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Perinatal effects of persistent organic pollutants on thyroid hormone concentration in placenta and breastmilk

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ABSTRACT

Thyroid hormones (TH) are known to play a critical role in regulating many biological processes including growth and development, energy homeostasis, thermogenesis, lipolysis and metabolism of cholesterol. Severe TH deficiency especially during fetal development results in cretinism, but can also lead to an imbalance in metabolism with, among others, an alteration in body weight composition. Over the past two decades, increasing evidence has shown that certain persistent organic pollutants (POP) can interfere with the endocrine system. These POP referred to as "endocrine disrupting chemicals" are widely present in the environment and populations are exposed globally. Moreover, epidemiological studies have shown that a particularly sensitive period is the pre- and postnatal time. Indeed, perinatal exposure to such chemicals could lead to the onset diseases in later life. It is known, that, maternal thyroid hormones are transported by the placenta to the fetus from 6 weeks of gestation and it seems that during the first trimester, and part of the second, the fetus is entirely dependent on maternal TH supply for its development. Interferences in the TH-network as a consequence of the exposure to such pollutants could cause variations in TH concentration. Only small changes in maternal thyroid hormone levels in early stages of pregnancy can influence fetal neurological and cardiovascular development, as well as according to recent studies, have effect on childhood body composition. With this review, we will report the most recent and important studies concerning the association between thyroid hormone concentration and POP levels measured during the perinatal period. We will mostly focus on the data recently reported on placenta and breastmilk as main sources for understanding the potential consequences of exposure. The possible link between exposure to pollutants, TH dysregulation and possible adverse outcome will also be briefly discussed. From our literature search, several studies support the hypothesis that pre- and postnatal exposure to different pollutants might play a role in causing variation in thyroid hormone concentration. However, few research papers have so far studied the relationship linking exposure to pollutants, TH concentration and possible health consequences. Therefore, this review highlights the need for further research in this direction.

1. Introduction

Persistent organic pollutants (POP) are a class of endocrine disrupting chemicals (ECD) produced by anthropogenic activities as well as in some cases by natural processes. Over time, many of those compounds were banned from the market, due to their toxic effects on health. However, they are still quite persistent in the environment (although at lower concentrations) due to their high lipophilicity and their resistance to degradation. Therefore, the entire global population is exposed. Many papers, have described the possible adverse effects as a consequence of the exposure and some of the main findings are summarized in several recent review papers (Darbre, 2017; Kumar et al., 2020; Lind and Lind, 2018; Wu et al., 2020; Yilmaz et al., 2020). POP can especially interfere with the thyroid hormone (TH) system due to the chemical similarity of some of them. These disruptive interactions have been known for several years (Boas et al., 2012; Kashiwagi et al., 2009; Patrick, 2009) and have prompted the scientific community to question more about POP exposure during the pre- and postnatal period. Indeed, it is well recognized

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that during this time any minimal difference in thyroid hormone concentration can have a detrimental effect on the correct fetal or infant development.

During pregnancy, maternal TH are transferred to the fetus via the placenta to support normal fetal growth (Kilby et al., 2005). This is particularly important during early stage of the pregnancy, when the fetus relies exclusively on TH of maternal origin (Adu-Gyamfi et al., 2020; Chan et al., 2009). Several papers have linked TH deficiency during pregnancy with alteration in offspring brain development (for reviews see (Moog et al., 2017; Prezioso et al., 2018)). However in recent years some authors have also shown that maternal thyroid function during early pregnancy may influence childhood body composition and/or cardiovascular development (Godoy et al., 2014; Rytter et al., 2016). Others have found that both maternal and neonatal free T3 levels consistently increase with increasing maternal obesity and this may be a potential mediator of fetal overgrowth and childhood obesity (Kahr et al., 2016). For many years, it was believed that placenta was a barrier against xenobiotic molecules, however, over the years, many scientific papers have proved the contrary. Several synthetic molecules have been detected in placenta and among them different POP have also been found (Jeong et al., 2018; Leonetti et al., 2016a; Li et al., 2020b; Vizcaino et al., 2014). Furthermore, studies on animal and human showed that some of these pollutants can also be detected in the fetal part of the placenta, or in different fetal organs thus demonstrating that they can also reach the fetus (Doucet et al., 2009; Nomiyama et al., 2020; Ruis et al., 2019; Zota et al., 2018). POP have been quantified in cord blood and in the meconium as well, further supporting the idea that such pollutants are able to cross the placenta (Fernandez-Cruz et al., 2020; Fisher et al., 2016; Guo et al., 2020; Luo et al., 2016; Muller et al., 2019). Exposure in the early stage of life may also continue during the first months of lactation. Breastmilk is a lipophilic matrix and therefore several pollutants can be easily dissolved in it. While breastfeeding is always considered the best nutrition for infants, measures to reduce human exposure need to be seriously considered. In fact, these chemicals can be found in many different human milk samples worldwide (Fang et al., 2015; van den Berg et al., 2017).

A large part of the research in this field try to study the possible relationship between TH levels in pregnancy (or in the first months of life) and pollutant concentrations by measuring them in plasma/serum or cord blood (Baba et al., 2018; Brucker-Davis et al., 2011; Li et al., 2014; Lignell et al., 2016). However, this is just one picture of the whole story. For example, some authors have found that in placenta POP concentration sometimes is exceeding maternal serum concentration probably due to the more lipophilic nature of that organ compared to blood. Additionally, at birth thyroid function undergoes rapid changes. In the work of Kurioka et al. the authors showed that 3–4 days after the delivery the values of free T3 and free T4 were already significant higher than that in the 3rd trimester of pregnancy (Kurioka et al., 2005). This increases the possible differences between TH values found at cellular level and those in the blood system. For this reason, several studies have appeared over the past two decades that have used placenta or breastmilk, instead of blood, to investigate the possible relationship between POP and TH. With this review, we want to focus on the latest reported findings on the interaction between POP and TH using the placenta or breastmilk as a matrix. After a brief description of the methodologies used for the analysis of POP and TH, we will report on the possible interference that POP exposure could have on the thyroid hormone levels. The potential link between POP exposure, changes in thyroid hormone concentrations and possible health consequences will also be discussed.

2. Thyroid hormones in placenta

TH are a class of tyrosine-based hormones. They are synthesized by the thyroid gland as a result of stimulation by the thyroid stimulating hormone (TSH). TSH is a glycoprotein produced by thyrotrope cells in the anterior pituitary gland and its released is regulated by the hypothalamic-pituitary axis. Neurons in the hypothalamus release thyroid-releasing hormone (TRH), which stimulates pituitary gland to secrete TSH. TSH controls the production of thyroid hormones by stimulating thyroid follicular cells, the main cell type in the thyroid gland. However, the main hormone (L-thyroxine (T4)) produced by the thyroid gland has only a minimal effect on stimulating body metabolism. T4 is converted into 3,3′,5-triiodothyronine (T3), the most active form, by intracellular removal of one iodine atom. This reaction is catalyzed by deiodinase type 2 (D2) or type 1 (D1). In turn, T3 and T4 are inactivated into 3,3′-diiodo-L-thyronine (3,3′-T2, T2) and 3,3′,5′-triiodothyronine (reverse T3 or rT3), respectively by deiodinase type 3 (D3) or D1. Further deiodination can generate lower iodinated analogues such as, 3,5- diiodo-L-thyronine (3,5-T2, reverse T2 or rT2) or monoiodothyronine (T1) (Cheng et al., 2010; Lopez et al., 2013). TH are also decarboxylated or deaminated giving rise to other metabolites. The main thyroid hormones that can be analyzed so far are shown in Fig. 1, however only T3, T4 and TSH are normally quantified in all human and animal samples. The other metabolites are targeted only in specific biological samples and/or specific diseases. In general their concentration in normal physiological conditions is quite low and their role is not well understood so far. At the level of placenta, it appears that maternal T4 is the primary thyroid hormone transported into the fetus. Then, the maternally derived T4 is converted into T3 by D2 or into the inactive rT3 by D3 (Shiao Y Chan, 2009). According to the work of Koopdonk-Kool *at al.* total placental D3 activity increases considerably during pregnancy, while the increase in total placental D2 activity is not significant. The authors calculated that the absolute placental D3 activity is about 200 times higher than that of D2 at all gestational ages (KoopdonkKool et al., 1996). This evidence suggests that probably D3 plays a crucial role in regulating T4 levels within fetus circulation. In placenta only T4, T3 and rT3 have been quantified so far (Leonetti et al., 2016b; Li et al., 2018a; Yoshida et al., 1987), although some others claimed the possibility to detect 3,3′-T2 as well (Li et al., 2018a). The first attempt to measure TH in placenta was reported by Yoshida et al. (Yoshida et al., 1987). They used an immunoassay technique however, the specificity of the antibodies used in this assay limits selectivity. Recently, analytical methods using liquid chromatography mass spectrometry (LC-MS) or tandem mass spectrometry (LC-MS/MS) have been emerged for the measurement of TH in human placenta. Unfortunately, no reference standard material is available so far, however all methodologies employed isotope dilution (Leonetti et al., 2016b; Li et al., 2018a, 2018b). With this technique the quantification is in general very robust and indeed in these works the concentration of TH found in placenta was quite consistent despite different clean-up strategies employed. In these studies, average T4 levels range from 11.8 to 68.4 ng/g wet weight (ww), T3 from 0.1 to 2.34 ng/g ww and rT3 from 0.73 to 9.03 ng/g ww. In all these reports the placenta samples were collected at the end of the 3rd trimester of pregnancy.

3. Thyroid hormones in breastmilk

In breastmilk, the first attempts to measure TH were performed about forty years ago by immunoassay methodology (Mizuta et al., 1983; Sack et al., 1979; Sato and Suzuki, 1979). In all these works, it was always possible to quantify T3 but not always T4 or rT3. Recently, in our group, we were able to develop for the first time an analytical methodology for the quantitation of TH in such matrix by LC-MS/MS (Li et al., 2020a). With this method, we could detect T4, T3 and rT3 in all 99 samples employed for the study. Over-all, the concentration found, in our work as well as in the previous ones is quite low (T4 from 0 to 77 μg L^{-1}, T3 from 0.1 to 4 μg L^{-1}, rT3 from 0.01 to 0.03 μg L^{-1}) and there is a general consensus that such low value of TH in breastmilk can only have a minimal impact on the thyroid function in the newborn (Mallya and Ogilvy-Stuart, 2018).

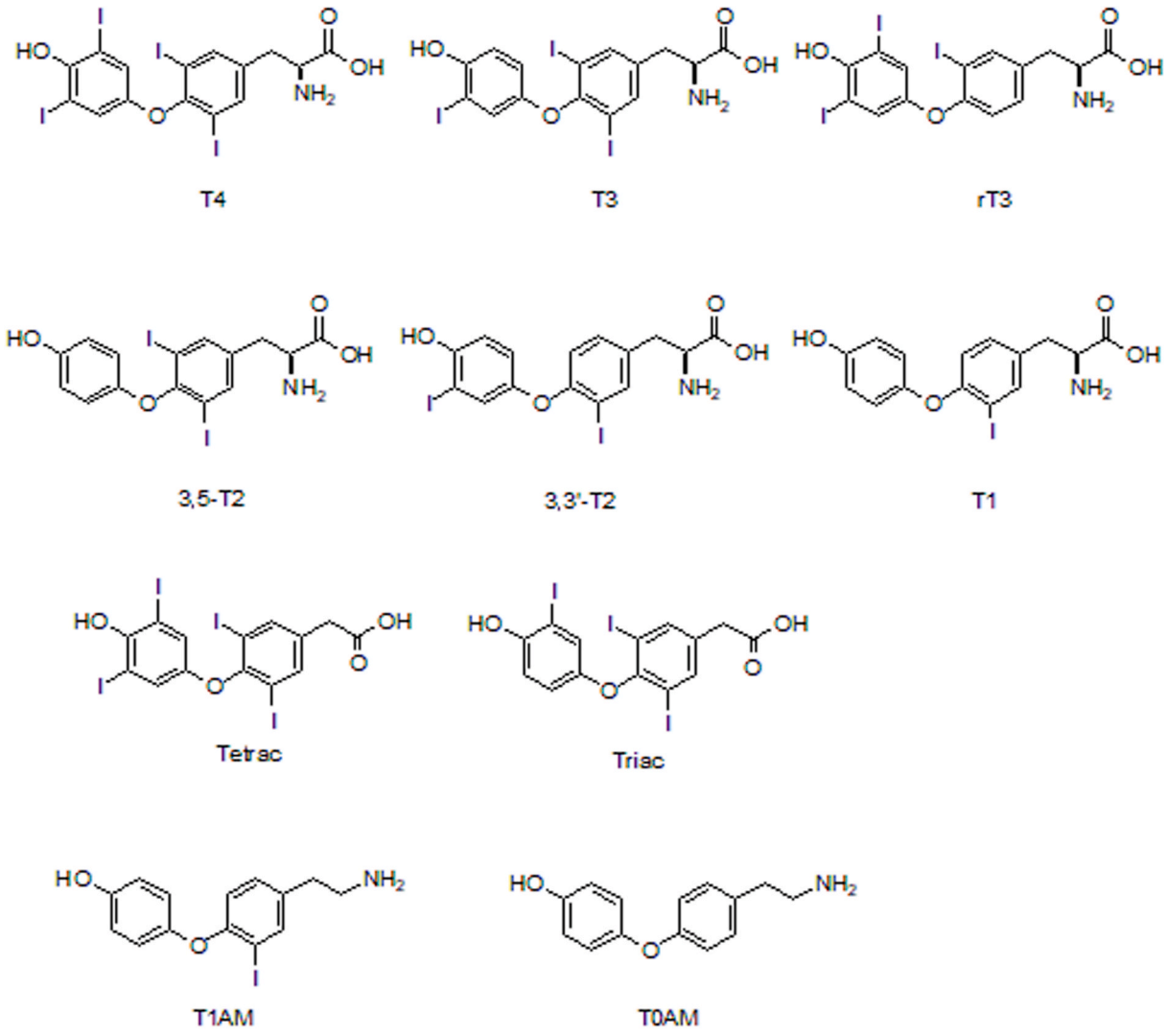

Fig. 1. Chemical structures of the most common TH metabolites.

4. Persistent organic pollutants in placenta and relationship with thyroid hormones

POP are normally measured by gas chromatography-mass spectrometry and the analytical methodologies employed follow the guidelines reported by the different authorities responsible for the quantification of such molecules in environmental or food samples. For this reason also standard reference material is easily available on the market and this makes the results coming from different studies quite robust. Table 1 shows all the studies found in literature in which the POP levels measured in the placenta were related to the concentration of TH measured in the placenta or in the blood.

Table 1
Summary of the studies concerning the relationship between persistent organic pollutants measured in placenta and thyroid hormone concentration.

Location	N of samples	Matrix for POP analysis	Matrix for TH analysis	POP analyzed	TH analyzed	Other parameters analyzed	Reference
USA	95 Human placenta	Placenta collected from week 37	Placenta	PBDE	T3, T4, rT3	2,4,6-TBP, D3 and TH SULT activities	Leonetti et al. (2016b)
Denmark	58 Human placenta from male birth	Placenta collected from week 36	Placenta	PBDE, PCB, PCDD/F, OCP	T3, T4, rT3		Li et al. (2018b)
USA	20 Female rats	Rat placenta, serum and fetal tissue	Rat placenta, serum and fetal tissue	PBDE	T3, T4	mRNA expression of transporters in placenta	Ruis et al. (2019)
Taiwan	118 Human placenta and 118 cord blood	Placenta collected at week 38.64 ± 1.33	Cord blood	PCB, PCDD/F	T3, T4, TSH, free T4	T3 uptake, TBG, IGF-1, BP3	Wang et al. (2005)
Spain	220 Human placenta and 220 cord blood from male birth	Placenta collected from week 32–42	Cord blood	OCP	TSH		Freire et al. (2011)
Germany	5 Human placenta, 3 porcine placenta	Placenta collected at term	Placenta	PBDE, PCB, PCDD/F, OCP	T3, T4, rT3	Heavy metals, elements, vitamin E	Li et al. (2020b)

Abbreviations: 2,4,6-tribromophenol (2,4,6-TBP); deiodinase type 3 (D3); sulfotransferases (SULT); thyroid-binding globulin (TBG); insulin-like growth factor 1 (IGF-1); binding globulin-3 (BP3).

Polybrominated diphenyl ethers (PBDE). PBDE are persistent, lipophilic compounds that have been extensively used as flame retardants. Despite some of them were phased out of use several decades ago, they are still widely found in the environment with consequent exposure to humans. Although, there are more than 200 different PBDE identified so far, many of them have very low concentrations and only BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-28 and BDE-209 are the most abundant in this family. Human studies conducted on stillborn fetuses showed that such pollutants are able to cross the placenta and reach fetal organs (Doucet et al., 2009; Schecter et al., 2007). A large part of the studies reported in human placenta have used for the analysis the entire organ (Fernandez-Cruz et al., 2020; Gomara et al., 2007; Jeong et al., 2018; Leonetti et al., 2016a, 2016b; Li et al., 2018b; Main et al., 2007) or specific regions of it (Li et al., 2020b; Ruis et al., 2019). Only few authors have investigated the different concentrations in the different placenta compartments. One of these few studies was conducted by Ruis et al. The authors studied the different concentration of such pollutants in the maternal and fetal part of the rat and human placenta. In both cases PBDE concentrations were higher in the fetal side of the placenta. The concentration ratio ranged from 1.2 to 5.5 for human and 1.9 to 3.2 for rats (Ruis et al., 2019). In another study, Chen et al. proved that, highly brominated congeners were able to cross placenta more easily than the lower brominated analogues (Chen et al., 2014b). When we look at the possible association between TH and PBDE in human placenta, at the best of our knowledge, only two studies are known. In the first one reported by Leonetti et al. the authors analyzed 95 placenta samples collected from women you gave birth either a boy or a girl. According to their results, PBDE accumulate in the placenta and potentially alter TH function in a sex specific manner. In fact, they found a statistically significant positive association between BDE-99 and T3 in females and a negative association between BDE-99 and T3 in males. The mechanism behind this sex-specific difference was not investigated by the authors. However, according to this study the sex of the infant seems to play a role in the bioaccumulation and/or metabolism of such chemicals in the placenta during pregnancy (Leonetti et al., 2016b). In the second work conducted in our laboratory, we analyzed 58 placentas and we found negative association with T4 and BDE-47, BDE-99 and BDE-100 (Li et al., 2018b). Unfortunately, all our placenta samples come from mothers who gave birth to boys thus it was not possible to confirm the results reported in the previous work. Over the past two decades, the hydroxylated PBDE (OH-PDBE) have also emerged as possible endocrine disrupted chemicals (Li et al., 2010; Mercado-Feliciano and Bigsby, 2008). They can be generated by PBDE metabolism but also be produced by various types of bacteria (Agarwal et al., 2014; Wan et al., 2009). They have been detected in different biological samples and among them also in the human placenta (Zota et al., 2018). Where, the four most common OH-PBDE (5-OH-BDE-47, 6-OH-BDE-47, 5-OH-BDE-99, and 4-OH-BDE-49) were analyzed. However, the possible interaction between OH-PBDE and TH during the perinatal period has so far only been investigated in biological fluids (Cowell et al., 2019; Stapleton et al., 2011).

Polychlorinated biphenyls (PCB). PCB are a group of chemicals that have been used for many years for commercial and industrial application. Due to their adverse effects, their production and usage was prohibited globally under the Stockholm Convention on Persistent Organic Pollutants, 2001 (http://www.pops.int/default.htm). Since then, little by little the background level of PCB has decreased, however, their lipophilic characteristics make some of them still persistent in the environment. The chemical structure of PCB and their hydroxylated metabolites (OH-PCB) resemble the one of TH. Due to this characteristic, some congeners, especially the hydroxyled ones, have shown the capability to bind to the TH transport proteins with high affinity (Cheek et al., 1999; Ucan-Marin et al., 2010). In total 209 different PCB congeners are known, however a large part of them have very low concentration and in general only few show a detection frequency higher than 80% in the measured samples. In particular seven are those with the greater abundance: CB-28, CB-52, CB-101, CB-118, CB-138, CB-153 and CB-180. In the human placenta, some authors have found CB-52 as the major congener (Gómara et al., 2012; Nanes et al., 2014; Naqvi et al., 2018), some others have reported CB-153 to be the one with the highest concentration (Virtanen et al., 2012; Vizcaino et al., 2014), while in a recent study CB-138 was found to be the one with the maximum level (Li et al., 2020b). The OH-PCB were first detected in human plasma, more than twenty years ago (Bergman et al., 1994). The authors found about 40 different congeners, however many more were detected within the time and today over 800 possible OH-PCB congeners were identified (Grimm et al., 2015). In the human placenta, the most abundant congeners found are 4OH-CB-187 and 4OH-CB-146 which, according to the work of Gómara et al., account for more than 50% in the proportion of the total OH-PCB congeners (Gómara et al., 2012). Exposure of pregnant rats to PCB or OH-PCB resulted in accumulation of these molecules in serum and brain of the developing fetus. This demonstrates, that such chemicals are both able to cross the placenta and even enter the brain (Meerts et al., 2002; Morse et al., 1996). This finding was corroborated by a study recently conducted on wild Japanese macaques. The authors were able to detect PCB and OH-PCB in the fetal brain and liver already during the 1st trimester of the pregnancy (Nomiyama et al., 2020). Also in human accumulation of PCB was found in the liver of stillborn fetus (Doucet et al., 2009). Many studies on humans report the association between PCB levels and TH concentrations using blood as a matrix (Brucker-Davis et al., 2011; Dallaire et al., 2009; Hisada et al., 2013, 2014; Wilhelm et al., 2008; Zhang et al., 2010). However, very few are those that have used human placenta as specimen (to the best of our knowledge only two). In the first reported by Wang et al., the authors analyzed in placenta (118 samples) various PCB congeners and in cord serum by radioimmunoassay thyroid hormones (free T4 and T4, T3), thyroid-stimulating hormone, thyroid-binding globulin (TBG), insulin-like growth factor (IGF)-1, and IGF-binding globulin-3 (BP3). The authors found a significant decrease in free T4 x TSH with increasing non-ortho PCB in infants (Wang et al., 2005). In the second work, conducted in our laboratory, we analyzed 58 placenta samples for both the quantification of thyroid hormones (T4, T3, rT3) and for PCB. We found positive associations between concentrations of rT3 and CB-81, CB-101, CB-183, and just negative tendencies toward associations between T4 and CB-99, CB-118, and CB-167 (Li et al., 2018b). Unfortunately, no quantification of OH-PCB and possible association with TH was reported in those studies or in any others involved placenta tissue. However, it is of note the work of Otake et al. The authors analyzed some OH-PCB in 23 cord tissue and free T4 and TSH in heel-prick blood. They found that the concentration of total OH-PCB and one congener (OH-CB-187) was related significantly to higher free T4 level in the newborn (Otake et al., 2007).

Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F). PCDD/F are a group of polyhalogenated organic compounds that can have serious effects on human health. They are commonly called “dioxins”, and count for 210 different congeners (75 PCDD and 135 PCDF). However, seven 2,3,7,8-substituted PCDD and ten 2,3,7,8-substituted PCDF are considered the most toxic compounds in this family. PCDD/F are produced in almost all combustions and due to their lipophilic nature, they can accumulate in adipose tissues and enter the food chain. The most abundant PCDF found in placenta is, according to different studies, 2,3,4,7,8-PeCDF, while the most abundant PCDD is 1,2,3,4,6,7,8,9-octachloro dibenzo-p-dioxin (OCDD) (Fernandez et al., 2012; Leino et al., 2013; Li et al., 2020b; Virtanen et al., 2012; Wang et al., 2004). Based on some animal and human studies, these pollutants are also able to cross the placenta and reach the fetus (Suutari et al., 2011; Tsukimori et al., 2013). PCDD/F can also interfere with thyroid hormone system. There is evidence suggesting a change in TH level in newborn and an alteration of thyroid function later in life after *in utero* exposure to PCDD/F (Baccarelli et al., 2008; Pluim et al., 1993; Su et al., 2010; Warner et al., 2020a). Few data are available in the literature correlating PCDD/F found in placenta with TH levels. Wang et al.,

analyzed in placenta 17 PCDD/F congeners and in cord serum by radioimmunoassay thyroid hormones (free T4 and T4, T3), thyroid-stimulating hormone (TSH), thyroid-binding globulin (TBG), insulin-like growth factor (IGF)-1, and IGF-binding globulin-3 (BP3). They found a significant and positive association between T4 concentrations with levels of PCDD/F and they also noted a significant relationship between TBG levels and increased PCDF levels (Wang et al., 2005). Li et al. analyzed in placenta three different thyroid hormones (T4, T3 and rT3) and about 17 different PCDD/F. The authors found some positive and negative associations with all three thyroid hormones and nine different PCDD/F (Li et al., 2018b).

Organochlorinated pesticides (OCP). OCP are a type of synthetic molecules that have been extensively used for several years in the agriculture and other applications. Some of them can also be generated in thermal processes like fires, combustion, sintering, metal-processing, welding, etc. Due to their nature, they are highly toxic, and slow to degrade. Although some OCP have largely been banned in the developed countries, their presence can be still detected in the environment. The most common OCP analyzed are: p,p'-dichlorodiphenylthrichloroethane (p,p'-DDT), hexachlorobenzene (HCB), p,p'-dichlodiphenyldichloroethylene (p,p'-DDE), and hexachlorocyclohexanes (HCHs). In some papers also heptachlor, endosulfans, aldrin, dieldrin, endrin, methoxychlor and chlordane are investigated. There are some studies, both in animal and human, that showed possible transplacental passage of these

Table 2
Summary of the studies examining the relationship between persistent organic pollutants measured in breastmilk and thyroid hormone concentration.

Location	N of samples	Matrix for POP analysis	Matrix for TH analysis	POP analyzed	TH analyzed	Other molecules analyzed	Reference
Norway	239 Breastmilk, 239 infant blood	Breastmilk collected at a median of 33 days post-partum	Infant blood collected after 3 days from birth	PBDE	TSH	HBCD	Eggesbø et al. (2011)
Taiwan	55 Breastmilk, 55 cord blood	Breastmilk collected within the 1st month after birth	Cord blood	OCP	T3, T4, free T3, free T4, TSH	IGF-1	Kao et al. (2019)
Japan	40 Breastmilk, 36 infant blood	Breastmilk collected at 3 months post-partum	Infant blood collected at 1 year age	PCDD/F, co-PCB	T3, T4, TSH	TBG	Nagayama et al. (1998)
Germany	99 Breastmilk	Breastmilk collected during the first 10 months of lactation	Breastmilk	PBDE, PCB, PCDD/F	T3, T4, rT3		Li et al. (2020a)
Uganda	30 Breastmilk	Breastmilk collected 2–9 days post-partum	Breastmilk	PBDE, PCB, PCDD/F	T3, T4, rT3		Matovu et al. (2021)
Taiwan	149 Breastmilk, 149 Cord blood	Breastmilk collected at 1 month post-partum	Cord blood	PBDE	T3, free T3, T4, free T4, TSH	IGF-1	Shy et al. (2012)
France	69 Breastmilk, 84 Cord blood from mothers who gave birth to boys	Cord blood. Breastmilk collected 3–5 days post-partum	Cord blood	PCB, p,p'-DDE, HCB	free T3, free T4, TSH	DBP, mBP, linuron, lindane, vinclozolin, procymidone, BPA	Brucker-Davis et al. (2011)
Netherlands	83 Cord plasma, 83 breastmilk, 83 heel prick	Cord plasma. Breastmilk collected at 2nd month post-partum	Heel prick collected at 4–7 days after birth	CB-153, p,p'-DDE	T4	DEHP, HCB, PFOS, PFOA	de Cock et al. (2014)
3-EU mother-child cohorts	1105 (Belgium) 230 (Norway) 449 (Slovakia)	Cord blood. Breastmilk collected within the 1st month post-partum	Heel prick collected at 4–6 days after birth	CB-153, p,p′-DDE, BDE-47, BDE-99	TSH	HCB, PFOS, PFOA, HBCD	de Cock et al. (2017)
South Korea	90 Cord blood, mother blood, infant blood, 21 breastmilk	Cord blood. Breastmilk collected during lactation	Maternal blood collected after delivery. Infant blood from neonatal screening	PBDE	free T4, T3, TSH	Total cholesterol, triglyceride	Kim et al. (2011)
Sweden	325 Maternal serum, 211 breastmilk, 265 infant blood	Maternal serum collected in late pregnancy. Breastmilk collected at 3rd week post-partum	Maternal serum. Infant blood collected at 3 weeks. Infant blood collected at 3 months	PCB, PCDD/F, p,p′-DDE	TSH, T3, free T4		Darnerud et al. (2010a)
Germany	232 Maternal blood, 232 cord blood, 232 breastmilk	Maternal blood collected at 32nd week of pregnancy. Breastmilk collected during the first 3 weeks post-partum	Maternal and cord blood	PCB, PCDD/F	TSH, T3, T4, free T3, free T4		Wilhelm et al. (2008)
South Korea	21 Cord and maternal blood, 21 breastmilk	Cord blood. Breastmilk collected 7 days post-partum. Maternal blood collected from cesarean section	Maternal and cord blood	PBDE	free T4, T3, TSH	Total cholesterol, triglyceride	Kim et al. (2012)
Netherlands[a]	38 Breastmilk, 38 cord blood, 38 infant blood at 1 week and 11 weeks	Breastmilk	Cord blood and infant blood	PCDD/F	T4, T3, TSH, free T4, rT3	TBG	Pluim et al. (1993)

Abbreviations: Hexabromocyclododecane (HBCD); dibutylphthalate (BPT); monobutylphthalate (mBP); bisphenol A (BPA); Bis-2-ethylhexyl phthalate (DEHP); perfluorooctanesulfonic acid (PFOS); perfluorooctanoic acid (PFOA); insulin-like growth factor 1 (IGF-1); thyroxine binding globulin (TBG).

[a] The same study has a follow-up at 2–2.5 years (Ilsen et al., 1996), 7–12 years (ten Tusscher et al., 2008), and 14–19 years (Leijs et al., 2012).

chemicals (Brown et al., 2016; Zhang et al., 2018) and the potential association between prenatal exposure to OCP and thyroid hormones concentration is also well documented (Leemans et al., 2019). A large part of the investigations are based on maternal or cord blood but since this is out of the scope of this review we will not report on that. Anyhow an interesting review recently published on this topic is that of Gheidarloo, M. et al. (Gheidarloo et al., 2020). In placenta, in one of our study, we found a negative association or tendency with all thyroid hormone analyzed (T4, T3, and rT3) and methoxychlor and β-hexachlorocychloexane (Li et al., 2018b). In the work of Freire et al., the authors investigated the exposure to 17 OCP in 220 placentas and TSH measured in the umbilical cord blood. Although some associations were detected, no clear pattern emerged from this study (Freire et al., 2011).

Unfortunately, only a limited number of studies were found on human placenta, however in all of them several possible confounders were taken into consideration. In general, the key possible confounders are: maternal and gestation age, smoking habits, alcohol consumption, body mass index (BMI), infant gender (when applicable), parity and birth weight. Some authors also take into account other parameters such as the time of delivery, the characteristics of the placenta or the educational level. We found that in general limited information is given on how the samples were selected. It is of note in this context, the work of Li et al. The authors investigated a possible sampling strategy not only for TH or POP analysis but also for other endogenous molecules that can be quantified in the human placenta (Li et al., 2020b).

5. Persistent organic pollutants in breastmilk and relationship with thyroid hormones

The breastmilk is the most used specimen to study the pre- and postnatal exposure to POP. In fact, through the measurement of the pollutants, it is possible to estimate both the exposure of the mother as well as the exposure of the infant. Just to give you an idea, in the review published in 2017 by Tang and Zhai on PBDE concentration in breastmilk, cord blood and placenta, the authors found 91 out of 117 documents in total, reporting data regarding the concentration of PBDE in breastmilk (Tang and Zhai, 2017). However, when we look at the publications focusing in the relationship between POP and TH concentration using breastmilk as matrix much less works are reported. We could find only fourteen different papers including also those on thyroid stimulating hormone (Table 2). In some studies, the POP concentration is measured in breastmilk only (Eggesbø et al., 2011; Kao et al., 2019; Li et al., 2020a; Matovu et al., 2021; Nagayama et al., 1998; Pluim et al., 1993; Shy et al., 2012) in some others in breastmilk and cord blood (Brucker-Davis et al., 2011; de Cock et al., 2014, 2017; Kim et al., 2011) while in others in breastmilk and mother blood (Darnerud et al., 2010b; Wilhelm et al., 2008). In only one paper POP were measured in mother blood, cord blood and breastmilk (Kim et al., 2012). TH are quite often measured in cord/mother blood or heel prick blood. Only in two recent papers, TH were measured in breastmilk together with the analysis of POP (Li et al., 2020a; Matovu et al., 2021). PCB are the main pollutants measured in almost all studies, followed by PBDE, PCDD/F and OCP. In general the most abundant congeners or chemicals reported in placenta are also those found in breastmilk, although often in this sample the concentration measured is higher due to the more lipophilic nature of such matrix. The measurement of TH is quite often, done by immunoassay and only T3 and/or T4 are targeted (in some works free T3 and/or free T4 in some others the total form). Only recently the measurement of TH in breastmilk was accomplished by LC-MS/MS. In these studies the concentration of total rT3 was measured together with that of total T3 and total T4 (Li et al., 2020a; Matovu et al., 2021). Several studies reported a weak association or correlation among the pollutants analyzed and TH concentration (Brucker-Davis et al., 2011; Darnerud et al., 2010a; Kim et al., 2011, 2012) while some others reported no association (Wilhelm et al., 2008). No association was also reported in the work of de Cock et al. among CB-153 (the only PCB measured), several other pollutants and T4. However, a positive association between p,p'-DDE exposure and T4 in the highest quartile of girls was also observed (de Cock et al., 2014). Some associations between T4 or free T4 and some PBDE were also found by Shy and co-workers (Shy et al., 2012). When TH were measured directly in breastmilk the concentration of T4, T3 and rT3 was inversely associated with several different pollutants in the work of Li et al. (Li et al., 2020a), while an association between CB-169 and CB-126 with lower levels of T3 was reported by others (Matovu et al., 2021). Also in the work of Nagayama et al. the authors found a negative correlation among T3 and T4 and different pollutants (Nagayama et al., 1998). However in that work a small number of samples were taken into consideration. Three papers described the relationship between some pollutants and thyroid stimulating hormone. In the work of de Cock et al., three European mother-child cohorts (FLEHSI-Belgium, HUMIS-Norway, and PCB cohort-Slovakia) were pooled. TSH neonatal values and cord plasma and/or breastmilk were investigated for different POP analysis. From this large study the authors found an association between CB-153, p-p′-DDE and newborn TSH level: higher exposure levels were associated with 12–15% of lower TSH values (de Cock et al., 2017). In the work of Kao et al. the authors measured several OCP in breastmilk and TH, TSH and IGF-1 in cord blood. At higher concentration (>75%th percentile) some OCP were associated with significantly lower level of thyroid and growth hormones. However, in that study the most abundant OCP (p,p'-DDE) did not show any significant association (Kao et al., 2019). In the work of Eggesbø et al., the authors investigated the association between six different PBDE, hexabromocyclododecane in breastmilk and TSH in baby. No statistically significant association between the pollutants under study and TSH was observed (Eggesbø et al., 2011). Of note is a study reported in the Netherlands on 38 mother-child pairs. Despite the low number of samples, the children were followed until the adolescence. The study was initially conducted to evaluate pre- and postnatal exposure to background dioxin level on human neonatal thyroid hormone concentration. Pollutants were measured in breastmilk, while TH was measured in cord blood and blood samples from infants aged 1 and 11 weeks. The authors found a tendency towards higher T4 concentration at birth and higher T4 level and TSH concentration at 11 weeks of age related to higher prenatal dioxin exposure (Pluim et al., 1993). However, when a similar study was repeated in children aged 2 to 2.5 and 7–12 years, a normalization of the TH value was observed (Ilsen et al., 1996; ten Tusscher et al., 2008). Furthermore, no correlation was found between prenatal dioxin exposure and TH level in 33 adolescents belonging to the same cohort (Leijs et al., 2012).

In almost all studies, several possible confounders were taken into consideration: maternal and gestational age, body mass index (BMI), smoking habits, alcohol consumption, infant gender, birth weight, plus others depending on the study design. In only three works correlation between TH level and POP concentration was investigated (Kim et al., 2011; Leijs et al., 2012; Nagayama et al., 1998). In all studies reported above the mother blood was collected during the 3rd trimester of pregnancy or shortly after the delivery, while in the work of Kim and co-workers the mother blood came from cesarean section (Kim et al., 2012). It is of note that, when mother blood is used for such study the reference interval per each trimester have to be taken into account since TH level changes during the pregnancy. According to the American Thyroid Association (ATA) the reference interval for TSH value is the following: 0.1–2.5 mIU/L (1st trimester), 0.2–3.0 mIU/L (2nd trimester) and 0.3–3.0 mIU/L (3rd trimester) (Stagnaro-Green et al., 2011).

6. Potential mechanisms for thyroid hormone disruption

While there is enough evidence that POP can interfere with thyroid hormone levels, the mechanisms involved are unclear. PBDE and in particular their hydroxylated metabolites (OH-PBDE) may interfere with T4 transport proteins such as transthyretin (TTR) or thyroxine binding globulin (TBG) (Cao et al., 2010; Marchesini et al., 2008; Meerts et al.,

2000). Others have found that OH-PBDE might bind to thyroid hormone receptors (TRs) (Kojima et al., 2009) or be able to dissociate TH receptors from TH response element (Ibhazehiebo et al., 2011). Further research on fish has suggested that PBDE might be substrate for deiodinases (Jarque and Pina, 2014), this possible mechanism also supported by *in silico* studies (Marsan and Bayse, 2017). Similar disruptive interactions have also been reported for PCB and OH-PCB. In fact, even the latter are reported to be able to interact with thyroid transport proteins (Chauhan et al., 2000; Cheek et al., 1999), deiodinases (Liu et al., 2014; Marsan and Bayse, 2020) or influence the release of TSH (Khan, 2003). Although PCDD/F can also affect thyroid hormone levels, little is known about the biological mechanisms leading to this effect. Some authors have suggested a possible interaction with TTR via their hydroxylated metabolites (Lans et al., 1994). Others, based on *in silico* studies, have concluded that some PCDD may interfere with the thyroid hormone system through the binding interaction to TRs (Akinola et al., 2021). Studies on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), have shown a possible interaction with type 1 deiodinase (Raasmaja et al., 1996), while in a recent paper, mice exposed to low dose of TCDD (0, 001 μg/kg/day) from E0.5 to PND30 showed reduced free T4 level and altered expression of thyroid specific transcripts (Reale et al., 2018). Regarding OCP, most mechanistic studies are based on the interaction between DDT or pp'-DDE and thyroid hormones (Leemans et al., 2019). Liu et al. exposed rats for 10 days to different doses of pp'-DDE (0, 20, 60, 100 mg/kg bw) and observed a reduction in serum T4 concentration and decreased levels of TTR (Liu et al., 2011). In vitro, it was observed antagonistic action of DDT in a TSH-induced cAMP production assay (Santini et al., 2003). However, thyroid hormone dysregulation can also occur as a consequence of some indirect mechanisms. Some POP have been reported to interfere with hepatic enzymes involved in TH clearance (Liu et al., 2014; Richardson et al., 2008). Some other pollutants appear to interfere with thyroid hormones homeostasis by disrupting TH sulfation (Schuur et al., 1998). Others have shown affinity towards the aryl hydrocarbon receptor (Ahr) (Gaspar-Ramirez et al., 2015; Safe, 1984; Sharma et al., 2017). Some POP might interact with other nuclear hormone receptors and this could affect thyroid activity through cross-talk mechanism (Kojima et al., 2009; Sharma et al., 2017).

7. Possible relationship among POP exposure, thyroid hormone concentrations and adverse outcome

Different studies have shown that the perinatal exposure to different pollutants can be linked to neurodevelopmental disorders as well as an increased risk of metabolic syndrome (Braun, 2017; De Long and Holloway, 2017). Since those effects are also observed as consequence of TH dysregulation, researchers have started questioning whether there was a link between exposure to pollutants, thyroid hormone system malfunctioning and health problem. As reported in previous sections, several studies found association between TH levels and pollutant concentrations during the pre- and postnatal period. However, if this can cause adverse outcome later in life is not well understood (Table 3). Talsness et *al.* exposed pregnant Wistar rats to a single dose BDE-47 (140 or 700 μg/kg body weight (bw)) on gestation day (GD) 6 and observed changes in the rat female reproductive system and thyroid gland (Talsness et al., 2008). Patisaul at *al.* exposed female rats to some flame retardants (100 and 1000 μg per day) across gestational and lactation. They observed increased serum thyroxine levels, reduced hepatic carboxylesterease activity in dam and induced phenotypic hallmarks associated with metabolic syndrome in the offspring (Patisaul et al., 2013). Also in the work of Kozlova et al., mouse offspring from mother exposed for 10 weeks (4 weeks pre-conception, 3 gestational week, and 3 week lactation) to a commercial mixture of PBDE (0.1 and 0.4 mg/kg bw per day) showed multi-symptom effects related to diabetes (Kozlova et al., 2020). In human, different epidemiological studies have examined associations between early life PBDE exposure and childhood adiposity, however the results are sometimes inconsistent (Erkin-Cakmak et al., 2015; Guo et al., 2020; Vuong et al., 2016) and no data on thyroid hormone concentration are given. Several other epidemiological studies tried to investigate the possible relationship between *in utero* exposure to PBDE and fetal growth. Serme-Gbedo et al., evaluated nine different human studies (Serme-Gbedo et al., 2016), however, only in the work of Miranda et al., also the concentration of TH was investigated. The authors examined the possible association between birth outcomes (birth weight, head circumference, birth length, and birth weight percentile for gestational age) maternal concentration of PBDE and TH levels in 140 pregnant women in their 3rd trimester. They found a deleterious

Table 3
Summary of the human studies concerning the relationship among perinatal exposure to POP, thyroid hormone concentration and possible adverse outcome.

Location	Study	Age	Outcome	Reference
USA	Association between PBDE, TH and birth outcomes.	Neonates	Association between PBDE and head circumference found. No role of TH.	Miranda et al. (2015)
Spain	Association between PBDE, TH and neurobehavioral development.	4 Years	Possible role of some PBDE on neurodevelopment. No association between PBDE and TH found.	Gascon et al. (2011)
China	Association between PBDE, TH and neurobehavioral development.	2–4 Years	Association between PBDE and neurodevelopment found. No role of TH.	Ji et al. (2019)
USA	Association between OH-PCB, maternal smoking, TH and size of birth	Neonates	Association between PCB and lower birth weight among smokers found. No role of TH.	Kezios et al. (2017)
Taiwan	Relationship between TH, growth hormone, PCDD/F and PCB.	Neonates and 2, 5, 8 years	Exposure to PCB and PCDD/F may affect growth and thyroid hormones especially at early age.	Su et al. (2010, 2015); Wang et al. (2005)
Japan	Association between PCB, TH and baby size.	Neonates	Association between PCB and TSH found. No association between PCB and baby size.	Hisada et al. (2014)
China	Association between PCB, TH and birth outcomes.	Neonates	Association between PCB and birth outcomes found. No association between PCB and TH.	Tang et al. (2018)
Germany	Influence of PCDD/F and PCB on TH and neurodevelopment.	2 Weeks, 18 months, 1 year, 2 years	No adverse effect on TH function and neurodevelopment until age of 2 years	Wilhelm et al. (2008)
Netherlands	Influence of PCDD/F exposure on growth, liver, thyroid-function and psychomotor and neuromotor development.	2–2.5 years	No difference between the high and low-exposure group	Ilsen et al. (1996)
Japan	Exposure to PCDD/F, PCB, OCP and incidence of congenital hypothyroidism.	Neonates	Exposure to organochloride alter TH system.	Nagayama et al. (2007)
Taiwan	Association between TH concentration, OCP and neurodevelopment.	Neonates	OCP exposure may be associated with infant neurodevelopment and changes in thyroid and growth hormones.	Kao et al. (2019)
Denmark	Relationship between birth weight, body fat in children exposed to pesticides.	3 Months, 6, 11 years	Exposure affect growth. Subtitle association between exposure and TSH.	Wohlfahrt-Veje et al. (2011)

association between maternal PBDE level and infant head circumference. However, they did not find evidence that suggests TH are involved in the pathway between PBDE exposure and head circumference (Miranda et al., 2015). Several epidemiological studies have also investigated the possible association between prenatal exposure to PBDE and neurobehavioral difficulties. Different studies, reported impaired attention (Cowell et al., 2015; Eskenazi et al., 2013) and externalizing behavior problems (Chen et al., 2014a; Zhang et al., 2017) as a consequence of the exposure. However, few are those in which the level of thyroid hormones has also been included. Gascon et al. studied the effect of pre- and postnatal exposure to low PBDE levels on neurological development and thyroid hormone concentration in 4-year-olds. Although they found a potential role for PBDE on neurodevelopment, no association was found between TH level and PBDE concentration (Gascon et al., 2011). Recently also Ji et al., studied the associations of prenatal exposure to low levels of PBDE with TH and neurobehavioral development in children at 2 and 4 years. They found positive associations between prenatal PBDE concentrations and children neurobehavior. They also observed inverse associations with some PBDE and TH. However, by adding TH into the statistical models examining associations between PBDE and behavior, the main results didn't change (Ji et al., 2019).

Experimental animal studies have also shown that exposure of pregnant rats to PCB can significantly reduce serum TH levels in both dams and offspring (Roegge et al., 2006; Yang et al., 2009). Others have observed, together with an alteration in TH concentration, also toxic effects in the thyroid gland (Kiliç N. et al., 2005). Furthermore, in a recent paper, the exposure of pregnant albino rats to PCB-126 (20 or 40 μg/kg bw) from gestation day (GD) 1–20 led to decreased body weight of the dams and fetuses and several histopathological changes to the placental tissues. Additionally, the maternal CB-126 exposure appeared to play a negative role for the fetal pituitary-thyroid axis (Ahmed et al., 2018). In human, fetal exposure to PCB or OH-PCB has been especially associated with fetal and childhood growth (Casas et al., 2015; Iszatt et al., 2015; Lamb et al., 2006; Leijs et al., 2014; Patandin et al., 1998; Patel et al., 2018; Tahir et al., 2020). In the work of Su et al. the authors examined the effect of *in utero* exposure of PCB and PCDD/F on thyroid and growth hormones in infants and at 2, 5 and 8 years of age (Su et al., 2010, 2015; Wang et al., 2005). The authors noted that the effect of *in utero* exposure was significant on both height and weight in 2-year-olds, especially in girls exposed to high levels of PCB and PCDD/F. This group also showed higher serum concentration of thyroid hormone compared to girls exposed to low levels of these pollutants. The authors concluded that *in utero* exposure to PCB and dioxins can affect the growth of children especially at an early age. In the work of Kezios et al. the authors examined associations between maternal prenatal exposure to OH-PCB and pregnancy outcomes, and whether associations were mediated by maternal TH levels and/or modified by maternal smoking. They found that maternal prenatal levels of some OH-PCB appeared to be influenced by maternal smoking and contribute to lower birth weight among smokers, however this association was not mediated by maternal TH levels (Kezios et al., 2017). In the work of Hisada et al., the authors investigated possible associations between concentrations of OH-PCB and PCB in the serum of women in the first trimester of pregnancy and TH levels and body size of newborn infants. They found a significant positive association between the concentrations of some OH-PCB isomers and that of neonatal TSH, however no significant association between levels of PCB and neonatal free T4, or between OH-PCB/PCB and body size of neonates was found (Hisada et al., 2014). In another recent work, the associations between PCB levels in umbilical cord sera, hormones and birth outcomes of mothers and newborns were investigated. In this study, the authors found that PCB congeners with different molecular weight have different associations with reproductive hormones and birth outcomes. However, no significant association of PCB and TH has been found (Tang et al., 2018). In some works the perinatal exposure to PCB seems also to affect the neurodevelopment (Pessah et al., 2019), however only one epidemiological study investigated the role of TH as a link between PCB exposure and neurodevelopment. In the work of Wilhelm *at al.* the prenatal background exposure level to PCB on TH status in newborns and neurodevelopment of infants until the age of 24 months was investigated. The authors found no adverse effects of PCB on thyroid function and on neurodevelopment of infant until the age of 2 years (Wilhelm et al., 2008). When the same study was conducted on PCDD/F exposure the results did not change. Similar results were also found by Ilsen et al. (1996), although other evidence suggests that dioxin exposure can also affect neurodevelopment and impairs multiple brain functions (Ikeno et al., 2018; Nakajima et al., 2006; Nghiem et al., 2019; Nishijo et al., 2012; The Tai et al., 2016, 2020; Tran et al., 2016). Different longitudinal birth cohort studies have examined the association between perinatal exposure to PCDD/F and child adiposity (Iszatt et al., 2016; Leijs et al., 2017; The Tai et al., 2016; Wang et al., 2019) but no information on thyroid hormone status is given. However, the results in offspring born to a highly exposed maternal population suggested an alteration in cardiometabolic endpoints in a sex specific manner (Warner et al., 2019, 2020b), with also possible alteration of thyroid function in adult life (Warner et al., 2020a).

Similar to other pollutants also the exposure to OCP during perinatal period is reported to be associated with several adverse effects such as: birth weight and size (Al-Saleh et al., 2012; Dewan et al., 2013), congenital malformation (Toichuev et al., 2018), preterm birth (Toichuev et al., 2018) and according to a recent study such exposure can also have an impact on fetal gender (Abdel Hamid et al., 2020). Furthermore, in different epidemiological studies the exposure to OCP was associated with neurodevelopmental disorders (Gaspar et al., 2015; Kao et al., 2019; Ribas-Fito et al., 2006; Torres-Sanchez et al., 2013). In this regard, it is of note, the work of Nagayama et al. The authors investigated the effects of prenatal exposure to dioxin-like compounds (PCDD, PCDF and dioxin-like PCB), PCB and organochlorine pesticides (DDT, HCH, chlordane, HCB and their metabolites) on the incidence of congenital hypothyroidism and/or cretinism. They found that the breastmilk of mothers who gave birth to neonates with cretinism was contaminated with these organochlorine compounds 2.1–2.7 times higher than the breastmilk of mothers who gave birth to normal neonates after adjusting for parity and mother age. The authors found that pollutant concentrations increased gradually from normal to hypothyroid children and children with cretinism. They concluded that this study strongly suggests that multiple exposures to these contaminants truly affect the thyroid hormone system in the fetus and/or neonates and probably play an important role in the incidence and causation of the cretinism (Nagayama et al., 2007). Also in the work of Kao et al. the authors investigated the role of thyroid and growth hormones as possible link between OCP exposure and neurodevelopment. The thyroid and growth hormone levels were analyzed in the cord blood samples. While the OCP levels were determined in the breastmilk within one month after childbirth. The neurodevelopment was examined at 10–12-months of age. The study suggested that early life exposure to OCP negatively impact neurodevelopment. Furthermore, prenatal exposure, was associated with changes in thyroid and growth hormones (Kao et al., 2019). Several studies have also linked the perinatal exposure to pesticides to the development of the obesity or overweight during the childhood (Agay-Shay et al., 2015; Liu and Peterson, 2015; Mendez et al., 2011; Valvi et al., 2014; Wohlfahrt-Veje et al., 2011) or the adult life (La Merrill et al., 2020). However, we could find only one study where the levels of TH were investigated. Wohlfahrt-Veje et al. studied 247 children born by women working in greenhouses in early pregnancy. The children underwent a clinical examination and blood sampling for analysis of IGF-I, IGFBP3 and TH, at three months, at 6–11 years of age. Maternal exposure to pesticides during early pregnancy was associated with affected growth, both prenatally and postnatally. The authors found a biphasic association with lower weight at birth followed by increased body fat accumulation from birth to school age. They found a stronger association with highly exposed than medium

exposed children. They also found subtle associations between exposure and TSH and IGF-I, but not IGFBP3 (Wohlfahrt-Veje et al., 2011).

8. Conclusion and outlook

We could find four studies on human placenta and fourteen on breastmilk concerning the relationship between TH concentration and

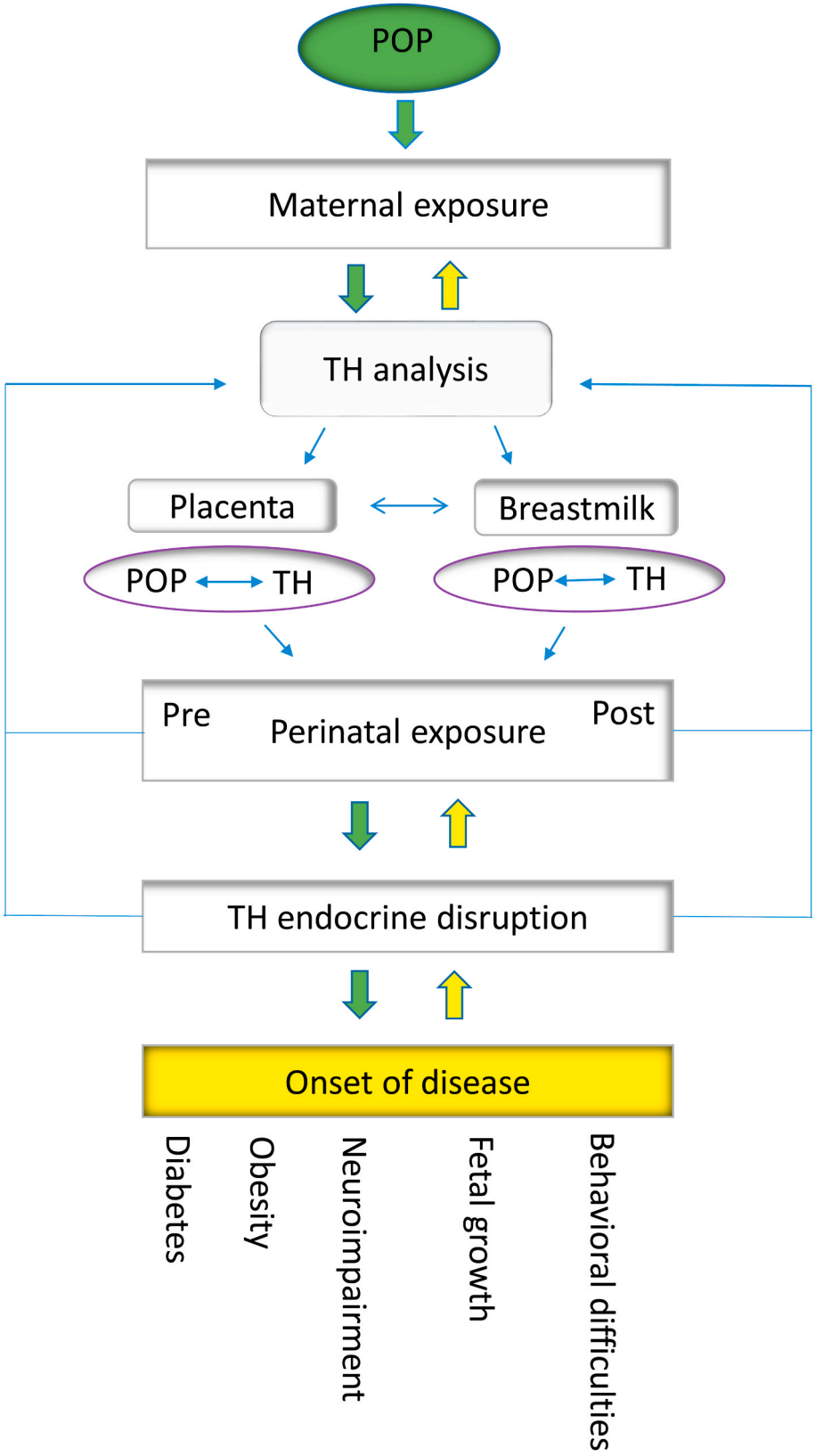

Fig. 2. Possible mechanism that from maternal exposure, through interference on the thyroid hormone system, can lead to the onset of diseases in the offspring.

POP level. In general, several possible confounders were taken into consideration despite in some cases the number of samples were limited. According to these reports, it appears that pre- and postnatal exposure to different pollutants, could play a role in causing variation in thyroid hormone concentration. We could find only twelve epidemiological studies in which the perinatal exposure to POP and the TH concentration were put in relationship to possible adverse outcomes. In half of the investigations, no role of TH was found. In nearly all of them, however, exposure to pollutants appears to play a part in the proper development of the fetus and/or baby. Unfortunately, few studies have followed up patients over long term thus, the effect of chronic POP exposure still remains unclear. Challenging is the interference caused by exposure to pollutants and/or diseases on the thyroid hormone system (Fig. 2). This aspect has also been slightly studied. Another limitation is that only the major TH are always analyzed. Little attention has been paid to the possible role that other minor metabolites may play. The reason for this is probably because a quite sensitive analytical technique like HPLC-MS/MS is needed to further elaborate the unsolved TH small molecule networking. However, this approach has so far found only limited application. Expanding analytical efforts aimed at studying endogenous molecules with scaffold similarities (Fig. 1) to thyroid hormones could be of great interest as it would help explain the impact that exogenous molecules can have on the TH system. Furthermore, in the genetic context environmental factors are often hypothesized, but finally speculatively reduced to iodine intake (Moreno et al., 2008) although indications are existing about the role of chlorine and bromine atoms instead of iodine (Solis et al., 2011) in molecules of similar scaffold (McTamney and Rokita, 2009). Thus, in conclusion our analysis clearly shows that further research is still necessary to better elucidate the relationship linking pollutant exposure, TH concentration and possible health consequences.

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