Chapter 6
Thyroid Hormone System and Development

Sachiko Itoh

Abstract In recent years, many studies have been published regarding thyroid hormones (THs)-disrupting effects of environmental chemicals. THs play a crucial role in normal fetal growth and maturation. Even before the fetal thyroid gland matures and starts to secrete THs, THs are detected in the fetal cerebral cortex, thereby confirming that fetuses completely rely on the maternal TH supply by the end of the first trimester. Therefore, exposure of pregnant women and their fetus to environmental chemicals that can interfere with THs has been of special concern. This chapter covers mainly recent findings on the epidemiological studies which investigated the associations between prenatal exposure to environmental chemicals and neonatal TH concentrations. In addition, possible mechanisms of thyroid-disrupting action by each chemical are drawn such as competitive bindings to TH transport proteins, interference of TH regulation, synthesis, and metabolism. Further, we emphasize a need for longitudinal studies to more completely assess whether the effects of chemical exposure on TH level, particularly during sensitive developmental windows, such as in fetal life and early infancy, are permanent.

Keywords Thyroid hormones · Environmental chemicals · Endocrine disrupters · Prenatal exposure

6.1 Importance of Thyroid Hormones

Thyroid hormones (THs) play a critical role in numerous physiological processes, including the regulation of metabolism, growth and bone remodeling, and development of the nervous system. The main THs, namely thyroxine (T4) and

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3,5,3′-triiodothyronine (T3), are produced by the thyroid gland and widely recognized as essential for fetal development, especially in terms of central nervous system and brain maturation, throughout gestation [1, 2].

The fetal thyroid gland matures by week 11–12 and starts to secrete THs by week 16–18 [3]. However, by week 12, T4 and T3 are already detected in the fetal cerebral cortex, thereby confirming that fetuses rely on maternal TH supply completely by the end of the first trimester [4, 5]. Even after the maturation of the fetal thyroid gland, maternal THs with essential iodine supplies are transferred to the fetus throughout pregnancy [6].

Previous studies have found that even a mild decrease in the level of maternal THs in early pregnancy is related to a lower intelligence quotient (IQ) among neonates [7, 8]. Moreover, a Danish cohort study reported that maternal hyperthyroidism diagnosed within 2 years of a child's birth increased the risk of attention deficit hyperactivity disorder (ADHD), whereas hypothyroidism increased the risk of autism spectrum disorder (ASD) [9]. Higher maternal free T4 (FT4) levels in the early stages of gestation are also associated with a lower birth weight and an increased risk of small-for-gestational age [10]. Therefore, abnormal levels of maternal THs during pregnancy may impair fetal development. Globally, for the detection of thyroid dysfunction and initiation of treatment in the early stages, TH screening programs have been established for pregnant women and their neonates by using blood spot thyroid-stimulating hormone (TSH) or T4 tests or both.

6.2 Regulation of Thyroid Hormone Levels

Circulatory TH levels are strictly maintained within a very narrow range by a negative feedback regulation system in the hypothalamus-pituitary-thyroid (HPT) axis (Fig. 6.1). Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and reaches the TSH-producing cells of the anterior pituitary. The released TSH then binds to the receptor in the thyroid gland, initiating TH synthesis; subsequently, TH is released predominantly as T4—a prohormone—and at low concentrations as an active hormone T3. THs have to be transported into cells for the exertion of their own effects. T4 has to be converted to T3 by deiodinating enzymes, since only T3 can bind to the TH receptor (TR). There are three types of deiodinases, namely type 1 (D1), type 2 (D2), and type 3 (D3).

More than 98% of THs in circulation bind to TH transporter proteins thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin [11]. In humans, TBG is the main transporter protein. TTR is not a major T4 transporter, and its binding capacity is weaker than that of TBG; however, it is considered to be the most important T4 carrier protein in fetuses because it can transfer placenta and cross the blood–brain barrier [12]. TTR is also reported to determine the FT4 levels in the brain's extracellular compartment.

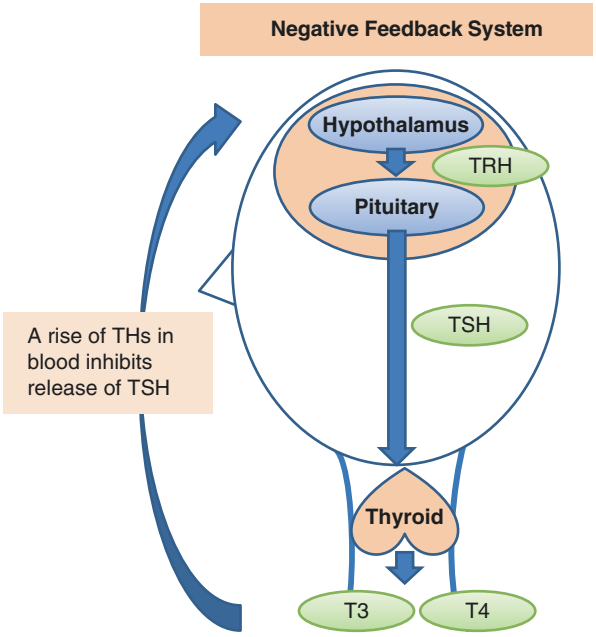

Fig. 6.1 Regulation of thyroid hormone concentrations by negative feedback system. Thyroid hormone (TH) concentrations are strictly controlled via feedback loop system. Thyrotropin-releasing hormone (TRH) is released from hypothalamus and reaches the TSH-producing cells of the anterior pituitary. Released thyroid-stimulating hormone (TSH) stimulates TH synthesis and subsequently T3 and T4 are released in the circulation. Once a rise of THs in blood is detected, it exerts a negative feedback at the level of the hypothalamus and pituitary, leading the inhibition of TSH releasing

6.3 Possible Mechanisms of Thyroid Disruption by Environmental Chemicals

In recent years, many studies have reported on the thyroid-disrupting effects of environmental chemicals. These chemicals are highly persistent and bio-accumulative, and humans and wildlife are constantly exposed to them. Of special concern is the adverse effect of environmental chemicals on pregnant women and their fetus and infants, as thyroid disruption during pregnancy and the early development stage may cause serious neurological dysfunction.

Some in vitro and animal studies have revealed that environmental chemical compounds, such as polychlorinated biphenyl (PCB), dioxin, and perfluoroalkyl substances (PFASs), affect TH levels. There are several possible thyroid-disrupting mechanisms behind this (Fig. 6.2). First, endocrine-disrupting chemicals (EDCs) may directly affect the thyroid gland through the disruption of TH production, interference with receptors and iodine uptake, and inhibition of thyroid peroxidase or

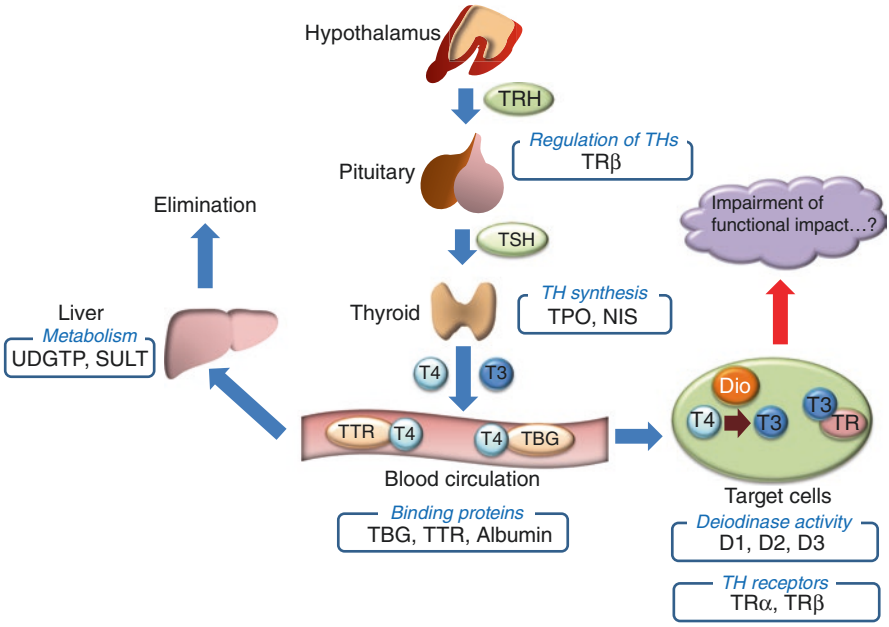

Fig. 6.2 Possible mechanisms of disruption of thyroid hormone homeostasis by EDCs. The pathway of thyroid hormone release, transport, and metabolism. Hypothalamus-pituitary-thyroid (HPT) axis and potential target sites may be disrupted by endocrine disrupting chemicals (EDCs) (Framed actions). *Dio* deiodinase, *NIS* sodium iodide symporter, *SULT* sulfotransferase, *TBG* thyroid biding globulin, *TH* thyroid hormone, *TPO* thyroid peroxidase, *TRH* thyroid releasing hormone, *TSH* thyroid-stimulating hormone, *TTR* transthyretin, *T4* thyroxine, *T3* triiodothyronine, *UDGTP* uridine diphosphate glucuronosyltransferase

sodium iodide symporter (NIS) activity. For example, perchlorate and thiocyanate are known as NIS inhibitors which block iodide uptake into the thyroid gland. Phthalates also change the activity of the NIS, leading to changes in iodide uptake. Second, altered TH levels may be caused by increased biliary excretion. THs are metabolized in the liver by phase two enzymes, namely, sulfotransferase (sulfation) and uridine diphosphate glucuronosyltransferase (conjugation). These enzymes are stimulated by PCBs, dioxin, and Bisphenol A (BPA), leading to the faster excretion of THs. Third, EDCs have a structure that is similar to that of T4. These compounds, mainly POPs such as PCBs, PFASs and PBDEs, competitively bind to TTR instead of T4 itself, leading to a decrease in TH concentrations, while TSH levels may also be disrupted as compensation. As mentioned above, TTR is not among the main TH transporters in humans. However, its binding to EDCs facilitates the transportation of EDCs across the placenta to the fetal compartment. In addition, EDCs can also reach targeted organs such as the brain. THs are transported across the targeted cells of targeted organs. In order to exert their biological effects, THs bind to the TR of the nucleus. Some EDCs reportedly interact with TR and disrupt TR expression by affecting the TR genes.

6.4 Thyroid Hormones and Environmental Chemicals

6.4.1 Polychlorinated Biphenyls and Dioxin

PCBs and dioxins (polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans) are persistent organic pollutants that have the potential to seriously harm human health. PCBs are among the oldest environmental chemicals and were produced, as early as 1881, in Germany. PCBs were widely used in the industrial production of plasticizers, lubricants, electrical equipment, as well as hydraulic and heat transfer fluids. Their manufacture was banned in the mid-1970s due to growing evidence on their toxic effects. However, the general population continues to be exposed to them thorough old products and contaminated food because of their long half-lives and strong bioaccumulation through the food chain. In addition, it is of great concern that they have the ability to cross the placenta, leading to fetal exposure. In particular, the adverse effects of PCBs on neurodevelopment and growth in infancy and early childhood have been reported on. A previous study conducted in the USA showed that the children of women who consumed PCB-contaminated fish from Lake Michigan showed lower IQ scores and behavioral deficits [13]. Subsequently, prenatal exposure to PCBs has been linked with reduced cognitive function [14], mental and motor deficits [15], and increased risk of ADHD and ASD development [16, 17]. Based on these and other studies, the neurodevelopmental impairment associated with PCB exposure in utero has been suspected to disrupt TH homeostasis, which regulates growth and development.

The presumed mechanism of toxicity of PCBs and dioxins is mainly the displacement of T4 with TTR. Numerous experimental publications have confirmed the association of PCB or dioxin exposure with reduced TH levels, especially T4 [18–20]. Moreover, experimental animal studies have presented substantial evidence that in utero exposure to the hydroxylated metabolites of PCB, namely OH-PCBs, affects TH concentrations in offspring [21, 22]. In fact, OH-PCBs are reported to possess a much higher binding affinity to TTR than T4, and their parent compounds, i.e., PCBs [23–25]. The binding of OH-PCBs to TTR is also a matter of great concern because it could promote the distribution of OH-PCBs to the placenta and even the brain. Recent evidence indicates that OH-PCBs may be more toxic than PCBs, although the toxicological effects of these compounds have not been entirely revealed. Additionally, OH-PCBs may inhibit TH sulfation and the D1 activities that convert T4 to T3 or the inactive metabolites (reverse T3), leading to the alteration of T4 levels in circulation [26]. Exposure to dioxins induces UDP-glucuronosyltransferase (UDPGT) activity and the increased excretion of T4 into bile [27]. Dioxins also activate the aryl hydrocarbon receptor (AhR) and thereby interfere with the UDPGTs, as well as PCBs via the constitutive androstane receptor (CAR) and pregnane × receptor (PXR) [28, 29]. Dioxins reportedly decrease the strength of dose-level liver deiodinase activity [30].

As shown in Table 6.1, epidemiological studies have reported that prenatal exposure to PCBs may reduce the TH levels in neonates and infants [31–34] or increase

Table 6.1 Overview of previous reports on POPs exposure and neonatal or infant thyroid hormone parameters (sorted by published year)

Author/year of publish	Year of research	Country	Sample size	Specimen for exposure assessment	Specimen for outcome assessment	PCBs-Dioxins			PFASs								PBDE
						PCDD/PCDF	PCB	OH-PCB	PFPeA	PFHxS	PFOS	PFOA	PFNA	PFDA	PFUnDA	PFTrDA	
Preston et al. 2018 [70]		USA	480	Maternal blood	Heel pick					T4↓	T4↓	T4↓	–				
Itoh et al. 2018 [51]	2002–2005	Japan	222	Maternal blood	Heel pick (day 4)			FT4↑									
Baba et al. 2018 [38]	2002–2006	Japan	385	Maternal blood	Heel pick (day 5)	FT4↑	FT4↑										
Soechitram et al. 2017 [39]	1998–2000	The Netherlands	100	Maternal blood	Cord blood Infant blood (at 3 and 18 months)		Cord blood T3↑, rT3↓	3 months blood T4↑, T3↑, TSH↓ 18 months blood T4↑, T3↑, TSH↓, T4S↑									
Tsai et al. 2017 [71]	2004–2005	Taiwan	118	Cord blood	Cord blood						TSH↑ T4↓	–	–		–		
Berg et al. 2016 [34]	2007–2009	Norway	391	Maternal blood	Heel pick		T3↓			–	TSH↑	–	–	T3↓, FT3↓	–		
Ding et al. 2017 [85]	2010–2011	China	123	Cord blood	Cord blood												TT4↑
Shah-Kulkarni et al. 2016 [74]	2006–2010	Korea	279	Cord blood	Cord blood				T4↑, T3↓	T3↑	–	–	TSH↓		–	–	
Kato et al. 2016 [73]	2002–2005	Japan	392	Maternal blood	Heel pick (day 4)						TSH↓	–					

Leonetti et al. 2016 [86]	2010–2011	USA	95	Placenta	Placenta												T3↑, rT3↓
Kim et al. 2015 [87]		Korea	104	Maternal blood	Cord blood Heel pick (2–7 day after birth)		–										–
				Cord blood	Cord blood Heel pick (2–7 day after birth)		–										Cord blood TSH↑ Heel pick TSH↑
Vuong et al. 2015 [84]	2003–2006	USA	389	Maternal blood	Cord blood												FT3↓
de Cock et al. 2014 [40]	2011–2013	The Netherlands	83	Cord blood	Heel pick		–				–	T4↑					
Wang et al. 2014 [72]	2005–2006	Taiwan	116	Maternal blood	Cord blood					–	–	–	TT3↓, TT4↓	–	–		
Hisada et al. 2013 [41]	2009–2010	Japan	79	Maternal blood	Heel pick (day 5)		–	TSH↑									
Abdelouahab et al. 2013 [50]	2007–2008	Canada	380	Maternal blood	Cord blood		–										FT4↓
Kim et al. 2011 [69]	2008–2009	South Korea	44	Maternal blood	Cord blood						T3↓	–				T3↓T4↓	
				Cord blood	Cord blood						–	–				–	
Chevrier et al. 2011 [88]	1999–2000	USA	289	Maternal blood	Heel pick (after 24 h)												–

(continued)

Table 6.1 (continued)

Author/year of publish	Year of research	Country	Sample size	Specimen for exposure assessment	Specimen for outcome assessment	PCBs-Dioxins			PFASs								PBDE
						PCDD/PCDF	PCB	OH-PCB	PFPeA	PFHxS	PFOS	PFOA	PFNA	PFDA	PFUnDA	PFTrDA	
Lin et al. 2011 [83]	2007–2008	Taiwan	54	Cord blood	Cord blood												T3↓, FT3↓, T4/T3 ratio↑
Lopez-Espinosa et al. 2010 [42]	2004–2006	Spain	453	Cord blood	Heel pick (>day 2)		–										
Darnerud et al. 2010 [33]	1996–1999	Sweden	150	Maternal blood	Infant blood (at 3 weeks/3 months)	–	TT3↓										
Dallaire et al. 2009 [43]	1995–2001	Canada	130	Maternal bloodCord blood	Cord blood		–	–									
Kim 2009	2007	Korea	108	Cord blood	Cord blood												–
Alvarez-Pedrerol et al. 2008 [36]	1997–1998	Spain	27	Cord blood	Infant blood (day 3)		TSH↑										
Wilhelm et al. 2008 [44]	2000–2002	Germany	84	Maternal blood	Cord blood	–	–										
Dallaire et al. 2008 [45]	1993–1997	Canada	2 cohorts 410 and 260	Cord blood	Cord blood		–										

Herbstman et al. 2008 [32]	2004–2005	USA	289	Cord blood	Cord blood Heel pick (day 2)		Cord blood TT4↓, FT4↓ Heel pick TT4↓										Cord blood TT4↓, FT4↓
Maervoet et al. 2007 [31]	2002–2004	Belgium	198	Cord blood	Cord blood	FT3↓ FT4↓	FT3↓ FT4↓										
Chevrier et al. 2007 [35]	1999–2000	USA	285	Maternal blood	Heel pick (after 25 h)		TSH↑										
Otake et al. 2007 [46]	2005	Japan	23	Placental tissue	Heel pick		–	FT4↑									
Wang et al. 2005 [37]	2000–2001	Taiwan	118	Placenta	Cord blood	–	FT4 × TSH↓										
Takser et al. 2005 [47]		Canada	92	Maternal blood Cord blood	Cord blood		–										
Ribas-Fitó 2003 [48]	1997–1999	Spain	70	Cord blood	Infant blood (day 3)		–										
Steuerwald et al. 2000 [49]	1994–1995	Denmark	182	Maternal blood	Cord blood		–										

↑/↓: arrows are indicated as follows: ↓ inversely associated ($p < 0.05$); ↑ positively associated ($p < 0.05$), and [–] no significant association. Blanks indicate not measured in the study

the TSH levels [35, 36]. This indicates that the TSH level is increased as a compensation by decreased peripheral TH levels. Low TH and/or high TSH levels are suggestive of hypothyroidism, as observed in experimental studies. Previous studies conducted in Taiwan have shown that high PCB levels in the placenta were associated with low FT4 × TSH levels in cord blood. This result indicates that PCBs may disrupt the peripheral hormonal balance by affecting the negative feedback system for the maintenance of TH levels [37]. However, some studies found increased TH levels [38, 39] or no significant association between PCBs and THs [40–50].

Regarding prenatal OH-PCB exposure, four of five previous studies demonstrated that it led to TH and TSH disruption [39, 41, 46, 51]. While it is noteworthy that Hisada et al. [41] and Otake et al. [46] observed significant associations between OH-PCBs and THs or TSH, they found no significant association in terms of PCBs. These findings suggest that OH-PCBs may have a stronger effect on THs than PCBs. Furthermore, Soechitram et al. [39] explored the associations of OH-PCBs in maternal blood during pregnancy with the TH levels in their children at three time points, i.e., at birth (cord blood), at 3 months, and 18 months, after birth; they reported that maternal PCB exposure was associated with cord blood TH levels, while maternal OH-PCB exposure was related to TH levels at 3 and 18 months after birth. This indicates that the effect of OH-PCB on THs lasts longer than that of PCBs. Additionally, the results of the aforementioned studies indicate that OH-PCBs have greater toxicity than PCBs. A Canadian study showed no such association among the Inuit [43], even though the exposure level of these people was higher than that observed in other studies, owing to a high consumption of PCB-containing fish. This may be explained by the fact that fish also contain a high amount of iodine. Iodine is an element required for the production of THs, and sufficient intake may prevent thyroid dysfunction.

Regarding dioxins, studies in Japan and Belgium have shown associations between dioxin exposure and neonatal TH levels, although the directions of the results varied [31, 38]. Possible reasons for the discrepancies in the results may be differences in the specimens used for the assessment of dioxin and TH levels. The Belgian study used cord blood for the assessment of both dioxins and THs, while the Japanese study measured the levels of dioxin in maternal blood during pregnancy and THs after birth. Another reason may be the difference in iodine intake via dietary habit. Three previous studies that examined the same association did not demonstrate the presence of any significant association [33, 44, 52].

Overall, epidemiological studies have shown that prenatal exposure to PCBs and dioxins interfere with the TH levels in neonates even after the production of those chemicals was banned. However, there is still inconsistency in the literature in terms of the relationship between PCB and dioxin exposure and TH levels, despite the firm associations between PCB and dioxin exposure and adverse neurodevelopment effects. Further studies are needed to assess whether impaired neurodevelopment is fully explained by disrupted THs in utero and in the early stages of life.

6.4.2 *Perfluoroalkyl Substances*

PFASs are widely used in industrial products such as surfactants, Teflon, carpets, fire-fighting foams, photographic films, and cosmetics due to their unique surfactant properties. They are very stable and therefore extremely persistent and are commonly accumulated in the environment. Human exposure to PFASs mainly occurs orally via the intake of contaminated food, releases from food packaging, drinking water, and dust [53]. As perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are the most commonly detected PFASs in the environment and in humans, their presence in human blood has been reported globally [54–57]. In 2009, PFOS was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants, and PFOA was also proposed to be listed in the Stockholm Convention in 2018. Although PFOS and PFOA are being voluntarily phased out by several industries, they are still present in older products and have long elimination half-lives in human serum (PFOS: 5.3 years, PFOA: 3.8 years) [58]. Recently, other PFASs have replaced PFOS and PFOA, such as perfluorononanoic acid and perfluorodecanoic acid [59]. All these PFASs can cross the placental barrier and be transferred from mother to fetus in humans [57, 60, 61]. Therefore, significant concerns have been raised regarding the adverse effects of in utero exposure to PFASs on the fetus. PFASs reportedly change the expression of synaptophysin and tau proteins in the cerebral cortex and hippocampus, which are essential for normal brain development [62]. Hence, prenatal PFAS exposure may impair infants' neurodevelopment through decreasing TH levels or by other means.

In vitro studies have suggested two possible mechanisms of TH disruption by PFASs; one is the competitive binding to TTR as well as other persistent organic pollutants (POPs) [63] and another is the upregulation of hepatic glucuronidation enzymes and deiodinase in the thyroid gland [64]. Several animal studies have found altered levels of TH after in utero exposure to PFASs. Prenatal exposure to PFOS reduced the T4 levels in rat pups as well as pregnant dams, and postnatal PFOS exposure decreased the T4 levels among rat pups [65–68].

In humans, several studies have examined the effect of PFASs on neonate or infant TH levels (Table 6.1). The effects of PFOS and PFOA exposure have been extensively explored, as much as in nine previous studies. Kim et al. investigated the association of PFASs in maternal blood sera and cord blood with neonatal TH levels in cord blood among participants in South Korea (n = 44) [69]. They reported a negative correlation between maternal PFOS and fetal total T3 and between maternal perfluorotridecanoic acid (PFTrDA) and total T3 and T4 in fetuses; moreover, maternal PFOA was positively correlated with fetal TSH. In addition, other studies have shown the inverse associations of PFAS exposure with TH levels in cord blood or a heel-prick blood test [34, 70–72]. These results of reduced TH levels are consistent with those observed in animal studies. One Japanese study found an inverse association of PFOS with TSH, while no association was observed with THs [73]. As TSH levels are more sensitive than T4 or T3 levels due to strict regulation by the negative feedback system, it may be reasonable to consider that altered TSH levels

are a result of affected THs in circulation. However, TH levels may also increase as a result of PFAS exposure [40, 74]. A Dutch study reported that a high level of PFOA in cord blood was associated with increased total T4 levels in girls, as measured during heel-prick blood draws (n = 83) [40]. In a Korean study, short-chain PFASs such as perfluoro-*n*-pentanoic acid (PFPeA) and perfluorohexanoic acid were associated with increased T3 and T4 levels in girls, while PFPeA was associated with reduced T3 levels in boys [74].

In summary, the effect of PFAS toxicity on TH disruption has generally been established in epidemiological studies. However, there are still issues to be investigated, particularly in terms of which PFASs are likely to have the strongest effect on neonatal THs, as not all PFASs pass through the placenta to fetuses at an equal rate.

6.4.3 Polybrominated Flame Retardants

Polybrominated diphenyl ethers (PBDEs) are synthetic chemicals widely used as flame retardants due to their high flash point. PBDEs are a group of POPs known for their properties such as bioaccumulation, lipophilicity, and persistence [75]. The structures of PBDEs are similar to those of PCBs; therefore, the adverse health impacts of PBDEs are a matter of concern.

Experimental studies have proposed some mechanisms by which PBDEs may interfere with TH levels. PBDEs bind to TH transporters, TBG and TTR, as well as other POPs, leading to a reduction in the T4 level [76, 77]. The binding of PBDEs to TRs is considered to lead to the suppression of T3 levels by the inhibition of T3 binding to TRs [78, 79]. In addition, decabromodiphenyl ether exposure in zebrafish parents downregulates the gene expression of TRs, with a decrease in T4 level, in offspring [80]. PBDEs can also alter thyroid deiodinase activity and upregulate the expression of clearance enzymes, leading to decreased hormone levels in circulation [81, 82]

Human studies have confirmed the effects of PBDE on TH disruption, although the directions of the associations are not consistent (Table 6.1). Three studies in Canada, Taiwan, and the USA reported that PBDE exposure in utero was associated with reduced levels of TH, T3, and T4 [32, 50, 83, 84]. One Chinese study found a positive association between PBDE levels and T3 in cord blood [85]. Leonetti et al. used PBDE and TH levels in placenta and observed associations between PBDE exposure and increased T3 levels in girls and decreased rT3 levels in boys [86]. A Korean study found associations between cord blood PBDE and increased TSH levels in cord blood and a heel-prick blood draw without alterations in the T3 or T4 levels [87], which are considered subclinical symptoms of hypothyroidism. On the other hand, a study in the USA reported no significant association between PBDE presence in maternal blood and neonatal TSH [88]. A Korean study showed no significant association between PBDEs and THs in cord blood [89].

PBDEs can be metabolized in human liver tissue and be converted to hydroxylated PBDEs (OH-PBDEs) [90]. OH-PBDEs have structures that are more similar to those of THs than PBDEs; however, few studies have investigated the potent adverse effects of OH-PBDEs on THs. OH-PBDEs should also be explored for the clarification of the underlying mechanisms of endocrine disruption.

6.4.4 Phthalates

Phthalates are a group of chemicals widely used as plastic emollients and additives in various consumer and industrial products. Their half-lives of elimination are relatively short compared to those of POPs; therefore, they do not accumulate in the body. However, they are included in daily necessaries, leading to continuous exposure.

In addition to competitive binding to TTR like POPs [91], the underlying mechanisms behind thyroid dysregulation by phthalate exposure have been examined in animal and in vitro studies. Previous studies have demonstrated histopathological changes in the thyroid of rats in association with bis(2-ethylhexyl) phthalate (DEHP) exposure [92, 93]. Some phthalates increase the activity of the human NIS promoter [94] and modulate the transcriptional activity of NIS, leading to changes in iodide uptake in rat thyroid cells [95]. Phthalate exposure also changes the transcription of the genes in the HPT axis and expression of TR genes [96, 97]. Furthermore, a recent study showed that DEHP downregulated the expression of the TRH receptor in the hypothalamus, upregulated the protein and mRNA levels of the TRH receptor in the pituitary gland, and downregulated the mRNA expression of the TSH receptor in the thyroid [98]. DEHP can affect TH levels through not only biosynthesis and biotransportation but also biotransformation [99].

Although some possible mechanisms of TH disruption as a result of phthalate exposure have been reported on, few epidemiological studies have examined the association between prenatal exposure to phthalates and neonatal or infant TH levels (Table 6.2). Huang et al. investigated the relationships between phthalates in maternal urine at three visits during pregnancy and TH levels in cord blood in a Taiwanese population. They reported that molar sum of urinary di-*n*-butyl phthalate (ΣDBPm) metabolites in the second trimester was associated with increased T3 and FT4 levels in cord blood, and mono-*n*-butyl phthalate exposure in the second trimester was associated with increased cord T3 levels [100]. The presence of phthalates in maternal urine in the first or third trimesters was not associated with cord TH levels. Another Taiwanese study found that the presence of methylbenzylpiperazine in maternal urine during the third trimester was inversely associated with cord TSH levels [101]. However, three studies conducted in Japan, the Netherlands, and China found no associations between prenatal phthalate exposure and TH levels in cord blood or a heel-prick blood test [40, 102, 103].

To draw firm conclusions, further studies should focus on the temporal profile of phthalate exposure during gestation.

6.4.5 *Bisphenols*

Bisphenol A (BPA) is an organic synthetic compound widely used in the production of plastic products such as food and drink containers, medical devices, and thermal paper receipts. BPA has been detected in amniotic fluid, cord blood, and placental tissue, indicating in utero exposure. Although the use of BPA in baby bottles and plastic food containers has been restricted in the USA and European countries, BPA exposure is still ubiquitous. Furthermore, a number of structural BPA analogues such as bisphenol S (BPS), bisphenol F (BPF), and bisphenol B (BPB) have replaced BPA.

As shown in Table 6.2, the effect of in utero exposure to BPA on neonatal TH levels is not consistent. One study in the USA observed an inverse association between BPA in maternal urine and boys' TSH levels on a heel-prick blood draw [104]. Another USA study also found an association between maternal urine BPA and decreased TSH levels in cord blood; however, this association was observed only in girls [105]. Minatoya et al. reported no association between BPA in cord blood and neonatal TH levels as estimated by a heel-prick blood test [106].

Mechanistic studies have indicated several pathways by which BPA could interfere with TH levels. BPA has been reported to have the ability to bind to the transport proteins of THs; however, its potency is weaker than that of environmental chemicals such as PCBs and PBDEs [107, 108]. A possible mechanism of BPA in the disruption of THs is TR binding. BPA shows T3-TR-mediated antagonistic effects by the suppression of transcriptional activity [109]. Another study suggested that BPA acts as an antagonist on the beta-TR [110]. Exposure to BPA and its analogues may change the thyroid-related gene expression of cells in the pituitary and thyroid glands [111–113]. BPA was shown to increase the activities of biotransformation enzymes such as glutathione S-transferase and UDPGT [114]. Few studies have assessed the effects of BPS, BPF, and BPB on thyroid function. Further study should focus on not only BPA but also its analogues.

6.5 Future Directions of Research on Thyroid Hormones

Several epidemiological studies have shown the thyroid-disrupting effects of various chemicals, through experimental animal and in vitro studies. However, the results of the studies are inconsistent. This may be attributed to the different periods in which biological samples were obtained for both chemical exposure and TH concentrations. As for exposure assessment, many studies used maternal blood or cord blood. Maternal blood volume increases during pregnancy; therefore, the blood obtained at different periods during pregnancy may have different concentrations of chemicals. Moreover, different chemicals pass from mothers to fetuses across the placenta at varying rates. Therefore, the chemical concentrations in maternal blood are likely to differentially represent the concentrations in cord blood or fetuses.

Table 6.2 Overview of previous reports on phthalates and BPA exposure and neonatal or infant thyroid hormone parameters (sorted by published year)

Author/ year of publish	Year of research	Country	Sample size	Specimen for exposure assessment	Specimen for outcome assessment	Phthalates											BPA
						ΣDBPm	MMP	MEP	MiBP	MnBP	MEHP	MEHHP	MEOHP	MECPP	MCMHP	MBzP	
Huang et al. 2018 [100]	2013–2014	Taiwan	98	Maternal urine	Cord blood	T3, FT4↑	–	–	–	T3↑	–	–	–	–	–		
Minatoya et al. 2016 [102]	2002–2005	Japan	328	Maternal blood	Heel pick (day 4)						–						
Yao et al. 2016 [103]		China	2521	Maternal urine	Cord blood		–	–	–		–	–	–			–	
Kuo et al. 2015 [101]	2009–2010	Taiwan	148	Maternal urine	Cord blood		–	–	–	–	–	–	–			TSH↓	
de Cock et al. 2014 [40]	2011–2013	The Netherlands	83	Cord blood	Heel pick							–	–	–			
Minatoya et al. 2017 [106]	2002–2004	Japan	283	Cord blood	Heel pick (day 3)												–
Romano et al. 2015 [105]	2003–2006	USA	249	Maternal urine (16 and 26 weeks gestation)	Cord blood												TSH↓
Chevrier et al. 2013 [104]	1999–2000	USA	364	Maternal urine	Heel pick												TSH↓

↑/↓: arrows are indicated as follows: ↓ inversely associated ($p < 0.05$); ↑ positively associated ($p < 0.05$), and [–] no significant association. Blanks indicate not measured in the study

As for neonatal THs, the levels in cord blood are affected by many factors such as mode of delivery, gestational age, duration and other additional factors. Since heel-prick blood is usually obtained 2–5 days after birth, the concentrations of THs are much more stable than those in cord blood. The various results obtained for neonatal THs need careful interpretation, taking the aforementioned different conditions into account.

In the future, there is a need for longitudinal studies to assess whether the effects of chemical exposure interference on TH levels during sensitive developmental windows such as in fetal life and early infancy are permanent. In particular, neurological development should be investigated, as the fetal stage is critical for the development of the central nervous system. Further study should also focus on understanding the effects of exposure to various environmental chemical mixtures, as exposure to various chemicals is ubiquitous in daily life. As iodide intake is essential, those with insufficiency or pre-existing thyroid disease may be more vulnerable.

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