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Environmental Thyroid Disruptors and Human Endocrine Health

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1. Introduction

In the last 30 years, there is increasing concern about chemical pollutants that have the ability to act as hormone mimics. Because of structural similarity with endogenous hormones, their ability to interact with hormone transport proteins, or their ability to disrupt hormone metabolism, these environmental chemicals have the potential mimic, or in some cases block, the effects of endogenous hormones (Safe, 2000). In either case, these chemicals serve to disrupt the normal actions of endogenous hormones and thus have become known as "*endocrine disruptors*". An endocrine disruptor is defined as "an exogenous agent which interferes with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body which are responsible for maintenance of homeostasis, reproduction, development or behavior" (Massart et al., 2006a). This wide definition includes all substances that can affect endocrine function via interference with estrogen, androgen or thyroid hormone (TH) signaling pathways.

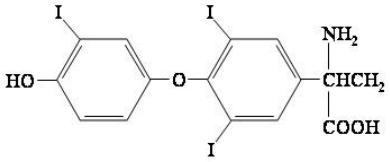
Chemicals such as dioxins, furans and organohalogens are widespread, man-made and persistent environmental pollutants, causing a variety of toxic effects. These environmental pollutants tend to degrade slowly in the environment, to bioaccumulate and to bioconcentrate in the food chain having long half-lives in mammalian fatty tissues. Animals fats and breastfeeding are the most important human dietary sources (Kavlock et al., 1996). Several biomonitoring studies have detected many environmental pollutants in adults, children, pregnant women and in the fetal compartments (Massart et al., 2005; Takser et al., 2005). Adverse effects induced by these compounds are due to their potentially toxic effects on physiological processes, particularly through direct interaction with nuclear receptors or affecting hormone metabolism (Moriyama et al., 2002).

In humans, adverse health outcomes such as neurodevelopmental toxicity, goiter and thyroid diseases are associated with TH disruption (Massart et al., 2007). Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzo-*p*-furans (PCDFs), polychlorinated biphenyls (PCBs) and polybrominated diphenylethers (PBDEs) can adversely affect thyroid function mainly resulting in hypothyroidism, which is known to cause permanent cognitive deficiencies (Guo et al., 2004; Stewart et al., 2003**;** Walkowiak et al., 2001). Indeed, their chemical effects on the brain development may be attributable, at least in part, to their

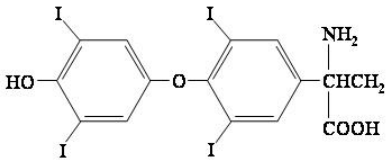
ability to affect the thyroid system (Zoeller et al., 2002). This hypothesis is supported in part by the overlap in neurological deficits observed in humans associated with chemical exposure and those deficits observed in the offspring to hypothyroxinemic women (Hagmar et al., 2001a; Koopman-Esseboom et al., 1994; Mirabella et al., 2000; Rogan et al., 1986).

2. Chemical interferences with the thyroid system

Several environmental pollutants (i.e. thyroid disruptors (TDs)) have high degree of structural resemblance to the endogenous thyroxine (T4) and triiodothyronine (T3) (Figure 1), and therefore, may interfere with binding to TH receptors (TRs) (Howdeshell, 2002; Massart et al., 2006b).



(a)



(b)

Fig. 1. Chemical structure of triiodothyronine (a) and thyroxine (b).

Moreover, because the mechanisms involved in the thyroid system homeostasis are numerous and complex (Figure 2), TDs may interfere with TH signaling at many levels (Howdeshell, 2002; Massart et al., 2006b).

A broad range of synthetic chemicals is known to affect the thyroid system at different points of regulation disrupting nearly every step in the production and metabolism of THs (Table 1) (Brouwer et al., 1998; Brucker-Davis, 1998). Chemical interference with uptake of iodide by the thyroid gland and, more specifically with the sodium/iodide symporter (which facilitates the iodide uptake), can result as decrease in the circulating levels of T4/T3 (Wolff, 1998). Chemical exposure can also lead to a decrease in serum protein-bound iodide levels, perhaps largely due to inhibition of the thyroid peroxidase enzyme, which disrupts the normal production of THs (Marinovich et al., 1997).

The displacement of T4/T3 from the transport proteins (e.g. thyroid binding globulin, transthyretin and albumin) may result in decreased ability of THs to reach its target tissue and then, may facilitate the transport of the chemicals into the fetus (Brouwer et al., 1998; Van den Berg et al., 1991).

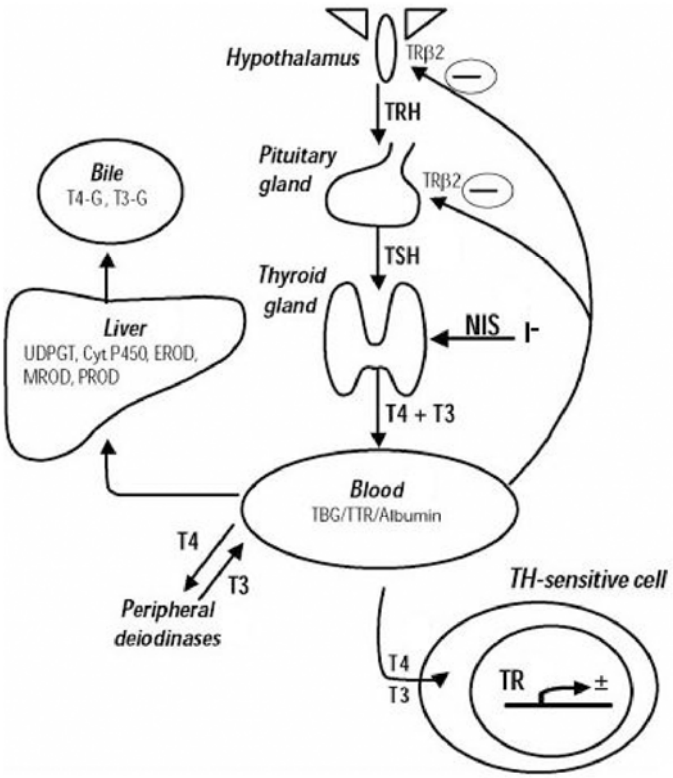


Fig. 2. Feedback mechanisms of thyroid system homeostasis (*modified from Boas M et al. European Journal of Endocrinology 2006;154:599-611*).

Chemical disruption of T4/T3 metabolism can influence deiodinase, glucuronidase and sulfatase activity, and may ultimately result in increased biliary elimination of T4/T3. Inhibition of deiodinase enzymes can result as decrease in T3 available to elicit thyroid action at tissue level (Maiti & Kar, 1997). Conversely, deiodinase activity may increase in response to TD exposure, either as direct effect or in response to increased clearance of T4/T3 by the chemical stimulation of glucuronidase or sulfatase enzymes (Spear et al., 1990; van Raaij et al., 1993). Brucker-Davis (Brucker-Davis, 1998) suggested that such increases in the metabolism and in the clearance of T3 could result in goiter as the thyroid gland increases production to maintain proper TH levels.

The TD list in Table 1 capable of disrupting normal TH production, transport, and metabolism is by no means exhaustive; further discussion of the effects of disruption of these processes can be found in specific reviews (Brouwer et al., 1998; Brucker-Davis, 1998). There are many more chemicals that have effects on the thyrotrophin-stimulating hormone (TSH) and T4/T3 levels, and thyroid histopathology for which no mechanism has been tested (Brucker-Davis, 1998). It is unlikely that these are working as T4/T3 agonists or antagonists at level of TR binding, as no chemical tested this far has demonstrated high affinity binding to the mammalian TRs (Cheek et al., 1999).

Uptake of iodide by thyroid gland
Aldrin
Amitrole
3-Amino-1,2,4-triazole
Aroclor
Catechol
4-Chlororesorcinol
Clofentezine
Cresol
Cythion
2,4-Dichlorophenoxyacetic Acid
Dihydroxynaphthalene
2,4-Dihydroxybenzaldehyde
2,4-Dihydroxybenzoic Acid
Ethiozin
Ethylene thiourea
Fipronil
Hexachlorobenzene
Hexadrin
4-Hexylresorcinol
Hydroxyquinol
Hydroxyquinol Triacetate
Lead
Mancozed
Mercuric Chloride
3-Methylcholanthrene
Methylmercuric Chloride
Methylparathion
2-Methylresorcinol
Mull-Soy
Nabam
Orcinol
Pendimethalin
Pentachloronitrobenzene
Phenobarbital
Phenol
Phloroglucinol
Polybrominated Biphenyls
Pregnenolone-16α-carbonitrile
Propylthiouracil
Pyrogallol
Pyrimenthanil
Resorcinol
Saligenin
Selenium
Thiocyanate

Sodium/iodide symporter
Perchlorate
Perrhenate

Serum protein-bound iodide level
Amitrole
Aroclor
Cythion
2,4-Dichlorophenoxyacetic Acid
1,1-Dichloro-2,2-bis (p-chlorophenyl) ethane
2,4-Dinitrophenol
Hexadrin
Malathion
Mancozeb
Mercuric Chloride
3-Methylcholanthrene

Thyroid peroxidase reactions
Aminotriazole
Amitrole
Ammonia
Cadmium Chloride
Endosulfan
Ethylene Thiourea
Fipronil
Lindane
Malathion
Mancozeb
Mercury Chloride
Methamizole
4,4′-Methylenedianiline
Polybrominated Biphenyls
Thiocyanate
Thiourea

Binding to albumin
Pentachlorophenol

Binding to thyroglobulin
1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane
Pentachlorophenol

Binding to transthyretin
Bromoxynil (3,5-bibromo-4-hydroxybenzonitril)
4-(Chloro-o-tolyloxy)acetic Acid
4-(4-Chloro-2-methylphenoxy) butyric Acid
Chlorophenol
Chlororoxuron
1,1-Dichloro-2,2-bis(p-chlorophenyl)ethanes
2,4-Dichlorophenoxyacetic Acid
2,4-Dichlorophenoxybutric Acid
Dioxtylphthalate
Dichlorophenols
Dichloroprop
Difocol
2,4-Dinitrophenol
2,4-Dinitro-6-methylphenol
Ethyl-bromophos
Ethyl-parathion
Fenoprop
Hexachlorobenzene
Hexachlorophene
Hydroxybiphenyls
Lindane
Linuron
Malathion
Pentachlorophenol
Phenol
Pyrogallol
Polybrominated Biphenyl 77
1,4-Tetrachlorophenol
Trichloroacetic Acid
Trichlorobenzene
Trichlorophenols
2,4,5-Trichlorophenoxyacetic Acid

Type I & II 5′-deiodinase catabolism
Aminotriazole
Amiodarone
Aroclor
Cadmium Chloride
Dimethoate
Fenvalerate
Hexachlorobenzene
3,3′,4,4′,5,5′-Hexachlorobiphenyl
Lead
3-Methylcholanthrene
Phenobarbital
Propylthiouracil
Polybrominated Biphenyl 77
TCDD

Glucuronidation of T4/T3
Acetochlor
Aroclor 1254
3,4-Benzopyrene
Clofentenzine
Clofibrate
DDT
Fenbuconazole
3,3′,4,4′,5,5′-Hexabromobiphenyl
Hexacholorobenzene
Hexacholorobiphenyls
3-Methylcholanthrene
Pendimethalin
Phenobarbital
Polybrominated Biphenyls
Pregnenolone-16□-carbonitrile
Promadiamine
Pyrimethanil
TCDD
Thiazopyr

Catabolism & biliary T4/T3 elimination
Aroclor
3,4-Benzopyrene
DDT
Hexachlorobenzene
3-Methylcholanthrene
Phenobarbital
Polybrominated Biphenyls

Table 1. Environmental chemical pollutants interfering with the normal production, transport, metabolism, and excretion of thyroid hormones (*modified from Howdeshell KL. Environmental Health Perspects 2002;110:337-348*).

Relatively few studies evaluated the mechanism of TD action in the fetal/neonatal organism. Darnerud et al. (Darnerud et al., 1996) reported that developmental exposure to 4-OH-3,5,3′,4′-tetracholorobiphenyl, a major metabolite of polychlorinated biphenyl (PCB) congener 3,3′,4,4′-tetrachlorobiphenyl (PCB77), binds to fetal and maternal transthyretin in mice on the gestation day 17 (GD17); significant decrease in the fetal T4 (free and total) was reported. Aminotriazole inhibited the catabolism of T4 to T3 in renal primary cell cultures from 4 to 5 months of gestation in human fetuses, indicating an interference with type 1 iodothyronine deiodinase function in the kidney (Ghinea et al., 1986). *In utero* exposure to PCB congener 3,3′,4,4′,5,5′-hexachlorobiphenyl alone or in combination with PCB77 increased type II deiodinase activity in whole-brain homogenates from fetal (GD20) and neonatal rats; total T4 levels in plasma were decreased by both treatments (Morse et al., 1992). Uridine diphosphoglucuronosyl transferase (UDP-GT) activity was increased in neonatal rats at postnatal day 21 (PND21) weanlings exposure to PCB congeners or TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) on the GD10 (Seo et al., 1995). The increase in UDP-GT activity was seen in the near absence of significant decreases in T4 concentration on the PND21 (Seo et al., 1995). Gestational exposure to Aroclor 1254 depressed UDP-GT activity in GD20 rat fetuses, while increasing the enzyme in PND21 rats (Morse et al., 1996). The total and free T4 levels in GD20 fetuses were significantly suppressed by both levels of Aroclor 1254 exposure during development, whereas the total T4 and total T3 were significantly depressed on the PND21 only by the highest dose of Aroclor 1254 (Morse et al., 1996).

In addiction, as reviewed by Zoeller et al. (Zoeller et al., 2002), many TDs can disrupt TH signaling without affecting circulating levels of THs. Many studies use circulating levels of THs as the sole indicator of an effect on the thyroid system by pollutants, or focus on mechanisms by which chemicals affect TH levels (Zoeller et al., 2002). Therefore, the prevailing view is that TDs interfere with TH signaling by reducing circulating levels of THs, thereby limiting the hormone available to act on the target tissues (Brouwer et al., 1998). However, the developmental effects of TD exposure in experimental animals are not fully consistent with mechanism attributable to hypothyroidism. For example, PCB exposure induces hearing loss in rats (Goldey et al., 1995) similarly to that observed in hypothyroid rats. Moreover, this PCB-induced hearing loss can be at least partially restored in PCB-treated rats by TH replacement (Goldey et al., 1998). On the other hand, circulating levels of TSH were not elevated by PCB exposure as it is after exposure to the goitrogen propylthiouracil (Goldey et al., 1995; Hood & Klaassen, 2000). Moreover, the timing of eye opening was advanced by PCB exposure, rather than delayed after exposure to the goitrogen 6-*n*-propyl-2 thiouracil (Goldey et al., 1995). These and other observations suggest that different TDs or their mixtures may produce heterogeneous disrupting effects on the thyroid system also without affecting circulating T4/T3 levels.

3. Thyroid toxicants

From the earliest reports in 1950s (Wyngaarden et al., 1952), many TDs have been identified by improving analytical methods. Here, we focused on some historical and emerging TDs.

3.1 Perchlorate

Over 50 years ago, Wyngaarden and colleagues (Wyngaarden et al., 1952; Stanbury & Wyngaarden, 1952) reported the inhibitory effect of perchlorate (ClO_4^-) (Figure 3) upon the

accumulation and retention of iodide by human thyroid gland. Such observation had immediate therapeutic application for thyrotoxicosis using 250-500 mg/day doses of potassium perchlorate (Loh, 2000).

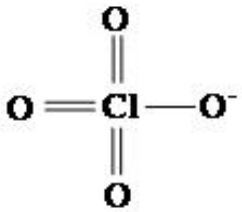


Fig. 3. Perchlorate

Because of its chemical properties, perchlorate is a competitive inhibitor of the process by which iodide, circulating in the blood, is actively transported into thyroid follicular cells (Clewell et al., 2004). The site of this inhibition is the sodium-iodide symporter, a membrane protein located adjacent to the capillaries supplying blood iodide to the thyroid gland (Carrasco, 1993). If sufficient inhibition of iodide uptake occurs, pharmacological effect results in subnormal levels of T4 and T3, and an associated compensatory increase in TSH secretion (Loh, 2000). Therefore, perchlorate exposure both results in hypothyroidism leading to the potential for altered neurodevelopment if observed in either dams or fetus/neonates, and increases in serum TSH leading to the potential for thyroid hyperplasia (Strawson et al., 2004).

Beside its pharmacological applications, perchlorate has been widely used as solid rocket propellants and ignitable sources in munitions, fireworks and matches (Strawson et al., 2004). Furthermore, perchlorates are laboratory waste by-products of perchloric acid. Perchlorate also occurs naturally in nitrate-rich mineral deposits used in fertilizers. An analysis of 9 commercial fertilizers revealed perchlorate in all samples tested ranging between 0.15-0.84% by weight (Collette et al., 2003).

In humans, there is clear and apparently linear relationship between perchlorate levels and inhibition of iodine uptake (Greer et al., 2002; Lawrence et al., 2000). Serum perchlorate levels of approximately 15 µg/l result in minimal inhibition of iodine uptake (about 2%) compared to serum 871 µg/l level, which results in about 70% inhibition of iodine uptake (Strawson et al., 2004). By contrast, several adult studies of differing exposure duration, reported serum T4 levels do not decrease after perchlorate exposure resulting in serum perchlorate levels up to 20,000 µg/l (Gibbs et al., 1998; Greer et al., 2002; Lamm et al., 1999; Lawrence et al., 2000).

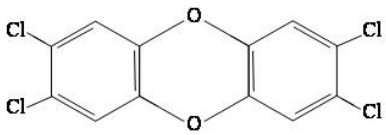
3.2 Dioxins and furans

Dioxins (e.g. PCDDs) and furans (e.g. PCDFs) are a group of structurally related compounds (Giacomini et al., 2006) (Figure 4). PCDDs and PCDFs are not commercially produced but

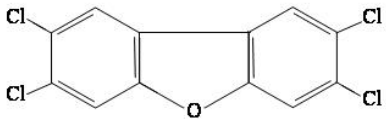
are formed unintentionally as by-products of various industrial processes (e.g. chlorine synthesis, production of hydrocarbons) during pyrolysis and uncompleted combustion of organic materials in the presence of chlorine.

During the last 20 years, an enormous public and scientific interest was focused on these substances, resulting in many publications on generation, input, and behavior in the environment (Giacomini et al., 2006; Lintelmann et al., 2003; US EPA, 1994). These toxicants have a potent concern for public health: several *in vitro* and *in vivo* experiments have suggested that PCDDs and PCDFs may interfere with thyroid function (Boas et al., 2006; Giacomini et al., 2006).

The 2,3,7,8-tetra-chloro-dibenzo-*p*-dioxin (TCDD), the most toxic, is the prototype among PCDD/F congeners. TCDD, used as standard for toxic equivalent (TEQ) calculation, shows high environmentally persistence and extremely long half-life in humans (seven or more years) (Michalek et al., 2002). TCDD is detectable at background levels in plasma or adipose tissues of individuals with no specific exposure to identifiable sources, usually at concentrations lower than 10 ppt (parts per trillion, lipid adjusted) (Michalek & Tripathi, 1999; Papke et al., 1996). Mean TCDD levels in subjects representative of the European and the US populations range between 2-5 ppt (Aylward et al., 2002; Papke et al., 1996). Nonetheless, Environmental Protection Agency (EPA) estimated that at least in the US population a number of people may have levels up to three-times higher than this average (Aylward et al., 2002; Flesch-Janys et al., 1996).



(a)



(b)

Fig. 4. Chemical structure of 2,3,7,8-tetra-chloro-dibenzo-*p*-dioxin (a) and tetrachlorodibenzo-furan (b).

3.3 Polychlorinated biphenyls

PCBs (Figure 5) comprise 209 highly environmental persistent, distinct congeners consisting of paired phenyl rings with various degrees of chlorination (Chana et al., 2002). It is estimated that since 1929, approximately 1.5 million tons of PCBs were produced.

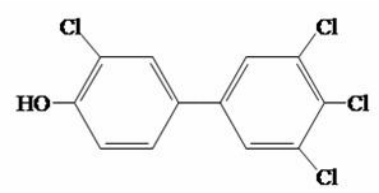


Fig. 5. 4OH-Tetrachlorobyphenyl.

The high persistence of PCBs in adipose tissues and their toxic potential for animals and humans (Breivik et al., 2002; Fisher, 1999), resulted in an almost international production stop in the 1970-80s (Lintelmann et al., 2003). However, the PCB properties, such as chemical and thermal stability, noninflammability, high boiling points, high viscosity, and low vapor pressure, are the reason for their worldwide distribution (Safe, 2000). Even after the ban of PCB production in most countries, the current world inventory of PCBs is estimated at 1.2 million tons with about one-third of this quantity circulating in the environment (Lintelmann et al., 2003).

PCBs, and especially the hydroxylated metabolites, have an high degree of structural resemblance to THs as well as thyroid-like activities (Hagmar, 2003). Laterally substituted chlorinated aromatic compounds such as *meta*- and *para*-PCBs particularly when hydroxylated, are ideally suited to serve as binding ligands to TRs and to TH-binding proteins (Arulmozhiraja et al., 2005; Cheek et al., 1999; Fritsche et al., 2005; Kitamura et al., 2005). Indeed, experimental studies indicated that PCB exposure may exert adverse effects on the developing brain by reducing circulating levels of THs, causing a state of relative hypothyroidism (Brouwer et al., 1998; Crofton, 2004). This is supported by animal data that PCBs reduce the TH levels (Gauger et al., 2004; Kato et al., 2004; Zoeller et al., 2000). PCBs may also exert direct actions on the TR independently from their effects on the TH secretion (Zoeller, 2002; Zoeller, 2003). This hypothesis is based in part on *in vitro* observations that PCBs can directly inhibit or enhance TR activity (Arulmozhiraja et al., 2005; Bogazzi et al., 2003; Iwasaki et al., 2002; Kitamura et al., 2005; Miyazaki et al., 2004; Yamada-Okabe et al., 2004) such as other TH-like actions in the developing brain (Bansal et al., 2005; Fritsche et al., 2005; Gauger et al., 2004; Zoeller et al., 2000). However, Sharlin et al. (Sharlin et al., 2006) demonstrated that PCB exposure during development does not recapitulate the full effect of hypothyroidism on the cellular composition of rat white matter.

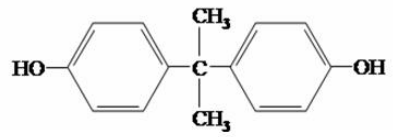
Multiple studies regarding PCB exposure have been carried out in human populations, the majority of which raises concern that environmental PCB levels may alter thyroid homeostasis (Hagmar, 2003). In subjects from highly PCB-exposed areas, the PCB concentration in blood samples negatively correlated to circulating TH levels (Hagmar et al., 2001a; Persky et al., 2001). However, few studies also demonstrated positive correlation between PCB exposure and TSH (Osius et al., 1999; Schell et al., 2004). By contrast, other studies found no association between PCBs and thyroid secretion (Bloom et al., 2003; Hagmar et al., 2001b; Sala et al., 2001).

3.4 Bisphenols

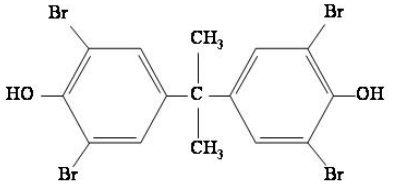
The 4,4′-isopropylidenediphenol or bisphenol A (BPA; Figure 6), produced at a rate of over 800 million kg annually in the US alone, is extensively used in plastic manufactures including polycarbonate plastics, epoxy resins that coat food cans, and in dental sealants (Howe et al., 1998; Kang et al., 2006; Lewis et al., 1999; Zoeller, 2005).

Howe et al. (Howe et al., 1998) estimated human PBA consumption from epoxy-lined food cans alone to be about 6.6 μg/person-day. BPA has been reported in concentrations of 1-10 ng/ml in the serum of pregnant women, in the amniotic fluid of their fetus, and in the cord serum taken at birth (Ikezuki et al., 2002; Schonfelder et al., 2002). Moreover, BPA concentrations of up to 100 ng/g were reported in the placenta tissues (Schonfelder et al., 2002).

Considering human pattern of BPA exposure, it is of endocrine concern that BPA shows thyroid antagonist activities (Kang et al., 2006; Moriyama et al. 2002). Best characterized as weak estrogen, BPA binds to TR and antagonizes T3 activation of TR with K_i of approximately 10^{-4} M, but as little as 10^{-6} M BPA significantly inhibits TR-mediated gene activation (Ikezuki et al., 2002; Moriyama et al. 2002). Moreover, BPA reduces T3-mediated gene expression by enhancing the interaction with the co-repressor N-CoR (Moriyama et al. 2002). Limited human data exist regarding BPA as TD.



(a)



(b)

Fig. 6. 4,4′-isopropylidenediphenol (a) and tetrabromo-bisphenol A (b).

Tetrabromobisphenol A (TBBPA; Figure 6), an halogenated BPA derivative, is widely used as flame retardant in electrical equipment such as televisions, computers, copying machines, video displays and laser printers (Kitamura et al., 2002) with over 60,000 tons of TBBPA annually produced (WHO EHC 1995; WHO EHC 1997). Thomsen et al. (Thomsen et al., 2002) reported that brominated flame retardants, including TBBPA, have increased in human serum from 1977 to 1999 with concentrations in adults ranging from 0.4 to 3.3 ng/g serum lipids. However, infants (0-4 years) exhibited serum concentrations that ranged from 1.6 to 3.5 times higher (Thomsen et al., 2002).

TBBPA is generally regarded a safe flame retardant because it is not readily accumulated in the environment, nor it is highly toxic (Birnbaum & Staskal, 2004). However, TBBPA and tetrachlorobisphenol A show even closer structural relationship to T4 than PCBs: both these tetrahalogenated bisphenols induce thyroid-dependent growth in pituitary GH3 cell line at concentrations 4-to-6 orders of magnitude higher than T3 (Kitamura et al., 2002). Unfortunately, no data are actually available on thyroid function in human exposed to these bisphenols.

3.5 Perfluoroalkyl acids

The perfluoroalkyl acids (PFAAs; Figure 7) are a family of synthetic, highly stable perfluorinated compounds with wide range of uses in industrial and consumer products, from stain- and water-resistant coatings for carpets and fabrics to fast-food contact materials, fire-resistant foams, paints, and hydraulic fluids (OECD, 2005).

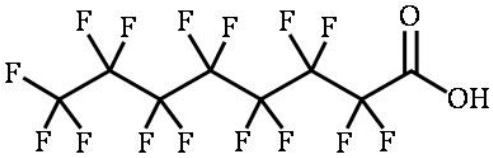


Fig. 7. Perfluoroalkyl Acids.

The carbon–fluoride bonds that characterize PFAAs and make them useful as surfactants are highly stable, and recent reports indicate the widespread persistence of certain PFAAs in the environment and in wildlife and human populations globally (Fromme et al., 2009; Giesy & Kannan, 2001; Lau et al., 2007; Saito et al., 2004). Two of the PFAAs of most concern are the eight-carbon–chain perfluorooctane sulfonate (PFOS) and perfluo-rooctanoic acid (PFOA, also known as C8).

Most persistent organic pollutants are lipophilic and accumulate in fatty tissues, but PFOS and PFOA are both lipo- and hydro-phobic, and after absorption bind to proteins in serum rather than accumulating in lipids (Hundley et al., 2006; Jones et al., 2003). The renal clearance of PFOA and PFOS is negligible in humans, leading to reported half-lives in blood serum of 3.8 and 5.4 years for PFOA and PFOS, respectively (Olsen et al., 2007).

Human biomonitoring of the general population in various countries (Calafat et al., 2006; Kannan et al., 2004; Metzer et al., 2010). has shown that, in addition to the near ubiquitous presence of PFOS and PFOA in blood, these may also be present in breast milk, liver, seminal fluid, and umbilical cord blood (Lau et al., 2007). Occupational exposure to PFOA reported in 2003 showed mean serum values of 1,780 ng/mL (range, 40–10,060 ng/mL) (Olsen et al., 2003a) and 899 ng/mL (range, 722–1,120 ng/mL) (Olsen et al., 2003b). Since then, voluntary industry reductions in production and use of other perfluorinated compounds, such as the US EPA–initiated PFOA Stewardship Program (US EPA, 2006), have contributed to a decreasing trend in human exposure for all perfluorinated compounds

(Calafat et al., 2007; Olsen et al., 2007). In May 2009, PFOS was listed under the Stockholm Convention on Persistent Organic Pollutants (Stockholm Convention on POPs, 2008).

Numerous studies have now shown PFAAs to impair thyroid homeostasis in animal studies. Depression of serum T4 and T3 in PFOS-exposed rats has been reported (Lau et al., 2003; Luebker et al., 2005; Seacat et al., 2003), without the concomitant increase in TSH that would be expected through feedback stimulation. Earlier mechanistic studies of structurally related perfluorodecanoic acid showed that it could reduce serum TH levels apparently by reducing the responsiveness of the hypothalamus-pituitary-thyroid axis and by displacing circulating THs from their plasma protein-binding sites (Gutshall et al., 1989). Although circulating hormone levels were depressed, the activities of TH–sensitive liver enzymes were elevated, suggesting that functional hypothyroidism was not occurring. A similar mechanism for PFOS has been hypothesized (Chang et al., 2008). A recent study of the mechanisms involved in PFOS-induced hypothyroxinemia in rats has indicated that increased conjugation of T4 in the liver, catalyzed by the hepatic enzyme UDP-GT 1A1, and increased thyroidal conversion of T4 to T3 by type 1 deiodinase may be partly responsible for the effects (Yu et al., 2009). Taken together, these findings suggest that the PFAA actions on the thyroid system are multiple and complex.

Disruption to TH balance was not found in previous studies of community exposure to PFOA (Emmett et al., 2006; Olsen et al., 2003c) or PFOS (Inoue et al., 2004). Modest associations between PFOA and THs (negative for free T4 and positive for T3) were reported in 506 PFOA production workers across three production facilities (Olsen & Zobel, 2007); there were no associations between TSH or T4 and PFOA, and the free TH levels were within the normal reference range. On the other hand, Metzer et al. (Metzer et al., 2010) recently determined whether increased serum PFOA or PFOS concentrations are associated with thyroid disease in a general adult US population sample (n = 3,974 individuals ≥ 20 years of age from NHANES waves 1999–2000 (n = 1,040), 2003–2004 (n = 1,454), and 2005–2006 (n = 1,480)). They found that, across all the available data from NHANES, thyroid disease associations with serum PFOA concentrations are present in women and are strongest for those currently being treated for thyroid disease (P=0.002) (Metzer et al., 2010). In men, they also found a significant association between PFOS and treated thyroid disease (P=0.043). An interaction term analysis suggested that the PFAA trends in men and women are not significantly different, despite the relative rarity of thyroid disease in men (Metzer et al., 2010).

3.6 Phthalates

Phthalates are recently proposed to be emerging TDs (Boas et al., 2006) (Figure 8). Phthalates are widely used as plastic emollients, and their amount used globally is rising (Hauser & Calafat, 2005; Latini, 2005; Schettler, 2006).

Environmental exposure to phthalates is inevitable, but for certain groups such as hospitalized subjects including neonates and infants, exposure may be massive (Shea, 2003). Phthalate exposure through necessary medical devices such as feeding tubes is correlated to the urinary content of mono(2-ethylexyl)phthalate (Green et al., 2005). Thus, an intensive phthalate exposure at potentially vulnerable point of development may cause permanent damage, despite the fast metabolism of phthalates.

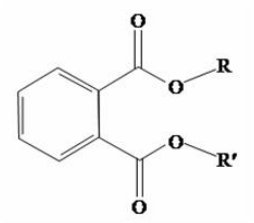


Fig. 8. Phathalates.

Rodent studies found histopathological changes in the rat thyroid glands after exposure to di(2-ethylhexyl) phthalate (DEHP), di-noctyl phthalate (DnOP) and di-n-hexyl phthalate (DnHP), corresponding to thyroid hyperactivity (Hinton et al., 1986; Howarth et al., 2001; Mitchell et al., 1985; Poon et al., 1997; Price et al., 1988). Long-term treatment with high doses of DEHP resulted in basophilic deposits in the colloid and enlargement of the lysosomes (Mitchell et al., 1985). The levels of circulating THs were not affected after oral rat exposure to DEHP (Bernal et al., 2002), whereas i.v. exposure in doses corresponding to levels of DEHP solubilized in blood bags for human transfusions resulted in significant increase in the serum T3 and T4, which returned to normal after 7 days (Gayathri et al., 2004). The thyroid glands examined in this study showed initial reactive hyperplasia. In contrast di-n-butyl phthalate (DBP) decreased T3 and T4 in rats in dose-dependent manner (O'Connor et al., 2002).

Only few data exist on the thyroid function of phthalate-exposed humans. However, recent studies reported significant associations between urine phthalate levels and altered THs (Jurewicz & Hanke, 2011; Rais-Bahrami et al., 2004).

4. Thyroid disruptors assays

Until recent years, all known TDs have been identified solely by their ability to reduce circulating TH levels, and to affect thyroid size or histopathology (e.g. colloid size, quantitative appearance of hypertrophic or hyperplastic effects) (Brucker-Davis, 1998; DeVito et al., 1999). However, TH levels vary with time and age, and then, caution must be taken in the result interpretation. In this view, histological changes in the exposed thyroid gland (particularly, increased weight and follicular cell number) are better *in vivo* markers (Janosek et al., 2006). In addition, TDs present in small amounts in the environment may not cause overt changes of TH levels but may nonetheless alter hormonal homeostasis (Boas et al., 2006). A well-established example is perchlorate, which in small amounts does not alter circulating TH levels but diminished T4 content in the thyroid gland (Isanhart et al., 2005; McNabb et al., 2004a; McNabb et al., 2004b). These data agreed with *in vitro* studies which proposed an perchlorate-induced inhibition of sodium-iodide symporter (Tonacchera et al., 2004).

Regarding *in vivo* toxicity assays for TDs, several tests have been proposed evaluating delayed eye-opening, abnormalities in the brain development, increased the sperm counts or the testes weight (DeVito et al., 1999). Perchlorate discharge test is also used as *in vivo* method for determining thyroid toxicity through TR (Atterwill et al., 1987). Finally, another

ex vivo parameter is hepatic UDP-GT activity (a marker of enhanced TH clearance form serum) (Barter & Kòaassen, 1994; Kohn et al., 1996; Okazaki & Katayama, 2003; Sewall et al., 1995). On the other hand, many TDs that directly act on the TRs, may produce variable and perhaps unpredicted effects on the TH target tissues (Zoeller, 2005).

Several *in vitro* assays have been developed to evaluate substances that may affect specific TH-related processes such as synthesis, metabolism, protein binding and downstream effects (transcription and translation). Expert panel reports reviewed the thyroid toxicological methods (Calamandrei et al., 2006; DeVito et al., 1999; Janosek et al., 2006;). Finally, intra-thyroidal T4 content, gene transcription activity and cellular growth appear to be more sensitive endpoints when assessing the significance of thyroid disruption for various chemicals (Boas et al., 2006). With respect to multiple recognized toxicity mechanisms, several screening methods should be used to characterize chemical potencies of potential thyroid disruptors.

5. Conclusions

Industrial compounds such thyroid disruptors are now ubiquitous, persistent environmental contaminants routinely found in samples of human and animal tissues (Boas et al., 2006; Massart et al., 2005; Zoeller et al., 2002). Their potency to disrupt TH pathways has been demonstrated in both *in vitro* and *in vivo* studies, in which they have been shown to typically evoke reductions in TH levels (Massart & Meucci, 2007; Zoeller, 2005). However, most important, as synthetic chemicals can interfere with nearly every step in the thyroid system (Massart et al., 2006b), more research should be targeted at understanding how TDs may impact normal brain development and functioning. Unfortunately, a toxicological profile of many chemicals is actually too incomplete and insufficient to perform an adequate human and ecological risk assessment. Furthermore, chemicals are not currently tested specifically for their ability to mimic, disrupt, or otherwise act as hormone agonists or antagonists, except on research basis. Finally, more studies are crucial to fill in the research gaps regarding permanent endocrine and neurological outcome in next generations exposed to background TDs.

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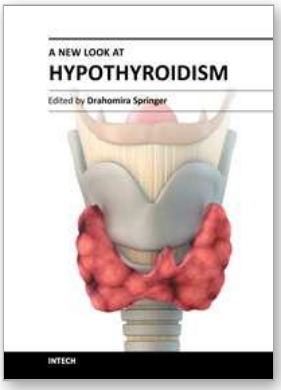

A New Look at Hypothyroidism

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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