

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,400

Open access books available

117,000

International authors and editors

130M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Environmental Thyroid Disruptors and Human Endocrine Health

Francesco Massart¹, Pietro Ferrara² and Giuseppe Saggese¹

¹St. Chiara University Hospital of Pisa,

²Sacro Cuore Catholic University of Rome,
Italy

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 to 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.

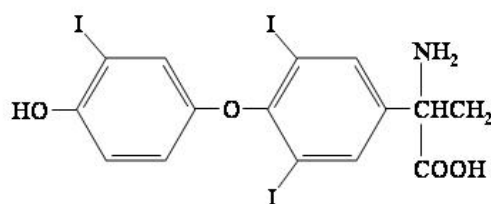
Chemicals such as dioxins, furans and organohalogenes are widespread, man-made and persistent environmental pollutants, causing a variety of toxic effects. These environmental pollutants tend to degrade slowly in the environment, to bioaccumulate and to bioconcentrate in the food chain having long half-lives 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

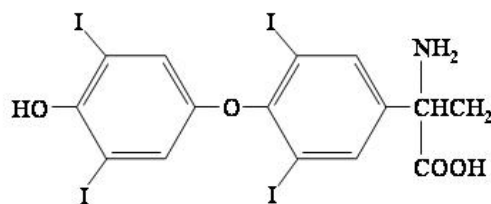
ability to affect the thyroid system (Zoeller et al., 2002). This hypothesis is supported in part by the overlap in neurological deficits observed in humans associated with chemical exposure and those deficits observed in the offspring to hypothyroxinemic women (Hagmar et al., 2001a; Koopman-Esseboom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

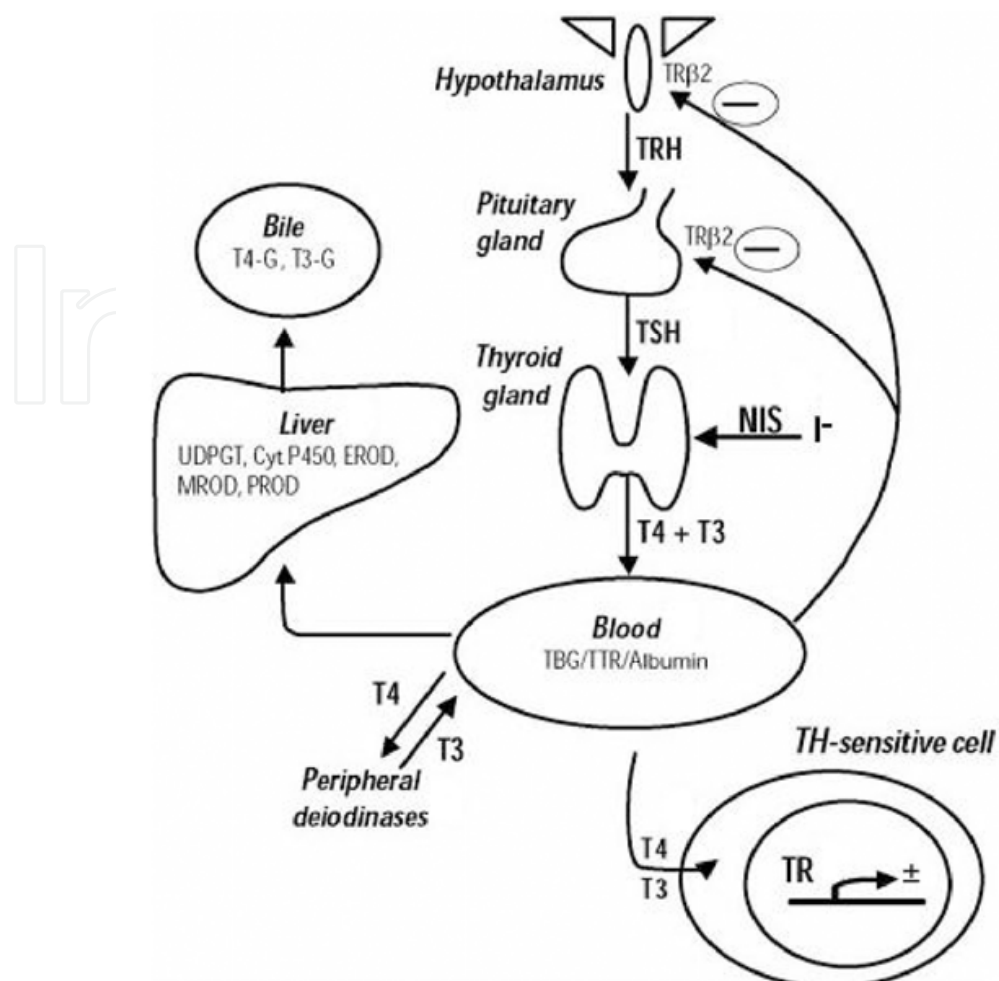


Fig. 2. Feedback mechanisms of thyroid system homeostasis (modified from Boas M et al. *European Journal of Endocrinology* 2006;154:599-611).

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	Thyroid peroxidase reactions	Type I & II 5'-deiodinase catabolism
Aldrin	Aminotriazole	Aminotriazole
Amitrole	Amitrole	Amiodarone
3-Amino-1,2,4-triazole	Ammonia	Aroclor
Aroclor	Cadmium Chloride	Cadmium Chloride
Catechol	Endosulfan	Dimethoate
4-Chlororesorcinol	Ethylene Thiourea	Fenvalerate
Clofentezine	Fipronil	Hexachlorobenzene
Cresol	Lindane	3,3',4,4',5,5'-Hexachlorobiphenyl
Cythion	Malathion	Lead
2,4-Dichlorophenoxyacetic Acid	Mancozeb	3-Methylcholanthrene
Dihydroxynaphthalene	Mercury Chloride	Phenobarbital
2,4-Dihydroxybenzaldehyde	Methamizole	Propylthiouracil
2,4-Dihydroxybenzoic Acid	4,4'-Methylenedianiline	Polybrominated Biphenyl 77
Ethiozin	Polybrominated Biphenyls	TCDD
Ethylene thiourea	Thiocyanate	
Fipronil	Thiourea	
Hexachlorobenzene		Glucuronidation of T4/T3
Hexadrin	Binding to albumin	Acetochlor
4-Hexylresorcinol	Pentachlorophenol	Aroclor 1254
Hydroxyquinol		3,4-Benzopyrene
Hydroxyquinol Triacetate	Binding to thyroglobulin	Clofentezine
Lead	1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane	Clofibrate
Mancozeb	Pentachlorophenol	DDT
Mercuric Chloride		Fenbuconazole
3-Methylcholanthrene	Binding to transthyretin	3,3',4,4',5,5'-Hexabromobiphenyl
Methylmercuric Chloride	Bromoxynil (3,5-bibromo-4-hydroxybenzoxonitril)	Hexachlorobenzene
Methylparathion	4-(Chloro-o-tolyloxy)acetic Acid	Hexachlorobiphenyls
2-Methylresorcinol	4-(4-Chloro-2-methylphenoxy) butyric Acid	3-Methylcholanthrene
Mull-Soy	Chlorophenol	Pendimethalin
Nabam	Chlororoxuron	Phenobarbital
Orcinol	1,1-Dichloro-2,2-bis(p-chlorophenyl)ethanes	Polybrominated Biphenyls
Pendimethalin	2,4-Dichlorophenoxyacetic Acid	Pregnenolone-16 α -carbonitrile
Pentachloronitrobenzene	2,4-Dichlorophenoxybutric Acid	Promadamine
Phenobarbital	Dioxyphthalate	Pyrimethanil
Phenol	Dichlorophenols	TCDD
Phloroglucinol	Dichloroprop	Thiazopyr
Polybrominated Biphenyls	Difocol	
Pregnenolone-16 α -carbonitrile	2,4-Dinitrophenol	Catabolism & biliary T4/T3 elimination
Propylthiouracil	2,4-Dinitro-6-methylphenol	Aroclor
Pyrogallol	Ethyl-bromophos	3,4-Benzopyrene
Pyrimethanil	Ethyl-parathion	DDT
Resorcinol	Fenoprop	Hexachlorobenzene
Saligenin	Hexachlorobenzene	3-Methylcholanthrene
Selenium	Hexachlorophene	Phenobarbital
Thiocyanate	Hydroxybiphenyls	Polybrominated Biphenyls
Sodium/iodide symporter	Lindane	
Perchlorate	Linuron	
Perrhenate	Malathion	
Serum protein-bound iodide level	Pentachlorophenol	
Amitrole	Phenol	
Aroclor	Pyrogallol	
Cythion	Polybrominated Biphenyl 77	
2,4-Dichlorophenoxyacetic Acid	1,4-Tetrachlorophenol	
1,1-Dichloro-2,2-bis (p-chlorophenyl) ethane	Trichloroacetic Acid	
2,4-Dinitrophenol	Trichlorobenzene	
Hexadrin	Trichlorophenols	
Malathion	2,4,5-Trichlorophenoxyacetic Acid	
Mancozeb		
Mercuric Chloride		
3-Methylcholanthrene		

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'-tetrachlorobiphenyl, 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 addition, 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 (ClO₄⁻) (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).

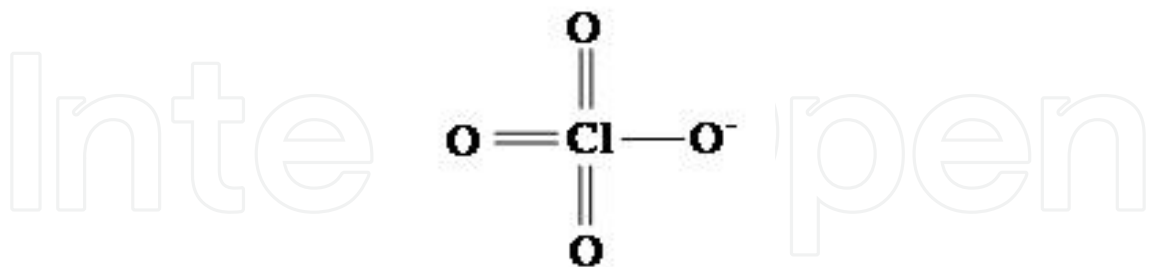


Fig. 3. Perchlorate

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 $\mu\text{g}/\text{l}$ result in minimal inhibition of iodine uptake (about 2%) compared to serum 871 $\mu\text{g}/\text{l}$ 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 $\mu\text{g}/\text{l}$ (Gibbs et al., 1998; Greer et al., 2002; Lamm et al., 1999; Lawrence et al., 2000).

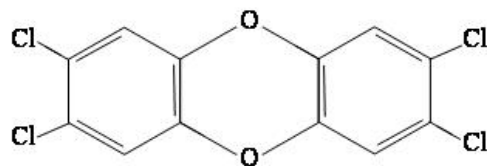
3.2 Dioxins and furans

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

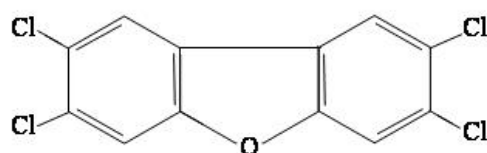
are formed unintentionally as by-products of various industrial processes (e.g. chlorine synthesis, production of hydrocarbons) during pyrolysis and uncompleted combustion of organic materials in the presence of chlorine.

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 environmental 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.

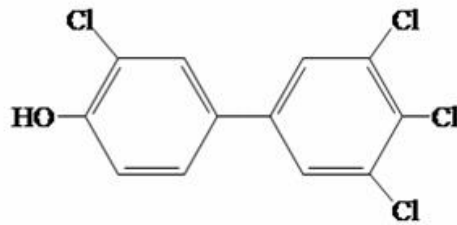


Fig. 5. 4OH-Tetrachlorobiphenyl.

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 a 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.

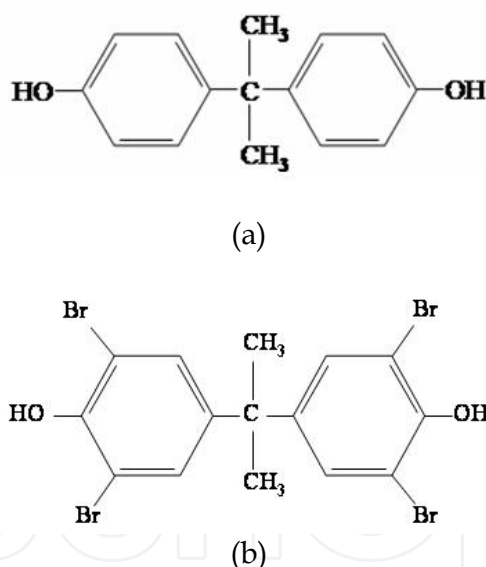


Fig. 6. 4,4'-isopropylidenediphenol (a) and tetrabromo-bisphenol A (b).

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).

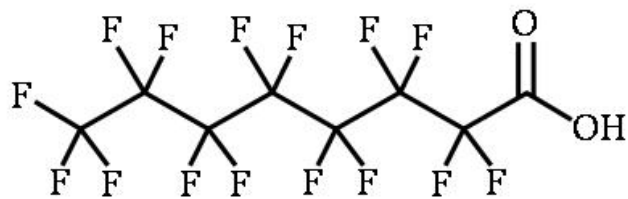


Fig. 7. Perfluoroalkyl Acids.

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 perfluorooctanoic 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; Metzger 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, Metzger et al. (Metzger 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 ($P=0.002$) (Metzger 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 (Metzger 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.

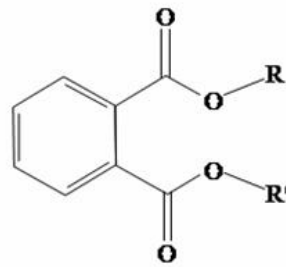


Fig. 8. Phthalates.

Rodent studies found histopathological changes in the rat thyroid glands after exposure to di(2-ethylhexyl) phthalate (DEHP), di-n-octyl 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 from serum) (Barter & Kòassan, 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.

6. References

- Arulmozhiraja, S.; Shiraishi, F.; Okumura, T.; Iida, M.; Takigami, H.; Edmonds, J.S. & Morita, M. (2005). Structural requirements for the interaction of 91 hydroxylated polychlorinated biphenyls with estrogen and thyroid hormone receptors. *Toxicological Sciences*, 84, 1, (March 2005), pp. 49-62.
- Atterwill, C.K.; Collins, P.; Brown, C.G. & Harland, R.F. (1987). The perchlorate discharge test for examining thyroid function in rats. *Journal of Pharmacological and Toxicological Methods*, 18, 3, (November 1987), pp. 199-203.
- Aylward, L.L. & Hays, S.M. (2002). Temporal trends in human TCDD body burden: decreases over three decades and implications for exposure levels. *Journal of Exposure Analysis and Environmental Epidemiology*, 12, 5, (September 2002), pp. 319-28.
- Bansal, R.; You, S.H.; Herzig, C.T. & Zoeller, R.T. (2005). Maternal thyroid hormone increases HES expression in the fetal rat brain: an effect mimicked by exposure to a

- mixture of polychlorinated biphenyls (PCBs). *Brain Research. Developmental Brain Research*, 156, 1, (April 2005), pp. 13-22.
- Barter, R.A. & Kòaaassen, C.D. (1994). Reduction of thyroid hormone levels and alteration of thyroid function by four representative UDP-glucuronosyltransferase inducers in rats. *Toxicology and Applied Pharmacology*, 128, 1, (September 1994), pp. 9-17.
- Bernal, C.A.; Martinelli, M.I. & Mocchiutti, N.O. (2002). Effect of the dietary exposure of rat to di(2-ethyl hexyl) phthalate on their metabolic efficiency. *Food Additives and Contaminants*, 19, 11, (November 2002), pp. 1091-1096.
- Birnbaum, L.S. & Staskal, D.F. (2004). Brominated flame retardants: cause for concern? *Environmental Health Perspects*, 112, 1, (January 2004), pp. 9-17.
- Bloom, M.S.; Weiner, J.M.; Vena, J.E. & Beehler, G.P. (2003). Exploring associations between serum levels of select organochlorines and thyroxine in a sample of New York state sportsmen: the New York State Angler Cohort Study. *Environmental research*, 93, 1, (September 2003), pp. 52-66.
- Boas, M.; Feldt-Rasmussen, U.; Skakkebaek, N.E. & Main, K.M. (2006). Environmental chemicals and thyroid function. *European Journal of Endocrinology*, 154, 5, (May 2006), pp. 599-611.
- Bogazzi, F.; Raggi, F.; Ultimieri, F.; Russo, D.; Campomori, A.; McKinney, J.D.; Pinchera, A.; Bartalena, L. & Martino, E. (2003). Effects of a mixture of polychlorinated biphenyls (Aroclor 1254) on the transcriptional activity of thyroid hormone receptor. *Journal of Endocrinological Investigation*, 26, 10, (October 2003), pp. 972-8.
- Breivik, K.; Sweetman, A.; Pacyna, J.M. & Jones, K.C. (2002). Towards a global historical emission inventory for selected PCB congeners--a mass balance approach. 1. Global production and consumption. *The Science of the Total Environment*, 290, 1-3, (May 2002), pp. 181-98.
- Brouwer, A.; Morse, D.C.; Lans, M.C.; Schuur, A.G.; Murk, A.J.; Klasson-Wehler, E.; Bergman, A. & Visser, T.J. (1998). Interactions of persistent environmental organohalogenes with the thyroid hormone system: mechanisms and possible consequences for animal and human health. *Toxicology and Industrial Health*, 14, 1-2, (January-April 1998), pp. 59-84.
- Brucker-Davis, F. (1998). Effects of environmental synthetic chemicals on thyroid function. *Thyroid*, 8, 9, (September 1998), pp. 827-56.
- Calafat, A.M.; Kuklennyik, Z.; Caudill, S.P.; Reidy, J.A. & Needham, L.L. (2006). Perfluorochemicals in pooled serum samples from United States residents in 2001 and 2002. *Environmental Science & Technology*, 40, 7, (April 2006), pp. 2128-2134.
- Calafat, A.M.; Wong, L.Y.; Kuklennyik, Z.; Reidy, J.A. & Needham, L.L. (2007). Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000. *Environmental Health Perspects*, 115, 11, (November 2007), pp. 1596-1602.
- Calamandrei, G.; Maranghi, F.; Venerosi, A.; Alleva, E. & Mantovani, A. (2006). Efficient testing strategies for evaluation of xenobiotics with neuroendocrine activity. *Reproductive toxicology*, 22, 2, (August 2006), pp. 164-74.
- Carrasco, N. (1993). Iodide transport in the thyroid gland. *Biochimica et Biophysica Acta*, 1154, 1, (June 1993), pp. 65-82.

- Chana, A.; Concejero, M.A.; de Frutos, M.; Gonzalez, M.J. & Herradon, B. (2002). Computational studies on biphenyl derivatives. Analysis of the conformational mobility, molecular electrostatic potential, and dipole moment of chlorinated biphenyl: searching for the rationalization of the selective toxicity of polychlorinated biphenyls (PCBs). *Chemical Research in Toxicology*, 15, 12, (December 2002), pp. 1514-26.
- Chang, S.C.; Das, K.; Ehresman, D.J.; Ellefson, M.E.; Gorman, G.S.; Hart, J.A.; Noker, P.E.; Tan, Y.M.; Lieder, P.H.; Lau, C.; Olsen, G.W. & Butenhoff, J.L. (2008). Comparative pharmacokinetics of perfluorobutyrate in rats, mice, monkeys, and humans and relevance to human exposure via drinking water *Toxicological Sciences*, 104, 1, (July 2008), pp.40-53.
- Cheek, A.O.; Kow, K.; Chen, J. & McLachlan, J.A. (1999). Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. *Environmental Health Perspects*, 107, 4, (April, 1999), pp. 273-8.
- Clewell, R.A.; Merrill, E.A.; Narayanan, L.; Gearhart, J.M. & Robinson, P.J. (2004). Evidence for competitive inhibition of iodide uptake by perchlorate and translocation of perchlorate into the thyroid. *International Journal of Toxicology*, 23, 1, (January-February 2004), pp. 17-23.
- Collette, T.W.; Williams, T.L.; Urbansky, E.T.; Magnuson, M.L.; Hebert, G.N. & Strauss, S.H. (2003). Analysis of hydroponic fertilizer matrixes for perchlorate: comparison of analytical techniques. *The Analyst*, 128, 1, (January 2003), pp. 88-97.
- Crofton, K.M. (2004). Developmental disruption of thyroid hormone: correlations with hearing dysfunction in rats. *Risk Analysis*, 24, 6, (December 2004), pp. 1665-71.
- Darnerud, P.O.; Morse, D.; Klasson-Wehler, E. & Brouwer, A. (1996). Binding of a 3,3', 4,4'-tetrachlorobiphenyl (CB-77) metabolite to fetal transthyretin and effects on fetal thyroid hormone levels in mice. *Toxicology* 106, 1-3, (January 1996), pp. 105-14.
- DeVito, M.; Biegel, L.; Brouwer, A.; Brown, S.; Brucker-Davis, F.; Cheek, A.O.; Christensen, R.; Colborn, T.; Cooke, P.; Crissman, J.; Crofton, K.; Doerge, D.; Gray, E.; Hauser, P.; Hurley, P.; Kohn, M.; Lazar, J.; McMaster, S.; McClain, M.; McConnell, E.; Meier, C.; Miller, R.; Tietge, J. & Tyl, R. (1999). Screening methods for thyroid hormone disruptors. *Environmental Health Perspects*, 107, 5, (May 1999), pp. 407-15.
- Emmett, E.A.; Zhang, H.; Shofer, F.S.; Freeman, D.; Rodway, N.V.; Desai, C. & Sham, L.M. (2006). Community exposure to perfluorooctanoate: relationships between serum levels and certain health parameters. *Journal of Occupational and Environmental Medicine*, 48, 8, (August 2006), pp. 771-779.
- Fisher, B.E. (1999). Most unwanted. *Environmental Health Perspects*, 107, 1, (January 1999), pp. A18-23.
- Flesch-Janys, D.; Becher, H.; Gurn, P.; Jung, D.; Konietzko, J.; Manz, A. & Papke, O. (1996). Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans in occupationally exposed persons. *Journal of Toxicology and Environmental Health*, 47, 4, (March 1996), pp. 363-78.
- Fritsche, E.; Cline, J.E.; Nguyen, N.H.; Scanlan, T.S. & Abel, J. (2005). Polychlorinated biphenyls disturb differentiation of normal human neural progenitor cells: clue for

- involvement of thyroid hormone receptors. *Environmental Health Perspects*, 113, 7, (July 2005), pp. 871-6.
- Fromme, H.; Tittlemier, S.A.; Volkel, W.; Wilhelm, M. & Twardella, D. (2009). Perfluorinated compounds – exposure assessment for the general population in Western countries. *International Journal of Hygiene and Environmental Health*, 212, 3, (May 2009), pp. 239–270.
- Gayathri, N.S.; Dhanya, C.R.; Indu, A.R. & Kurup, P.A. (2004). Changes in some hormones by low doses of di (2-ethyl hexyl) phthalate (DEHP), a commonly used plasticizer in PVC blood storage bags and medical tubing. *Indian Journal of Medical Research* 119, 4, (April 2004), pp. 139–144.
- Gauger, K.J.; Kato, Y.; Haraguchi, K.; Lehmler, H.J.; Robertson, L.W.; Bansal, R. & Zoeller, R.T. (2004). Polychlorinated biphenyls (PCBs) exert thyroid hormone-like effects in the fetal rat brain but do not bind to thyroid hormone receptors. *Environmental Health Perspects*, 112, 5, (April 2004), pp. 516-23.
- Ghinea, E.; Dumitriu, L.; Stefanovici, G.; Pop, A.; Oprescu, M. & Ciocirdia, C. (1986). Action of some pesticides on T4 to T3 conversion in cultured kidney and liver cells in the presence or absence of cysteine. *Endocrinologie*, 24, 3, (July-September 1986), pp. 157-66.
- Giacomini, S.M.; Hou, L.; Bertazzi, P.A. & Baccarelli, A. (2006). Dioxin effects on neonatal and infant thyroid function: routes of perinatal exposure, mechanisms of action and evidence from epidemiology studies. *International Archives of Occupational and Environmental Health*, 79, 5, (May 2006), pp.396-404.
- Gibbs, J.P.; Ahmad, R.; Crump, K.S.; Houck, D.P.; Leveille, T.S.; Findley, J.E. & Francis, M. (1998). Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function. *Journal of Occupational and Environmental Medicine*, 40, 12, (December 1998), pp. 1072-82.
- Giesy, J. & Kannan, K. (2001). Global distribution of perfluorooctanoate sulfonate in wildlife. *Environmental Science & Technology*, 35, 7, (April 2001), pp. 1339–1342.
- Goldey, E.S.; Kehn, L.S.; Lau, C.; Rehnberg, G.L. & Crofton, K.M. (1995). Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. *Toxicology and Applied Pharmacology*, 135, 1, (November 1995), pp. 77-88.
- Goldey, E.S. & Crofton, K.M. (1998). Thyroxine replacement attenuates hypothyroxinemia, hearing loss, and motor deficits following developmental exposure to Aroclor 1254 in rats. *Toxicological Sciences*, 45, 1, (September 1998), pp. 94-105.
- Green, R.; Hauser, R.; Calafat, A.M.; Weuve, J.; Schettler, T.; Ringer, S.; Huttner, K. & Hu, H. (2005). Use of di(2-ethylhexyl) phthalate-containing medical products and urinary levels of mono(2-ethylhexyl) phthalate in neonatal intensive care unit infants. *Environmental Health Perspects*, 113, 9, (September 2005), pp. 1222-5.
- Greer, M.A.; Goodman, G.; Pleus, R.C. & Greer, S.E. (2002). Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. *Environmental Health Perspects*, 110, 9, (September 2002), pp. 927-37.

- Guo, Y.L.; Lambert, G.H.; Hsu, C.C. & Hsu, M.M. (2004). Yucheng: health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. *International Archives of Occupational and Environmental Health*, 77, 3, (April 2004), pp. 153-8.
- Gutshall, D.M.; Pilcher, G.D. & Langley, A.E. (1989). Mechanism of the serum thyroid hormone lowering effect of perfluoro-n-decanoic acid (PFDA) in rats. *Journal of Toxicology and Environmental Health*, 28, 1, (1989), pp. 53-65.
- Hagmar, L.; Rylander, L.; Dyremark, E.; Klasson-Wehler, E. & Erfurth, E.M. (2001a). Plasma concentrations of persistent organochlorines in relation to thyrotropin and thyroid hormone levels in women. *International Archives of Occupational and Environmental Health* 74, 3, (April 2001), pp. 184-8.
- Hagmar, L.; Bjork, J.; Sjodin, A.; Bergman, A. & Erfurth, E.M. (2001b). Plasma levels of persistent organohalogenes and hormone levels in adult male humans. *Archives of Environmental Health*, 56, 2, (March-April 2001), pp. 138-43.
- Hagmar, L. (2003). Polychlorinated biphenyls and thyroid status in humans: a review. *Thyroid*, 13, 11, (November 2003), pp. 1021-8.
- Hauser, R. & Calafat, A.M. (2005). Phthalates and human health. *Occupational and Environmental Medicine*, 62, 11, (November 2005), pp. 806-18.
- Hinton, R.H.; Mitchell, F.E.; Mann, A.; Chescoe, D.; Price, S.C.; Nunn, A.; Grasso, P. & Bridges, J.W. (1986). Effects of phthalic acid esters on the liver and thyroid. *Environmental Health Perspectives*, 70, (December 1986), pp. 195-210.
- Hood, A. & Klaassen, C.D. (2000). Differential effects of microsomal enzyme inducers on in vitro thyroxine (T₄) and triiodothyronine (T₃) glucuronidation. *Toxicological Sciences*, 55, 1, (May 2000), pp. 78-84.
- Howarth, J.A.; Price, S.C.; Dobrota, M.; Kentish, P.A. & Hinton, R.H. (2001). Effects on male rats of di(2-ethylhexyl) phthalate and di-n-hexylphthalate administered alone or in combination. *Toxicology Letters*, 121, 1, (April 2001), pp. 35-43.
- Howdeshell, K.L. (2002). A model of the development of the brain as a construct of the thyroid system. *Environmental Health Perspects*, 110, S3, (June 2002), pp. 337-48.
- Howe, S.R.; Borodinsky, L. & Lyon, R.S. (1998). Potential exposure to bisphenol A from food-contact use of epoxy coated cans. *Journal of Coatings Technology*, 70, (February 1998), pp. 69-74.
- Hundley, S.; Sarrif, A. & Kennedy, G. (2006). Absorption, distribution and excretion of ammonium perfluorooctanoate (APFO) after oral administration in various species. *Drug and Chemical Toxicology*, 29, 2, (2006), pp. 137-145.
- Ikezuki, Y.; Tsutsumi, O.; Takai, Y.; Kamei, Y. & Taketani, Y. (2002). Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Human Reproduction*, 17, 11, (November 2002), pp. 2839-41
- Inoue, K.; Okada, F.; Ito, R.; Kato, S.; Sasaki, S.; Nakajima, S.; Uno, A.; Saijo, Y.; Sata, F.; Yoshimura, Y.; Kishi, R. & Nakazawa, H. (2004). Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. *Environmental Health Perspects*, 112, 11, (August 2004), pp. 1204-1207.
- Isanhart, J.P.; McNabb, F.M. & Smith, P.N. (2005). Effects of perchlorate exposure on resting metabolism, peak metabolism, and thyroid function in the prairie vole (*Microtus ochrogaster*). *Environmental Toxicology and Chemistry*, 24, 3, (May 2005), pp. 678-84.

- Iwasaki, T.; Miyazaki, W.; Takeshita, A.; Kuroda, Y. & Koibuchi, N. (2002). Polychlorinated biphenyls suppress thyroid hormone-induced transactivation. *Biochemical and Biophysical Research Communications*, 299, 3, (December 2002), pp. 384-8.
- Janosek, J.; Hilscherova, K.; Blaha, L. & Holoubek, I. (2006). Environmental xenobiotics and nuclear receptors--interactions, effects and in vitro assessment. *Toxicology In Vitro*, 20, 1, (February 2006), pp. 18-37.
- Jones, P.; Hu, W.; De coen, W.; Newsted, J. & Giesy, J. (2003). Binding of perfluorinated fatty acids to serum proteins. *Environmental Toxicology and Chemistry*, 22, 11, (November 2003), pp. 2639-2649.
- Jurewicz, J. & Hanke, W. (2011). Exposure to phthalates: reproductive outcome and children health. A review of epidemiological studies. *International Archives of Occupational and Environmental Health* 24, 2, (June 2011), pp. 115-141.
- Kang, J.H.; Kondo, F. & Katayama, Y. (2006). Human exposure to bisphenol A. *Toxicology* 226, 2-3, (September 2006), pp. 79-89.
- Kannan, K.; Corsolini, S.; Falandysz, J.; Fillmann, G.; Kumar, K.S.; Loganathan, B.G.; Mohd, M.A.; Olivero, J.; Van Wouwe, N.; Yang, J.H. & Aldoust, K.M. (2004). Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. *Environmental Science & Technology*, 38, 17, (September 2004), pp. 4489-4495.
- Kato, Y.; Ikushiro, S.; Haraguchi, K.; Yamazaki, T.; Ito, Y.; Suzuki, H.; Kimura, R.; Yamada, S.; Inoue, T. & Degawa, M. (2004). A possible mechanism for decrease in serum thyroxine level by polychlorinated biphenyls in Wistar and Gunn rats. *Toxicological Sciences*, 81, 2, (October 2004), pp. 309-15.
- Kavlock, R.J.; Daston, G.P.; DeRosa, C.; Fenner-Crisp, P.; Gray, L.E.; Kaattari, S.; Lucier, G.; Luster, M.; Mac, M.J.; Maczka, C.; Miller, R.; Moore, J.; Rolland, R.; Scott, G.; Sheehan, D.M.; Sinks, T. & Tilson, H.A. (1996). Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. *Environmental Health Perspects*, 104, S4, (August 1996), pp. 715-40.
- Kitamura, S.; Jinno, N.; Ohta, S.; Kuroki, H. & Fujimoto, N. (2002). Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. *Biochemical and Biophysical Research Communications*, 293, 1, (April 2002), pp. 554-9.
- Kitamura, S.; Jinno, N.; Suzuki, T.; Sugihara, K.; Ohta, S.; Kuroki, H. & Fujimoto, N. (2005). Thyroid hormone-like and estrogenic activity of hydroxylated PCBs in cell culture. *Toxicology*, 208, 3, (March 2005), pp. 377-87.
- Kohn, M.C.; Sewall, C.H.; Lucier, G.W. & Portier, C.J. (1996). A mechanistic model of effects of dioxin on thyroid hormones in the rat. *Toxicology and Applied Pharmacology*, 136, 1, (January 1996), pp. 29-48.
- Koopman-Esseboom, C.; Morse, D.C.; Weisglas-Kuperus, N.; Lutkeschipholt, I.J.; Van der Paauw, C.G.; Tuinstra, L.G.; Brouwer, A. & Sauer, P.J. (1994). Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatric Research*, 36, 4, (October 1994), pp. 468-73.
- Lamm, S.H.; Braverman, L.E.; Li, F.X.; Richman, K.; Pino, S. & Howearth, G. (1999). Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational

- health study. *Journal of Occupational and Environmental Medicine*, 41, 4, (April 1999), pp. 248-60.
- Latini, G. (2005). Monitoring phthalate exposure in humans. *Clinica Chimica Acta*, 361, 1-2, (November 2005), pp. 20-9.
- Lau, C.; Thibodeaux, J.R.; Hanson, R.G.; Rogers, J.M.; Grey, B.E.; Stanton, M.E.; Butenhoff, J.L. & Stevenson, L.A. (2003). Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: Postnatal evaluation. *Toxicological Sciences*, 74, 2, (August 2003), pp. 382-392.
- Lau, C.; Anitole, K.; Hodes, C.; Lai, D.; Pfahles-Hutchens, A. & Seed, J. (2007). Perfluoroalkyl acids: a review of monitoring and toxicological findings. *Toxicological Sciences*, 99, 2, (October 2007), pp. 366-394.
- Lawrence, J.E.; Lamm, S.H.; Pino, S.; Richman, K. & Braverman, L.E. (2000). The effect of short-term low-dose perchlorate on various aspects of thyroid function. *Thyroid* 10, 8, (August 2000), pp. 659-63.
- Lewis, J.B.; Rueggeberg, F.A.; Lapp, C.A.; Ergle, J.W. & Schuster, G.S. (1999). Identification and characterization of estrogen-like components in commercial resin-based dental restorative materials. *Clinical Oral Investigations*, 3, 3, (September 1999), pp. 107-13.
- Lintelmann, J.; Katayama, A.; Kuhihara, N. & Wenzel, A. (2003). Endocrine disruptors in the environment (IUPAC Technical Report). *Pure and Applied Chemistry*, 75, 5, (2003), pp. 631-681.
- Loh, K.C. (2000). Amiodarone-induced thyroid disorders: a clinical review. *Postgraduate Medical Journal*, 76, 893, (March 2000), pp. 133-40.
- Luebker, D.J.; Case, M.T.; York, R.G.; Moore, J.A.; Hansen, K.J. & Butenhoff, J.L. (2005). Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. *Toxicology*, 215, 1-2, (November 2005), pp. 126-148.
- Maiti, P.K. & Kar, A. (1997). Dimethoate inhibits extrathyroidal 5'-monodeiodination of thyroxine to 3,3',5-triiodothyronine in mice: the possible involvement of the lipid peroxidative process. *Toxicology Letters*, 91, 1, (March 1997), pp. 1-6.
- Marinovich, M.; Guazzetti, M.; Ghilardi, F.; Viviani, B.; Corsini, E. & Galli, C.L. (1997). Thyroid peroxidase as toxicity target for dithiocarbamates. *Archives of Toxicology*, 71, 8, (1997), pp. 508-12.
- Massart, F.; Harrell, J.C.; Federico, G. & Saggese, G. (2005). Human breast milk and xenoestrogen exposure: a possible impact on human health. *Journal of Perinatology*, 25, 4, (April 2005), pp. 282-8.
- Massart, F.; Parrino, R.; Seppia, P.; Federico, G. & Saggese, G. (2006a). How do environmental estrogen disruptors induce central precocious puberty? *Minerva Pediatrica*, 58, 3, (June 2006), pp. 247-254.
- Massart, F.; Massai, G.; Placidi, G. & Saggese, G. (2006b). Child thyroid disruption by environmental chemicals. *Minerva Pediatrica*, 58, 1, (February 2006), pp. 47-53.
- Massart, F. & Meucci, V. (2007). Environmental thyroid toxicants and child endocrine health. *Pediatric Endocrinology Reviews*, 5, 1, (September 2007), pp. 500-509.
- McNabb, F.M.; Larsen, C.T. & Pooler, P.S. (2004a). Ammonium perchlorate effects on thyroid function and growth in bobwhite quail chicks. *Environmental Toxicology and Chemistry*, 23, 4, (April 2004), pp. 997-1003.

- McNabb, F.M.; Jang, D.A. & Larsen, C.T. (2004b). Does thyroid function in developing birds adapt to sustained ammonium perchlorate exposure? *Toxicological Sciences*, 82, 1, (November 2004), pp. 106-13.
- Metzer, D.; Rice, N.; Deplege, M.H.; Henley, W.E. & Galloway, T.S. (2010). Association between Serum Perfluorooctanoic Acid (PFOA) and Thyroid Disease in the U.S. National Health and Nutrition Examination Survey. *Environmental Health Perspectives*, 118, 5, (May 2010), pp. 686-692.
- Mirabella, G.; Feig, D.; Astzalos, E.; Perlman, K. & Rovet, J.F. (2000). The effect of abnormal intrauterine thyroid hormone economies on infant cognitive abilities. *Journal of Pediatric Endocrinology & Metabolism*, 13, 2, (February 2000), pp. 191-4.
- Michalek, J.E. & Tripathi, R.C. (1999). Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 15-year follow-up. *Journal of Toxicology and Environmental Health. Part A*, 57, 6, (July 1999), pp. 369-78.
- Michalek, J.E.; Pirkle, J.L.; Needham, L.L.; Patterson, D.G. Jr.; Caudill, S.P.; Tripathi, R.C. & Mocarelli, P. (2002). Pharmacokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso adults and veterans of operation Ranch Hand. *Journal of Exposure Analysis and Environmental Epidemiology*, 12, 1, (January-February 2002), pp. 44-53.
- Mitchell, F.E.; Price, S.C.; Hinton, R.H.; Grasso, P. & Bridges, J.W. (1985). Time and dose-response study of the effects on rats of the plasticizer di(2-ethylhexyl) phthalate. *Toxicology and Applied Pharmacology*, 81, 3 Pt 1, (December 1985), pp. 371-392.
- Miyazaki, W.; Iwasaki, T.; Takeshita, A.; Kuroda, Y. & Koibuchi, N. (2004). Polychlorinated biphenyls suppress thyroid hormone receptor-mediated transcription through a novel mechanism. *The Journal of Biological Chemistry*, 279, 18, (April 2004), pp. 18195-202.
- Moriyama, K.; Tagami, T.; Akamizu, T.; Usui, T.; Saijo, M.; Kanamoto, N.; Hataya, Y.; Shimatsu, A.; Kuzuya, H. & Nakao, K. (2002). Thyroid hormone action is disrupted by bisphenol A as an antagonist. *The Journal of Clinical Endocrinology and Metabolism*, 87, 11, (November 2002), pp. 5185-90.
- Morse, D.C.; Groen, D.; Veerman, M.; van Amerongen, C.J.; Koeter, H.B.; Smits van Prooije, A.E.; Visser, T.J.; Koeman, J.H. & Brouwer, A. (1993). Interference of polychlorinated biphenyls in thyroid hormone metabolism: Possible neurotoxic consequences in fetal and neonatal rats. *Toxicology and Applied Pharmacology*, 122, 1, (September 1993), pp. 27-33.
- Morse, D.C.; Wehler, E.K.; Wesseling, W.; Koeman, J.H. & Brouwer, A. (1996). Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254). *Toxicology and Applied Pharmacology*, 136, 2, (February 1996), pp. 269-79.
- O'Connor, J.C.; Frame, S.R. & Ladics, G.S. (2002). Evaluation of a 15-day screening assay using intact male rats for identifying antiandrogens. *Toxicological Sciences*, 69, 1, (September 2002), pp. 92-108.
- Okazaki, Y. & Katayama, T. (2003). Effects of dietary carbohydrate and myo-inositol on metabolic changes in rats fed 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (DDT). *The Journal of Nutritional Biochemistry*, 14, 2, (February 2003), pp. 81-9.
- Olsen, G.W.; Burris, J.M.; Burlew, M.M. & Mandel, J.H. (2003a). Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA)

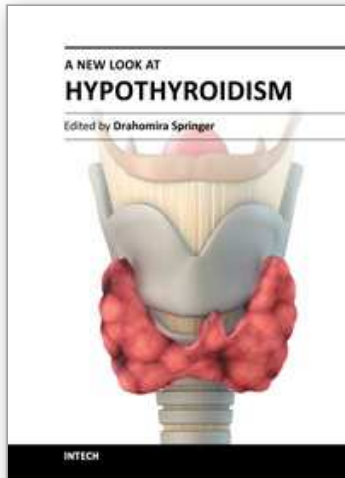
- concentrations and medical surveillance examinations. *Journal of Occupational and Environmental Medicine*, 45, 3, (March 2003), pp. 260-270.
- Olsen, G.W.; Logan, P.W.; Hansen, K.J.; Simpson, C.A.; Burris, J.M.; Burlew, M.M.; Vorarath, P.P.; Venkateswarlu, P.; Schumpert, J.C. & Mandel, J.H. (2003b). An occupational exposure assessment of a perfluorooctanesulfonyl fluoride production site: biomonitoring. *American Industrial Hygiene Association journal*, 64, 5, (September-October 2003), pp. 651-659.
- Olsen, G.W.; Church, T.R.; Miller, J.P.; Burris, J.M.; Hansen, K.J.; Lundberg, J.K.; Armitage, J.B.; Herron, R.M.; Medhdizadehkashi, Z.; Nobiletti, J.B.; O'Neill, E.M.; Mandel, J.H. & Zobel, L.R. (2003c). Perfluorooctanosulfonate (PFOS) and other fluorochemicals in the serum of American Red Cross adult blood donors. *Environmental Health Perspects*, 111, 16, (December 2003), pp. 1892-1901.
- Olsen, G. & Zobel, L. (2007). Assessment of lipid, hepatic and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. *International Archives of Occupational and Environmental Health*, 81, 2, (November 2007), pp. 231-246.
- Organisation for Economic Co-operation and Development (OECD), (2005). *Results of Survey on Production and Use of PFOS and PFOA, Related Substances and Products/Mixtures Containing These Substances*. Organisation for Economic Co-operation and Development, Paris.
- Osius, N.; Karmaus, W.; Kruse, H. & Witten, J. (1999). Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. *Environmental Health Perspects*, 107, 10, (October 1999), pp. 843-9.
- Papke, O.; Ball, M.; Lis, A. & Wuthe, J. (1996). PCDD/PCDFs in humans, follow-up of background data for Germany, 1994. *Chemosphere*, 32, 3, (February 1996), pp. 575-82.
- Persky, V.; Turyk, M.; Anderson, H.A.; Hanrahan, L.P.; Falk, C.; Steenport, D.N.; Chatterton, R. Jr.; Freels, S. & Great Lakes Consortium. (2001). The effects of PCB exposure and fish consumption on endogenous hormones. *Environmental Health Perspects*, 109, 12, (December 2001), pp. 1275-83.
- Poon, R.; Lecavalier, P.; Mueller, R.; Valli, V.E.; Procter, B.G. & Chu, I. (1997). Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. *Food and Chemical Toxicology*, 35, 2, (February 1997), pp. 225-239.
- Price, S.C.; Chescoe, D.; Grasso, P.; Wright, M. & Hinton, R.H. (1988). Alterations in the thyroids of rats treated for long periods with di-(2-ethylhexyl) phthalate or with hypolipidaemic agents. *Toxicology Letters*, 40, 1, (January 1988), pp. 37-46.
- Rais-Bahrami, K.; Nunez, S.; Revenis, M.E.; Luban, N.L. & Short, B.L. (2004). Follow-up study of adolescents exposed to di(2-ethylhexyl) phthalate (DEHP) as neonates on extracorporeal membrane oxygenation (ECMO) support. *Environmental Health Perspects*, 112, 13, (September 2004), pp. 1339-40.
- Rogan, W.J.; Gladen, B.C.; McKinney, J.D.; Carreras, N.; Hardy, P.; Thullen, J.; Tinglestad, J. & Tully, M. (1986). Neonatal effects of transplacental exposure to PCBs and DDE. *Journal of Pediatrics*, 109, 2, (August 1986), pp. 335-41.
- Safe, S.H. (2000). Endocrine disruptors and human health--is there a problem? An update. *Environmental Health Perspects*, 108, 6, (June 2000), pp. 487-93.

- Saito, N.; Harada, K.; Inoue, K.; Sasaki, K.; Yoshinaga, T. & Koizumi, A. (2004). Perfluorooctanoate and perfluorooctane sulfonate concentrations in surface water in Japan. *Journal of Occupational Health*, 46, 1, (January 2004), pp. 49-59.
- Sala, M.; Sunyer, J.; Herrero, C.; To-Figueras, J. & Grimalt, J. (2001). Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. *Occupational and Environmental Medicine*, 58, 3, (March 2001), pp. 172-7.
- Schell, L.M.; Gallo, M.V.; DeCaprio, A.P.; Hubicki, L.; Denham, M.; Ravenscroft, J. & The Akwesasne Task Force on the Environment. (2004). Thyroid function in relation to burden of PCBs, *p,p'*-DDE, HCB, mirex and lead among Akwesasne Mohawk youth: a preliminary study. *Environmental Toxicology and Pharmacology*, 18, 2, (November 2004), pp. 91-99.
- Schettler, T. (2006). Human exposure to phthalates via consumer products. *International Journal of Andrology* 29, 1, (February 2006), pp. 134-9 and 181-5.
- Schonfelder, G.; Wittfoht, W.; Hopp, H.; Talsness, C.E.; Paul, M. & Chahoud, I. (2002). Parent bisphenol A accumulation in the human maternal-fetal-placental unit. *Environmental Health Perspects*, 110, 11, (November 2002), pp. A703-7.
- Seacat, A.M.; Thomford, P.J.; Hansen, K.J.; Clemen, L.A.; Eldridge, S.R.; Elcombe, C.R. & Butenhoff, J.L. (2003). Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicology*, 183, 1-3, (February 2003), pp. 117-131.
- Seo, B.W.; Li, M.H.; Hansen, L.G.; Moore, R.W.; Peterson, R.E. & Schantz, S.L. (1995). Effects of gestational and lactational exposure to coplanar polychlorinated biphenyl (PCB) congeners or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on thyroid hormone concentrations in weanling rats. *Toxicology Letters*, 78, 3, (August 1995), pp. 253-62.
- Sewall, C.H.; Flagler, N.; Vanden Heuvel, J.P.; Clark, G.C.; Tritscher, A.M.; Maronpot, R.M. & Lucier, G.W. (1995). Alterations in thyroid function in female Sprague-Dawley rats following chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicology and Applied Pharmacology*, 132, 2, (June 1995), pp. 237-44.
- Sharlin, D.S.; Bansal, R. & Zoeller, R.T. (2006). Polychlorinated biphenyls exert selective effects on cellular composition of white matter in a manner inconsistent with thyroid hormone insufficiency. *Endocrinology*, 147, 2, (February 2006), pp. 846-58.
- Shea, K.M. (2003). American Academy of Pediatrics Committee on Environmental Health. Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics*, 111, 6 Pt 1, (June 2003), pp. 1467-74.
- Spear, P.A.; Higuieret, P. & Garcin, H. (1990). Increased thyroxine turnover after 3,3',4,4',5,5'-hexabromobiphenyl injection and lack of effect on peripheral triiodothyronine production. *Canadian Journal of Physiology and Pharmacology*, 68, 8, (August 1990), pp. 1079-84.
- Stanbury, J.B. & Wyngaarden, J.B. (1952). Effect of perchlorate on the human thyroid gland. *Metabolism* 1, 6, (November 1952), pp. 533-9.
- Stewart, P.; Fitzgerald, S.; Reihman, J.; Gump, B.; Lonky, E.; Darvill, T.; Pagano, J. & Hauser, P. (2003). Prenatal PCB exposure, the corpus callosum, and response inhibition. *Environmental Health Perspects*, 111, 13, (October 2003), pp. 1670-7.
- Stockholm Convention on Persistent Organic Pollutants (POPs), (2008). Available: <http://chm.pops.int/> [accessed 2 October 2009].

- Strawson, J.; Zhao, Q. & Dourson, M. (2004). Reference dose for perchlorate based on thyroid hormone change in pregnant women as the critical effect. *Regulatory Toxicology and Pharmacology*, 39, 1, (February 2004), pp. 44-65.
- Takser, L.; Mergler, D.; Baldwin, M.; de Grosbois, S.; Smargiassi, A. & Lafond, J. (2005). Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. *Environmental Health Perspects*, 113, 8, (August 2005), pp. 1039-45.
- Thomsen, C.; Lundanes, E. & Becher, G. (2002). Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. *Environmental Science & Technology*, 36, 7, (April 2002), pp. 1414-8.
- Tonacchera, M.; Pinchera, A.; Dimida, A.; Ferrarini, E.; Agretti, P.; Vitti, P.; Santini, F.; Crump, K. & Gibbs, J. (2004). Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. *Thyroid*, 14, 12, December 2004, pp. 1012-9.
- US Environmental Protection Agency (EPA), (1994). *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo- p-dioxin (TCDD) Related Compounds. External review draft.* EPA/600/BP-92/001a.
- US Environmental Protection Agency (EPA), (2006). *The 2010/2015 PFOA Stewardship Program.* Available: <http://www.epa.gov/oppt/pfoa/pubs/stewardship/index.html> [accessed 10 October 2009].
- Van den Berg, K.J.; van Raaij, J.A.; Bragt, P.C. & Notten, W.R. (1991). Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels in vivo. *Archives of Toxicology*, 65, 1, (1991), pp. 15-9.
- van Raaij, J.A.; Kaptein, E.; Visser, T.J. & van den Berg, K.J. (1993). Increased glucuronidation of thyroid hormone in hexachlorobenzene-treated rats. *Biochemical Pharmacology*, 45, 3, (February 1993), pp. 627-31.
- Walkowiak, J.; Wiener, J.A.; Fastabend, A.; Heinzow, B.; Kramer U.; Schmidt, E.; Steingruber, H.J.; Wundram, S. & Winneke, G. (2001). Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *The Lancet*, 358, 9293, (November 2001), pp. 1602-7.
- Wyngaarden, J.B.; Wright, B.M. & Ways, P. (1952). The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland. *Endocrinology*, 50, 5, (May 1952), pp. 537-49.
- World Health Organization (WHO) E.H.C. (1995). *Tetrabromobisphenol A and derivatives.* World Health Organization, Geneva, Switzerland.
- World Health Organization (WHO) E.H.C. (1997). *Flame-retardants: a general introduction.* World Health Organization, Geneva, Switzerland.
- Wolff, J. (1998). Perchlorate and the thyroid gland. *Pharmacological Reviews*, 50, 1, (March 1998), pp. 89-105.
- Yamada-Okabe, T.; Aono, T.; Sakai, H.; Kashima, Y. & Yamada-Okabe, H. (2004). 2,3,7,8-tetrachlorodibenzo-p-dioxin augments the modulation of gene expression mediated by the thyroid hormone receptor. *Toxicology and Applied Pharmacology*, 194, 3, (February 2004), pp. 201-10.

- Yu, W.G.; Liu, W. & Jin, Y.H. (2009). Effects of perfluorooctane sulfonate on rat thyroid hormone biosynthesis and metabolism. *Environmental Toxicology and Chemistry*, 28, 5, (May 2009), pp. 990-996.
- Zoeller, R.T.; Dowling, A.L. & Vas, A.A. (2000). Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. *Endocrinology*, 141, 1, (January 2000), pp. 181-9.
- Zoeller, T.R.; Dowling, A.L.; Herzig, C.T.; Iannacone, E.A.; Gauger, K.J. & Bansal, R. (2002). Thyroid hormone, brain development, and the environment. *Environmental Health Perspects*, 110, S3, (June 2002), pp. 355-61
- Zoeller, R.T. (2003). Thyroid toxicology and brain development: should we think differently? *Environmental Health Perspects*, 111, 12, (September 2003), pp. A628.
- Zoeller, R.T. (2005). Environmental chemicals as thyroid hormone analogues: new studies indicate that thyroid hormone receptors are targets of industrial chemicals? *Molecular and Cellular Endocrinology*, 242, 1-2, (October 2005), pp. 10-5.

IntechOpen



A New Look at Hypothyroidism

Edited by Dr. Drahomira Springer

ISBN 978-953-51-0020-1

Hard cover, 256 pages

Publisher InTech

Published online 17, February, 2012

Published in print edition February, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Francesco Massart, Pietro Ferrara and Giuseppe Saggese (2012). Environmental Thyroid Disruptors and Human Endocrine Health, A New Look at Hypothyroidism, Dr. Drahomira Springer (Ed.), ISBN: 978-953-51-0020-1, InTech, Available from: <http://www.intechopen.com/books/a-new-look-at-hypothyroidism/environmental-thyroid-disruptors-human-endocrine-health>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen