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Review

Thyroid effects of endocrine disrupting chemicals

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ABSTRACT

In recent years, many studies of thyroid-disrupting effects of environmental chemicals have been published. Of special concern is the exposure of pregnant women and infants, as thyroid disruption of the developing organism may have deleterious effects on neurological outcome. Chemicals may exert thyroid effects through a variety of mechanisms of action, and some animal experiments and in vitro studies have focused on elucidating the mode of action of specific chemical compounds. Long-term human studies on effects of environmental chemicals on thyroid related outcomes such as growth and development are still lacking. The human exposure scenario with life long exposure to a vast mixture of chemicals in low doses and the large physiological variation in thyroid hormone levels between individuals render human studies very difficult. However, there is now reasonably firm evidence that PCBs have thyroid-disrupting effects, and there is emerging evidence that also phthalates, bisphenol A, brominated flame retardants and perfluorinated chemicals may have thyroid disrupting properties.

Contents

Abbreviations: BP2, benzophenone 2; BP3, benzophenone 3; BPA, bisphenol A; DBP, di-*n*-butyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEHP, di(2-ethylhexyl) phthalate; HCB, hexachlorobenzene; 4-MBC, 4-methylbenzylidene-camphor; MBP, mono-*n*-butyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; NIS, sodium iodide symporter; NP, nonyl phenol; OMC, octyl-methoxycinnamate; PBB, polybrominated biphenyls; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxin; PFC, perfluorinated chemicals; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; T3, triiodothyronine; T4, thyroxine; TBBPA, tetrabromobisphenol A; TBG, thyroxin-binding globulin; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TPO, thyroid peroxidase enzyme; TR, thyroid receptor; TRE, thyroid response element; TSH, thyroid-stimulating hormone; TTR, transthyretin.

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1. Introduction

The abundant industrial use of chemicals in a wide variety of products causes a constant exposure of humans and wildlife to synthetic chemicals with the potential of interfering with biological systems. Numerous chemicals are suspected to be detrimental to human health, ranging from effects on the immune system, the brain and general body growth and composition to the reproductive system and disturbances of pancreatic function. Some environmental chemicals are specifically suspected to have thyroid-disrupting properties.

Thyroid hormones are involved in numerous physiological processes as regulators of metabolism, bone remodeling, cardiac function and mental status. Thus, maintenance of normal thyroid function is essential for psychological and physiological well-being. However, thyroid hormones are of special importance in fetal development, as development of the brain is dependent on normal levels of thyroid hormones. Absence of thyroid hormones reduces neuronal growth and differentiation in the cerebral cortex, hippocampus, and cerebellum (Auso et al., 2004; Lavado-Autric et al., 2003; Nicholson and Altman, 1972). During the first part of pregnancy, the fetus relies entirely on transplacental transfer of maternal thyroid hormones and thus on a normal maternal thyroid function, but maternal thyroid homeostasis is also contributing substantially to fetal development during the remaining part of pregnancy.

In recent years, the presence of subclinical hypothyroidism in large populations, especially if iodine-insufficient, and the long-term health consequences and the need of treatment have been much debated. Epidemiological studies have indicated that even a marginally low thyroxine level in a pregnant woman may give rise to reduction of cognitive functions of the offspring (Berbel et al., 2009; Haddow et al., 1999; Pop et al., 2003). Thus, even minor changes in the thyroid homeostasis may affect fetal neurological development.

Exposure to thyroid-disrupting chemicals may potentially result in such subtle reductions of serum hormone levels, which in turn may have significant consequences for public health.

In this review, we will give an overview of the current knowledge about the human effects of potentially thyroid-disrupting chemicals. Wildlife observations and experimental animal and in vitro studies are referred to if they serve to explain potential modes of action.

2. Thyroid-disrupting chemicals – mechanisms of action

Thyroid function is regulated by a finely tuned negative feedback mechanism of circulating thyroid hormones at the hypothalamic and pituitary levels, maintaining relatively stable serum levels of thyroid hormones with each individual having his or her specific set point (Feldt-Rasmussen et al., 1980). Alterations in the thyroid gland, binding proteins, peripheral metabolism and clearance also affect thyroid function. The mechanisms involved in thyroid homeostasis are thus numerous and complex, and environmental chemicals may interfere at all levels.

The large physiological range of TSH and peripheral thyroid hormones in human, resulting in a large variation of measurements between individuals makes studies of human populations very difficult. In addition, human exposure is constant, cumulative for persistent chemicals, and involves a vast number of chemicals.

At the level of the thyroid gland itself, chemicals may disturb the overall activity of the gland by interference with the TSH-receptor, as thyroid-stimulating hormone (TSH) stimulates all steps of the hormone production. The function of the sodium iodide symporter (NIS) or thyroid peroxidase (TPO) can be affected by chemicals through stimulation or inhibition. Chemicals may also interfere with other receptors on the thyrocyte whereby interference with intracellular mechanisms (e.g. cytokine actions) may occur.

Thyroid hormones are in humans mainly bound to thyroid binding globulin (TBG), whereas transthyretin (TTR), being the most important carrier protein in rodents, binds only a minor proportion of the hormones. However, TTR has been proposed to be of importance by transferring thyroid hormones over the blood–brain barrier as well as over placenta to the fetal compartment. In contrast to TTR, to which hydroxylated PCBs can competitively bind, no EDCs have been demonstrated to compete with thyroid hormones for binding to TBG or albumin with significant strength (Lans et al., 1994; van den Berg, 1990). Competitive binding of environmental chemicals to transport proteins may result in increased bioavailibility of endogenous thyroid hormones, but feedback regulation via TSH may compensate for this change in binding capacity of the transport proteins. Displacement of T4 from TTR by EDCs is not believed to be a major health hazard in humans (Purkey et al., 2004). Another potential effect of binding of EDCs to natural transport proteins may facilitate their transport to thyroid dependent tissues such as the brain or the fetus.

At target cells, thyroid hormones are probably actively transported across the cell surface via membrane bound transporters. Interference of EDCs with these proteins may compromise the bioavailibity of thyroid hormones to the nuclear thyroid hormone receptors (TR). Several chemicals have been shown to interact with the TR, either directly as agonists or antagonists, or by regulating expression of the TR genes.

In the brain, thyroid hormones are involved in oligodendrocyte development and myelination as well as extension of Purkinje cell dendrites, which is essential for normal neuronal circuit formation (synaptogenesis) and subsequent behavioral functions. Alterations in TR-expression or thyroid hormone receptor binding may disturb the normal development of the central nervous system.

Thyroid hormones are metabolised in peripheral tissues by the iodothyronine deiodinases, thus regulating the levels of the biologically active T3 by activation of T4 and inactivation of T4 and T3. Furthermore, thyroid hormones are metabolised in the liver by sulphation and conjugation by UDPGTs, and stimulation of these enzymes by EDCs may lead to faster clearance of the thyroid hormones.

Due to the physiological feedback regulation between TSH and peripheral hormones, the effects of EDCs are not easily predictable or detectable, as no ‘exposure free’ state exists in humans. Unfortunately, very few human studies include long term health effects of thyroid related outcomes such as neurological development or growth in their outcomes. Despite the compensating capacity of the thyroid gland the combined long-term effects of numerous EDCs, some of which accumulate with time, may potentially result in hypothyroidism.

3. Endocrine disrupting chemicals and thyroid effects

3.1. Polychlorinated biphenyls (PCBs) and dioxins

Polychlorinated biphenyls (PCBs) and dioxins (PCDD) comprise a group of highly persistent lipophilic chemicals deriving from industrial production, such as pesticides or combustion processes. They are accumulated through the food chain and are, despite being banned for decades, widely detectable in human, wildlife and environmental samples. Many of these compounds, especially the hydroxylated metabolites, which are also biologically active, have a high degree of structural resemblance to thyroxine (T4).

Human studies have raised concern that environmental levels of PCBs may reduce peripheral thyroid hormone levels (Abdelouahab et al., 2008; Hagmar et al., 2001b; Persky et al., 2001; Schell et al., 2008; Turyk et al., 2007) or increase TSH (Osius et al., 1999; Schell et al., 2008). Furthermore, some studies of pregnant women show that environmental levels of PCBs are associated with reduced thyroid hormone levels and/or positive associations with TSH (Chevrier et al., 2008; Takser et al., 2005), although not all studies found similar tendencies (Wilhelm et al., 2008). This indicates, that PCBs reduce peripheral hormone levels with a compensatory increase in TSH. Results of studies in newborns and infants are less consistent. Two studies of PCB and dioxin in breast milk and thyroid function in 2 weeks – 3 months old children found negative associations between levels of thyroid hormone and PCB (Darnerud et al., 2010; Koopman-Esseboom et al., 1994). Another study found that PCB levels in cord blood were positively correlated with TSH in 3 days old infants. Peripheral thyroid hormones were not analyzed in this study (Ribas-Fito et al., 2003). Some studies of newborns have confirmed these associations (Chevrier et al., 2007; Herbstman et al., 2008), but others have not (Dallaire et al., 2009; Dallaire et al., 2008; Longnecker et al., 2000; Lopez-Espinosa et al., 2010; Steuerwald et al., 2000; Wang et al., 2005; Wilhelm et al., 2008). As TSH and peripheral thyroid hormone levels around the time of birth are highly dependent on gestational age, birth weight, mode of delivery and neonatal health, it may not be possible to avoid these inconsistencies, unless timing of samples is strictly standardized. Studies of long-term effects of perinatal exposure found no associations between levels of PCB or dioxin and thyroid hormones at the age of 1 or 2 years (Matsuura et al., 2001), but at 5 years serum T3 was higher in highly exposed individuals (Su et al., 2010). In older children, several studies have found negative correlations between PCB levels in serum and thyroid hormone levels at the age of 4 years (T3 and FT4) (Alvarez-Pedrerol et al., 2008), 7–10 years (FT3) (Osius et al., 1999), and 10–15 years (T4 and FT4) (Schell et al., 2004).

In experimental animal studies, exposure to PCBs or dioxin results in reduction of serum thyroid hormone levels, especially affecting T4 (Gauger et al., 2004; Hallgren et al., 2001; Hallgren and Darnerud, 2002; Martin and Klaassen, 2010; Nishimura et al., 2002; van der Plas et al., 2001; Viluksela et al., 2004). Similarly, monkeys exposed to PCB for 18–23 weeks showed dose-dependent reductions of thyroid hormone levels (van den Berg et al., 1988). Mixtures of dioxin-like compounds also decreased levels of T4 (van der Plas et al., 2001), possibly in an additive manner (Crofton et al., 2005).

There is substantial evidence that perinatal exposure to PCBs and their hydroxylated metabolites decrease thyroid hormones in the offspring. This has been shown for PCB-exposure in rats (Crofton et al., 2000; Donahue et al., 2004; Meerts et al., 2002; Meerts et al., 2004; Zoeller et al., 2000), but also in sledge dogs (Kirkegaard et al., 2011), as well as dioxin-exposure in rats (Nishimura et al., 2003; Seo et al., 1995). Accumulation of hydroxylated metabolites in the fetal compartment has been demonstrated (Darnerud et al., 1996). Negative correlations between serum levels of PCBs or other organochlorine pollutants and thyroid hormones are also reported from wildlife, both in polar bears (Skaare et al., 2001), seals (Chiba et al., 2001; Sormo et al., 2005), and nesting eagles (Cesh et al., 2010).

In vitro studies have indicated that hydroxylated PCBs bind to TTR (Meerts et al., 2002; Purkey et al., 2004). The metabolites and derivatives of PCBs had stronger binding affinity than their parent compounds, indicating an important role for hydroxylation and halogenation in thyroid toxicity (Meerts et al., 2000).

PCBs may also interact with thyroid function at receptor or DNA level. PCBs have T3-like properties in thyroid-dependent rat pituitary cell line GH3 cells (Kitamura et al., 2005a), and can also suppress transcription through inhibiting the binding of T3 to the TR (Iwasaki et al., 2002) or by dissociation of the TR/retinoid X receptor heterodimer complex from the thyroid response element (TRE) (Miyazaki et al., 2004). Thyroid-like activity of PCB-metabolites was positively associated with the degree of chlorination, but not with the number of hydroxyl groups (Arulmozhiraja et al., 2005). At post-receptor level, a PCB mixture (Aroclor 1254) dose-dependently inhibited TSH-stimulated adenylate cyclase activity and the cAMP production (Santini et al., 2003). Expression of TH-responsive genes in the fetal cortex was significantly increased by Aroclor 1254, including the genes related to neuroendocrine-specific protein A (NSP-A), RC3/neurogranin, and Oct-1 (Gauger et al., 2004; Zoeller et al., 2000) and HES (Bansal et al., 2005). Brain protein extracts from chicken embryos showed that 17 of 109 differentially expressed thyroid-related proteins differed with PCB treatment resulting in both thyromimetic and hypothyroid effects (Roelens et al., 2005).

Furthermore, PCBs have been suggested to interfere with neural development through thyroid function modulation. In rat brain tissue, some PCBs mimicked some of the effects of hypothyroidism on white matter, as total cellular density and the number of oligodendrocytes decreased after exposure (Sharlin et al., 2006), whereas PCB 118 in cultures of normal human neural progenitor (NHNP) cells mimicked T3-effects by dose-dependently stimulating the differentiation into oligodendrocytes (Fritsche et al., 2005). Culture of cerebellar cells with hydroxylated PCBs, thus mimicking the human metabolites of PBCs, caused an abnormal development of Purkinje cell dendrites, which are involved in neuronal circuit formation (Kimura-Kuroda et al., 2005).

Hydroxylated PCBs affected peripheral metabolism of thyroid hormones by inhibiting thyroid hormone sulphation (Schuur et al., 1998b; Schuur et al., 1998c; Schuur et al., 1998a), whereas dioxin induced UDPGT activity in both exposed adult rats (Nishimura et al., 2002) and their offspring (Nishimura et al., 2003), and decreased the activity of hepatic deiodinases (Viluksela et al., 2004).

In summary, the combined data from human studies and experimental observations provide firm evidence that PCBs and dioxins negatively affect thyroid function by interference with transport and metabolism.

3.2. Polybrominated flame retardants

Flame retardants, including chemicals such as tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs), are used in a variety of products such as electronic equipments, plastics, paints and synthetic textiles. TBBPA and PBDEs show even closer structural relationship to T4 than PCBs.

Few human studies exist regarding thyroid disruption by flame retardants and their results are not consistent. Two studies showed negative associations between PBDE exposure and serum TSH levels in adult men (Hagmar et al., 2001a) and pregnant women, respectively (Chevrier et al., 2010). One study reported negative associations between PBDE in serum and T3 and TSH, but a positive relation with T4 (Turyk et al., 2008).

Evidence from mammalian studies is more stringent. In rats, several individual PBDE congeners as well as commercial PBDE mixtures decreased the levels of circulating thyroid hormones (Fowles et al., 1994; Hallgren et al., 2001; Lee et al., 2010; Stoker et al., 2004; Zhou et al., 2001). Perinatal maternal exposure of rats to PBDE similarly reduced thyroid hormones pre- and postnatally in both dams and fetuses (Kim et al., 2009; Kodavanti et al., 2010; Zhou et al., 2002). Studies of other species have shown similar reductions in thyroid hormone levels in fish (Lema et al., 2008; Tomy et al., 2004), kestrels (Fernie et al., 2005) and minks, the

latter also demonstrating a transgenerational effect (Zhang et al., 2009). Interestingly, multigenerational studies of low-dose exposure levels, comparable to levels of environmental human exposure, showed similar thyroid-disrupting effects in rat pups (Kuriyama et al., 2007) and lambs (Abdelouahab et al., 2009).

Flame retardants appear to interfere with thyroid function at several levels, by interacting with TR, binding proteins and hepatic clearance. Thus, TBBPA binds TR directly and impairs TH-dependent metamorphosis in amphibian models (Fini et al., 2007; Jagnytsch et al., 2006; Kitamura et al., 2005b). TBBPA acts antagonistically in a competition assay (Hofmann et al., 2009). Similarly, TBBPA interferes with binding proteins (Meerts et al., 2000). PBDE may act through induction of hepatic enzymes involved in glucuronidation (Hallgren et al., 2001) or by down-regulating the transport protein transthyretin (TTR) and transmembranal thyroid hormone transport (Richardson et al., 2008). Derivatives of TBBPA and PBDEs exhibited higher thyroid hormone activities than their mother compounds, indicating that hydrogen bonds are an important factor governing thyroid hormone activities (Li et al., 2010; Meerts et al., 2000).

In summary, experimental evidence suggests strongly that polybrominated flame retardants are capable of disrupting thyroid homeostasis, but human studies are still sparse.

3.3. Pesticides

Innumerable different chemicals are used as pesticides and are as such part of potentially widespread human exposure. Many animal and toxicological studies suggest that multiple pesticides may have thyroid-disrupting properties. Thus, both persistent organochlorine pesticides and non-persistent pesticides such as organophosphorus, carbamates and pyrethroids, may interfere with thyroid function. The persistent chemicals dichlorodiphenyltrichloroethane (DDT) (and its metabolite DDE), hexachlorobenzene (HCB), and nonylphenol (NP) are among the most examined as regards thyroid-disrupting effects. Although use of these chemicals has long been banned in many countries, they are still present in the environment due to their long environmental half-lives and continuous use in some countries for pest control such as malaria.

A few human studies of pesticide exposure have found inverse associations between HCB and thyroid hormone levels (Bloom et al., 2003).

Numerous animal studies have shown negative associations between thyroid hormone levels and exposure to pesticides. In rats thyroid hormones were reduced by exposure to DDT (Scollon et al., 2004), HCB (Alvarez et al., 2005; Foster et al., 1993; Rozman et al., 1986; van Raaij et al., 1993b; van Raaij et al., 1993a), and mixtures (den Besten et al., 1993; Rawlings et al., 1998). Similarly, NP decreases the level of T4 in studies of salmon (McCormick et al., 2005) and lambs (Beard et al., 1999).

In vitro studies showed TPO inhibition by phenol compounds (Schmutzler et al., 2004) as well as interference with binding proteins (Kudo and Yamauchi, 2005; Yamauchi et al., 2003). Methoxychlor was found to decrease hepatic deiodinase activity (Zhou et al., 1995).

Thus, pesticides, in particular chlorinated compounds and phenols, show thyroid disrupting properties. It will be a challenge, however, to establish valid human data for any particular substance given the vast range of modern pesticides in addition to historically used persistent pesticides.

3.4. Perfluorinated chemicals

Perfluorinated chemicals (PFC) possess surface protection properties, which are advantageous in many industrial and consumer products as stain- and oil-resistant coatings, including coated cardboard packaging for fast food, floor polishes and insecticide formulations. The group comprises several chemicals, e.g. perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). PFCs are extremely persistent in the environment.

A large study of 506 employees in a PFC manufacturer company showed negative associations between PFOA and FT4 (Olsen and Zobel, 2007), indicating that exposure to high levels of PFOS may interfere with human thyroid function. In a substudy of the NHANES study in US, women with high levels of PFOA and men with high levels of PFOS were more likely to report current treated thyroid disease (Melzer et al., 2010).

Several animal studies found decreased levels of T4 after both short-term (Chang et al., 2007; Martin et al., 2007) and long-term exposure (Yu et al., 2009a) to PFOS. However, single-dose exposure to PFOS resulted in transiently increased FT4 and decreased TSH, followed by decreased T4 and T3 (Chang et al., 2008). Similarly, PFOA decreased levels of T3 (Martin et al., 2007), and a study of monkeys showed reduction of T3 after exposure to PFOS (Seacat et al., 2003). Perinatal exposure to PFOS also reduced serum levels of T4, both in pregnant dams (Thibodeaux et al., 2003) and in the offspring (Lau et al., 2003; Luebker et al., 2005). Cross-over studies of rats exposed in utero and/or in lactation, document that both prenatal and postnatal exposure to PFOS may reduce thyroid hormone levels in the offspring (Yu et al., 2009b).

In vitro studies of exposed rat tissues showed up-regulation of hepatic glucuronidation enzymes and deiodinases in the thyroid gland (Yu et al., 2009a) as well as binding to TTR (Weiss et al., 2009).

In summary, perfluorinated chemicals appear to interfere with thyroid hormone metabolism, and as these chemicals are highly persistent their extensive use in consumer products including food packaging should raise concern.

3.5. Phthalates

Phthalates comprise a group of chemicals, which are widely used as plastic emollients and additives in various industrial and consumer products. Despite the ban of use of some phthalates such as DEHP for children's toys, many different types of phthalates are still employed in i.e. cosmetics, paints, food packaging, cleaning agents and medical devices such as tablet coatings, blood bags and tubes. Phthalates are not accumulating in the body, but are metabolised and mainly excreted in the urine within hours or few days. However, their ubiquitous use leads to inevitable constant exposure.

For certain groups, such as hospitalized neonates and patients on repetitive transfusion schemes and dialysis, exposure may be massive.

Thus far, only few studies in humans on thyroid disrupting effects of phthalates have been carried out, whereas their adverse effects on male reproductive health are better investigated. In studies, urinary concentrations of phthalate metabolites are measured as a proxy for phthalate exposure. In 76 pregnant women, a significant negative association between the metabolite of DBP and free and total T4 was found (Huang et al., 2007). Likewise, negative associations between DEHP-exposure and free T4 and total T3 have been reported in adult men (Meeker et al., 2007). We performed a large cohort study of children, documenting that children are exposed to similar amounts of phthalates as adults. Their exposure was negatively associated with serum levels of T3 and height attainment (Boas et al., 2010).

Animal studies on thyroid-disrupting effects of phthalates are also scarce. In rats, di-n-butyl phthalate (DBP) decreased T3 and T4 in a dose-dependent manner (O'Connor et al., 2002), and several studies have shown morphological changes in the thyroid after exposure to phthalates (Howarth et al., 2001; Poon et al., 1997).

Experimental studies suggest different mechanisms of action of phthalate effects on the thyroid homeostasis. Some phthalates (DIDP, butyl benzyl phthalate (BBP) and DnOP) have been shown to interfere with the activity of the NIS (Breous et al., 2005), and others (DBP, BBP) to inhibit T3 uptake in cells (Shimada and Yamauchi, 2004). Furthermore, phthalates competitively bind to transthyretin (TTR) (Ishihara et al., 2003) and inhibit the expression of the TR-beta gene (Sugiyama et al., 2005).

In summary, although experimental studies suggest that phthalates are likely to have thyroid disrupting properties, our current knowledge about human effects is too sparse to draw firm conclusions.

3.6. Bisphenol A (BPA)

Bisphenol A (BPA, 4,4′-isopropylidenediphenol) is widely used in plastic products such as clear plastic bottles, water dispensers and food can linings, and human exposure is extensive (Calafat et al., 2008; Ye et al., 2008). Potential public health effects, in particular with respect to reproduction are heavily debated, and BPA has been banned from baby bottles in many countries by precautionary principle. However, to our knowledge, no human studies of the thyroid-disrupting effects of BPA have been performed.

In animals, study results are conflicting. In adult rats, either no effects or no consistent effects were found on thyroid hormone levels (Nieminen et al., 2002b; Nieminen et al., 2002a; Xu et al., 2007) after BPA exposure. One study of prenatally exposed pups showed a significant increase in T4 levels (Zoeller et al., 2005). Exposure to BPA in polecats (Nieminen et al., 2002a) and field voles (Nieminen et al., 2002b) did not elicit significant effects on thyroid hormone levels. However, BPA exposure doses were significantly correlated to the activity of UDPGT catalyzing the conjugation of thyroid hormones and thereby potentially increasing the elimination rate.

Mechanistic studies indicate several mechanisms by which BPA may interfere with thyroid function. BPA inhibits human recombinant TPO activity (Schmutzler et al., 2007) and, accordingly, blocks T3-induced metamorphism of tadpoles (Iwamuro et al., 2003). Furthermore, BPA was found to bind TTR (Kudo and Yamauchi, 2005). At receptor level, BPA binds to the thyroid hormone receptor (TR) as a weak ligand and acts as an antagonist to T3 thus inhibiting TR-mediated transcriptional activity (Freitas et al., 2010; Moriyama et al., 2002; Sun et al., 2009). The derivatives of BPA, TBBPA and TCBPA, showed an even higher affinity for the receptor (Fini et al., 2007; Hofmann et al., 2009; Jagnytsch et al., 2006; Kitamura et al., 2005b). BPA exposure may also modulate expression of thyroid-related genes in the brain, although the mechanisms are not clear (Seiwa et al., 2004; Zoeller et al., 2005).

As BPA is produced in large amounts world wide, its potential effect on thyroid metabolism and thyroid related brain function should precipitate more research into human health effects. It may be in particular the fetus and infant that are most vulnerable to BPA exposure.

3.7. UV-filters

Ultraviolet (UV) filters are used in sunscreens, other cosmetic products like night creams and anti-wrinkle remedies, but also in household materials to preserve coloring. Thus, exposure is not limited to sunny seasons. 4-methylbenzylidene-camphor (4-MBC), octyl-methoxycinnamate (OMC), and benzophenone 2 and 3 (BP2, BP3) are suspected to have thyroid-disrupting properties.

To our knowledge, no human studies of thyroid effects of UV-filters exist, but rat studies have shown a significant reduction in circulating thyroid hormone levels and increased levels of TSH after exposure to 4-MBC (Seidlova-Wuttke et al., 2006), OMC (Klammer et al., 2007), and BP2 (Jarry et al., 2004; Schmutzler et al., 2007). A multi-generational study of effects of OMC in rats showed significant reduction in circulating T4 levels in the dams and in the male, but not female, offspring (Axelstad et al., 2011).

Experimental studies indicate that OMC and 4-MBC reduce the activity of type I deiodinase in the liver, thus reducing the conversion from T4 to T3 (Klammer et al., 2007; Schmutzler et al., 2004). BP2 was shown to be a potent inhibitor of human recombinant TPO (Schmutzler et al., 2007).

Thus, experimental studies indicate that some UV-filters interfere with thyroid function, but human and wildlife studies are still lacking.

3.8. Perchlorate

Perchlorate is a chemical with well known antithyroidal effects, which has earlier been exploited in diagnosis and treatment of thyrotoxicosis, as it is known to compromise iodine uptake to the thyroid follicular cells by inhibiting the sodium iodide symporter (NIS) (Tonacchera et al., 2004). It is used in the production of ordnance and fireworks, and the presence of perchlorate in drinking water in the US has been a source for concern (Strawson et al., 2004).

Despite the well-described antithyroid effects of perchlorate, the lowest effects level and thus potential harm from environmental contamination levels remains unclear. Thyroid gland iodine uptake in workers in an ammonium perchlorate production plant was negatively associated with their presence at work (Braverman et al., 2005). However, it remains controversial whether environmentally occurring levels of perchlorate have any effects on human, and especially neonatal, thyroid function, as results from human observational studies are conflicting (Brechner et al., 2000; Kelsh et al., 2003; Li et al., 2000).

4. Discussion

Many groups of chemicals may have thyroid-disrupting potential as judged by experimental studies. However, only the effects of environmental levels of PCBs have been extensively investigated in humans, wildlife, animal experiments and in vitro. Most chemicals have been studied sporadically, and research results are not always consistent.

Interference of chemical substances with thyroid homeostasis may result in discrete changes of serum hormone levels, which may be difficult to document in small clinical studies (Boas et al., 2009). Up to a yet unknown threshold of exposure the human body may be able to compensate for adverse effects, i.e. decrease in peripheral T4 and T3, by negative feedback mechanisms, i.e. increase in TSH. Taking into account the wide reference ranges of thyroid hormone levels, discrete alterations may seem insignificant. However, serum levels of TSH, T3 and T4 are tightly regulated within a given individual, maintaining an individual set-point. Therefore, intra-individual variations in thyroid hormone levels are small compared to the wide reference ranges (Feldt-Rasmussen et al., 1980). Consequentially, minor changes in thyroid hormone levels may not be detected in small cross-sectional human studies, where the expected inter-individual variations may camouflage real differences associated with exposure.

Minor alterations in thyroid homeostasis in the individual may have effects on general health, especially during sensitive developmental windows such as the development of the central nervous system in fetal life and infancy (Auso et al., 2004; Lavado-Autric et al., 2003; Nicholson and Altman, 1972). Adverse effects may be permanent if the exposure occurs in a critical phase (Berbel et al., 2009; Pop et al., 2003; Sala et al., 2001). However, such discrete effects may be difficult to detect in observational human

studies of ambient environmental exposure. Current human studies at large lack to include thyroid related outcomes in addition to measurement of peripheral hormones, such as neurological development or growth in order to strengthen our understanding of the effects of EDCs on public health. Future studies will also need to address the significant challenge of designing the optimal time point at which to assess thyroid function. This is particularly true for newborns and pregnant women. It may be difficult to obtain ethical permission for biological samples from healthy newborns for evaluation of thyroid function and EDC exposure, and therefore samples of cord blood are often used. However, in the neonate, TSH increases dramatically immediately after birth, peaking at 30 min, followed by an increase in both T4 and T3. All hormone levels subsequently decrease, leaving evaluation of TSH and thyroid hormone levels highly dependent on exact age and individual factors. Gestational age, mode of delivery and neonatal health are additional factors that may cause variations in thyroid hormone levels. Thus, thyroid function measurements in neonates may result in large variations that may obscure any real effects of EDCs. Likewise, in pregnancy, endocrinological and physiological alterations stimulate the maternal thyroid gland and result in marked gestation-specific changes in thyroid-hormone levels. Thus, evaluation of especially TSH, but also thyroid hormone levels needs to account for gestational age, maternal height and weight and smoking. In addition, results from observational human studies presenting associations between exposure and thyroid hormone levels may be difficult to interpret as thyroid hormones influence metabolic processes in the body, including detoxification processes serving to eliminate EDCs from the body. It remains unclear if thyroid hormone levels may influence the actual levels of EDC in biological samples, thus potentially giving rise to reverse causality. These questions have not yet been addressed in neither experimental nor human studies. A normal thyroid function requires a successful development of the thyroid gland itself and establishment of a well-functioning HPT-axis. It is not yet clear, whether some EDCs may interfere with thyroid function through affecting thyroid development, development of anti-thyroid antibodies or by interaction with other substances of importance in thyroid metabolism such as iodine or selenium.

Human and animal studies of thyroid-disrupting effects in fetal life or infancy are greatly needed, and should aim to include sufficient numbers of exposed participants, monitoring both the thyroid function with measurements of TSH and peripheral thyroid hormones as well as thyroid-related endpoints such as psychomotor development.

5. Conclusion

A variety of different groups of chemicals that humans are currently exposed to appear to have thyroid-disrupting potential. Experimental animal and in vitro studies have indicated possible mechanisms of action for chemicals, but evidence from mammalian and human studies is often sparse. There is substantial evidence that PCBs have adverse effects on thyroid function, and, although sparse, studies of other halogenated compounds, BPA, UV filters and phthalates suggest that these chemicals also have thyroid-disrupting properties. The unavoidable life long human exposure to mixtures of such environmental chemicals raises serious concerns about their potential to adversely affect thyroid function. Subtle changes in the individual set point of thyroid homeostasis may have significant acute and long-term effects, especially if this occurs during sensitive developmental periods. Pregnant women and their foetuses, premature children, infants and toddlers are particularly sensitive to permanent effects on neurodevelopment, whereas older children and adolescents may mainly exhibit adverse effects related to growth and reproductive development. Some of these effects will not become obvious unless large study groups are followed over time, as most biological parameters show a considerable inter-individual variation and many different chemicals need to be considered.

Disclosure statement

The authors have nothing to disclose.

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