of BDE-47, 99, 100 and 153) showed an inverse association with birth weight, and the associations became stronger among boys [30]. In Northern Tanzania, BDE-47, -99, -100, and -153 concentrations measured in colostrum were significantly correlated with birth weight and birth length [31].

The associations with preterm birth or gestational age are seldom investigated. One report suggests that high levels of maternal BDE-47 might increase the risk of preterm birth [32]. On the contrary, cord blood concentrations of PBDEs were associated with increased gestational age in Chinese birth cohort, i.e., 0.73 weeks increase for 1 log unit increase of PBDEs [25]. It is not clear whether PBDEs are associated with the gestational period, because only a small number of studies have been conducted, and the directions of the association are conflicting.

Despite accumulating evidence from epidemiological and cross-sectional studies, mechanisms underlying the association between PBDEs and birth outcome are not well understood. For example, maternal BMI or weight gain during pregnancy has been associated with fetal growth, and these maternal somatic characteristics can be influenced by various factors other than PBDEs. Further research is needed to study

whether PBDEs affect fetal growth independently, apart from maternal BMI and weight gain during pregnancy. Moreover, biological mechanisms underlying different responses by the infant sex are not known, and warrant further experimental studies.

14.2.2 Cryptorchidism and Hypospadias

Incidences of congenital malformation among male infants, including cryptorchidism and hypospadias, have been increasing significantly. It is suspected that cryptorchidism and hypospadias may share common risk factors [33]. Chemical-induced sex hormone disruption is one reason for these malformations, as it depends on the fetal conversion of testosterone to dihydrotestosterone, binding of dihydrotestosterone to the androgen receptor, and proper subsequent androgen receptor signaling [34]. The epidemiological studies have suggested associations of flame retardant exposure with genital malformation. Breast milk PBDE concentrations were found to be significantly higher in the boys with cryptorchidism than in controls, in a prospective Danish-Finnish study, 1997–2001 [35]. In a case–control study of Canada, concentrations of BDE-99, 100, and 154 in maternal hair were found to be significantly higher in the cases [36]. In another Canadian population, in utero exposure to PBDEs, as measured in maternal hair, was found to be higher by 48% in mothers who gave birth to infants with hypospadias [37]. Exposure to PBDEs that were measured in cord plasma samples also has been shown to be inversely associated with anogenital distance at birth, 6 months, 12 months, and 48 months of age in Shanghai birth cohort [38]. Considering the anti-androgenic potentials of PBDEs, not only congenital malformation but also adverse consequences in later life stages, warrant further investigations.

14.2.3 Neurodevelopment and Neurobehavioral Disorders

Prenatal exposure to PBDEs has been associated with alterations in behavioral domains, especially motor activity and cognitive function in later stages of life. This association was first reported in a US based study, which showed that children with higher cord serum concentrations of PBDEs scored lower mental and physical test scores at 12–48 and 72 months of age [39]. Subsequently, a number of epidemiological studies of similar design have been published. Maternal serum BDE-47 levels were associated with internalizing and externalizing problems in the Child Behavior Checklist, in toddlers of 18–24 months of age, in Korea [40]. In a Chinese population, cord serum BDE-99 and BDE-47 concentrations were observed to be significantly associated with lower language developmental index and social developmental index, respectively, at 24 months of age, but not at 12 months [41]. In a US population, prenatal exposure to BDE-47 was also shown to be associated with attention problems at 3–7 years of age [42].

Postnatal exposure also has been found to be associated with neurodevelopmental indices in several studies. In a Taiwanese infant population ($N = 70$), elevated PBDE levels in breast milk were shown to be associated with developmental delays in cognition [43]. In a North Carolina study cohort ($N = 222$), lactational PBDE exposure was observed to be correlated with increased activity and impulsive behavior in early childhood [29]. However, there are conflicting observations as well. In a prospective birth cohort in Spain ($N = 88$ for cord blood samples, and $N = 244$ for serum at age 4), no association was seen between PBDE body-burden and motor or cognitive alteration in 4-year-old children [44]. In Belgium adolescents ($N = 515$), no significant association was observed between serum PBDEs, HBCD, and TBBPA concentrations and attention, visual scanning, or working memory test scores. The only exception is the motor function scores in the finger tapping test which were shown to only be significantly associated with serum PBDEs levels in this population, showing a decrease in the number of taps by 5.31, by a two-fold increase of the sum of serum PBDEs [45].

In a California birth cohort, which was conducted in highly contaminated regions of the USA, both prenatal and childhood PBDE exposures were shown to be associated with poor attention, fine motor coordination, and cognition (Full-Scale IQ) at 7 years of age [46]. Several other studies have reported significant associations of prenatal and postnatal PBDE exposure with neurodevelopmental indices in the Health Outcomes and Measures of the Environment (HOME) Study. In the HOME study, maternal serum BDE-28 concentrations were associated with autistic behavior at 4–5 years of age [47], and BDE-47 concentrations were observed to be associated with a decrease in intelligence quotient (IQ) at 5 years of age [48]. However, neither psychomotor nor mental indices of the Bayley Scales of Infant Development-II (BSID-II) at ages 1, 2, and 3 years were shown to be significantly associated with prenatal PBDEs exposure in this cohort [48]. Recently, a follow-up of the HOME study showed that PBDEs concentrations measured in children of 8 years old were significantly associated with poorer emotional and impulse control [49], but those measured in children of 1, 2, 3, and 5 years old did not show an association. The results of the HOME study suggest that at the environmentally relevant levels of exposure, potential of neurodevelopmental toxicity cannot be ignored among children.

The exact mechanisms underlying PBDE neurotoxicity are unclear, but generally, two modes of action affecting brain development have been suggested [6]. One mode of action is a capacity of PBDEs to alter thyroid hormone homeostasis which can eventually result in brain development. The other possibilities include the oxidative stress potential of PBDEs, disruption of calcium signal transduction, and decrease in neural and oligodendrocyte differentiation, thereby affecting nervous system cells directly.

14.2.4 Reproductive Systems

Toxicities of PBDEs on the human reproductive system have not thoroughly studied, and, therefore, there remain gaps in knowledge. Among various reproductive dysfunction indicators, menstruation characteristics and age at puberty have been

studied among female population. In Taiwan, PBDE concentrations in breast milk were not associated with maternal menstruation characteristics (N = 20), even though their concentrations were shown to be significantly related to the birth size of infants [28]. In another study conducted in Taiwanese women (N = 46), higher concentrations of PBDEs were shown to be significantly associated with prolonged length of menstrual cycle and irregular menstruation periods [50]. Menstruation characteristics are closely related to fertility. Age at puberty is also an important indicator of reproductive system toxicity in humans. One longitudinal study in the USA explored the association between pubertal timing and PBDE exposure. In this study, the age at pubertal transition was observed to be significantly higher among girls with greater PBDE levels [51]. Among a small male population recruited through a US infertility clinic (N = 62), positive associations of house dust penta- and octa-PBDE concentrations with hormone levels of estradiol, and sex hormone binding globulin (SHBG), luteinizing hormone (LH) and testosterone were observed, although an inverse association of deca-BDE concentrations with testosterone was seen [52].

14.2.5 Thyroid Hormones

Thyroid hormones play a crucial role in the maintenance and activation of metabolic function, neurodevelopment, and cognitive function. Moderate changes in thyroid hormone levels during pregnancy may be associated with adverse outcomes in offspring [53, 54]. For example, significantly lower IQ scores were found in children of women with thyroid deficiency during pregnancy, even though hormone levels were found within the reference range [55].

Significant associations between PBDEs exposure and thyroid hormone levels among adults are summarized in Table 14.1. Thyroid hormone disruptive effect of PBDEs has been suggested in diverse populations including the general population,

Table 14.1 Summary of associations between PBDE concentrations in serum and thyroid hormone levels reported in adults or pregnant women

Target population	N	Thyroid hormone					Reference [No.]
		fT3	TT3	fT4	TT4	TSH	
Adults	405			↑	↑	↓	Turyk et al. (2008) [56]
Adults	623		↑				Dallaire et al. (2009) [57]
Adults	325	↓	↓	↓		↓	Wang et al. (2010) [58]
Adult, women	745				↓	↑	Oulhote et al. (2016) [59]
Pregnant women	270			–		↓	Chevrier et al. (2010) [60]
Pregnant women	140	–	↑	↑	↑	–	Stapleton et al. (2011) [61]
Pregnant women	380	↓	↓	↓	↓	–	Abdelouahab et al. (2013) [62]
Pregnant women	105	–	–	↓	↓	↑	Kim et al. (2013) [63]
Pregnant women	187	↑	↑	↑	↑		Vuong et al. (2015) [64]

'–' no association; '↑' positive association; '↓' negative association; blank indicates data not provided or available. 'fT3' free T3; 'TT3' total T3; 'fT4' free T4; 'TT4' total T4. Studies with target population of $N > 100$ are included in the table

fish consumers, and workers [56–58]. In recent studies, hypothyroidism, i.e., low T4 and high TSH, was shown to be associated with higher PBDE concentrations [59]. One study reported significant associations between PBDE concentrations and low status of free T3, total T3, free T4, and TSH simultaneously, but the participants were recruited from highly contaminated and occupational exposure conditions (e-waste site) [60]. Similarly, one large population study based on Inuit adults showed that exposure to BDE-47 was positively associated with total T3 [61].

Among pregnant women, the associations between PBDEs and subclinical hypothyroidism or hyperthyroidism were reported in several studies. For example, higher PBDE exposure were associated with lower TSH [62] or higher thyroid hormone levels without lower TSH [63, 64] in pregnant women. Significant disruption of thyroid hormone homeostasis by PBDEs exposure was shown in other studies based on pregnant women as well [65, 66].

The adverse effects of prenatal expsoure in newborn infants have been documented. Herbstman et al. [67] found significant association between cord serum PBDEs and lower T4 or higher TSH among babies born by spontaneous vaginal delivery. Although evidence showing otherwise is often found [68], most studies with neonatal population show significant associations between PBDEs exposure and hypothyroidism, e.g., a decrease in thyroid hormones or increased TSH (Table 14.2). Prenatal PBDE exposure was inversely associated with cord blood free T4 and total T4 in a large population-based study ($N = 260$) [65]. In addition, PBDEs exposure was inversely associated with free T3 and total T3 in cord blood serum in a small population-based study ($N = 50$) [69]. In both studies, however TSH was not influenced by PBDE level. In Korean general population, however, PBDE exposure as measured in cord blood serum was associated with increased TSH in newborn infants without change in T3 and T4 [70].

The adverse effects of PBDEs on thyroid function have also been reported in children and post-menopausal women. In children of China, serum PBDE concentrations were associated with increased T3 [71]. Unlike previous reports, the direc-

Table 14.2 Summary of associations between prenatal PBDE concentrations and thyroid hormone levels of newborn infants or children

Target population	Matrix for PBDEs measurement	*N*	Thyroid hormone					Reference [No.]
			fT3	TT3	fT4	TT4	TSH	
Newborn infants	Cord serum	297			–	↓	↑	Herbstman et al. (2008) [67]
Newborn infants	Maternal serum	260	–	–	↓	↓	–	Abdelouahab et al. (2013) [62]
Newborn infants	Cord serum	104	–	–	–	–	↑	Kim et al. (2015) [69]
Newborn infants	Maternal Serum	104	–	–	–	–	↑	
Children	Serum	T74	↑	–	–	–	–	Guo et al. (2018) [70]

'–' no association; '↑' positive association; '↓' negative association; blank indicates data not provided or available. 'fT3' free T3; 'TT3' total T3; 'fT4' free T4; 'TT4' total T4. Studies with target population of $N > 100$ are included in the table. Those reported null associations were not shown [68]

tion of thyroid hormone change is toward hyperthyroidism, and hence this observation warrants further validations in other children populations. Because thyroid hormones are in apparent crosstalk with estrogens [72], menopausal status of women may influence thyroid hormone disruption by exogenous chemicals, due to the difference in estrogen reserves. One study based on the NHANES data suggested that general adult women with higher PBDE concentrations exhibited increased odds of having thyroid disease. In stratified analysis, this association became stronger in post-menopausal population, suggesting enhanced effects of PBDEs on thyroid signaling by the lowered estrogen levels [73]. In contrast, but partly supporting the crosstalk between thyroid and sex hormones, premenopausal adult women aged between 30 and 50 years of age showed stronger associations between PBDE exposure levels and prevalence of hypothyroidism, compared to older women aged between 51 and 79 years old [59].

PBDEs share structural similarity with T4 (Fig. 14.1) and cause thyroid hormone disruption through alteration of transport and metabolism/deactivation of thyroid hormones. UDP-GT induction catalyzes the glucuronidation of T4, eventually leading to the clearance of circulating T4 [74, 75]. Circulating T4 hormone may competitively binds to the thyroid hormone transport protein [76] and thyroid hormone receptor [77], and therefore has a potential to interfere with the normal transport of thyroid hormones to peripheral tissues, and inhibits cellular uptake of thyroid hormones in thyroid hormone-sensitive cells.

14.2.6 Obesity and Diabetes

Obesity, diabetes and other metabolic dysfunctions are closely related to the thyroid hormone system. Obesity and related diseases are therefore associated with chemicals disrupting thyroid function, e.g., BFRs including PBDEs. The associations of PBDEs and PBBs with diabetes and metabolic syndrome have been reported in a population participating in the US NHANES 2003–2004 [78]. In mothers, who participated in the Salinas birth cohort ($N = 468$), positive associations with BMI were observed for BDE-47, while BDE-153 was shown to be inversely associated [79]. Most recently, a very large French cohort ($N = 71{,}415$) showed that HBCD and PBDEs exposure were associated with type 2 diabetes (T2D) risk [80]. Among children of a California birth cohort ($N = 224$), prenatal exposure to total PBDEs showed positive associations with BMI z-score in boys, while a negative association in girls at age 7 years was observed [81]. However, children's serum BDE-153 concentrations were inversely associated with BMI [81]. Similar negative associations were also observed in the HOME study. PBDEs during pregnancy were shown to be associated with anthropometric measures in children aged 1–8 years ($N = 318$), while maternal serum PBDEs were shown to be associated with lower BMI z-score, decreased waist circumference, and lower percent body fat [82]. In HOME study participants, at age 8 years, ($N = 206$), BDE-153 concentrations in children's serum were shown to be inversely

associated with adiposity measures, but no significant association was found for BDE-28, -47, -99, and -100 [83]. In both studies, negative associations between BDE-153 concentrations and adiposity measures were clear [82, 83]. For BDE-153, the mechanisms involved in reduction of adipose tissue are unknown. For example, a significant increase in serum BDE-153 levels has been shown after weight loss treatments in a group of 94 obese adolescents, without changes in BDE-47 and -100 [84]. BDE-153 has a longer half-life than BDE-47, -99, and -100 [85], leading to greater storage of PBDEs in the adipose tissue of person with higher adiposity. Thus, while experimental studies suggest obesogenic effects of PBDEs [86, 87], reverse causality may be observed in cross-sectional studies.

14.3 Conclusions

Epidemiological evidence indicating endocrine disruption by PBDEs are accumulating, even though inconsistent observations are also reported. PBDEs are associated with thyroid hormone disruption and negative neurodevelopmental outcomes in many populations including newborn children and pregnant women. However, their associations with sex hormone disruption or obesity are less studied and uncertain. Studies on populations at high levels of exposure such as e-waste disposal site residents or people with occupational BFR exposure are also warranted.

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