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REVIEW

Chemical contamination and the thyroid

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Abstract Industrial chemical contaminants have a variable impact on the hypothalamic-pituitary-thyroid axis, this depending both on their class and on confounding factors. Today, mounting evidence is pointing to the role of environmental factors, and specifically EDCs, in the current distressing upsurge in the incidence of thyroid disease. The unease is warranted. These substances, which are nowadays rife in our environments (including in foodstuffs), have been shown to interfere with thyroid hormone action, biosynthesis, and metabolism, resulting in disruption of tissue homeostasis and/or thyroid function. Importantly, based on the concept of the "nonmonotonic dose–response curve", the relationship between dose and effect has often been found to be nonlinear. Thus, small doses can induce unpredictable, adverse effects, one case being polychlorinated biphenyls (PCBs), of which congener(s) may centrally inhibit the hypothalamic-pituitary-thyroid axis, or dissociate thyroid receptor and selectively affect thyroid hormone signaling and action. This means that PCBs can act as agonists or antagonists at the receptor level, underlining the complexity of the interaction. This review highlights the multifold activity of chemicals demonstrated to cause thyroid disruption. It also represents a call to action among clinicians to undertake systematic monitoring of thyroid function and registering of the classes of EDs and additionally urges broader scientific collaborations to clarify these chemicals' molecular mechanisms of action, substances whose prevalence in our environments is disrupting not only the thyroid but all life on earth.

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Introduction

> "Feeble though we may seem, we have the power to influence the course of our planet…."
>
> Colin Hiram Tudge.[1]

An endocrine-disruptor (ED) is defined by the U.S. Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process" [1, 2]. This comprises a highly heterogeneous group including synthetic chemicals and their byproducts, plastics, plasticizers, pesticides, and fungicides. In addition, natural chemicals found in human and animal food such as phytoestrogens, as well as thyroid drugs, e.g., thyrostatics and, for non-thyroidal illness amiodarone, can all exert endocrine disrupting activity.

Our planet as a whole is increasingly exposed to these agents that seriously affect human, animal, and plant life. In particular, dioxins, pesticides, and bisphenol A, by mimicking or blocking hormones such as testosterone, estrogen, and insulin, have been shown to play a pivotal role in the incidence of obesity, insulin resistance, and diabetes mellitus in animal models and, crucially, are hypothesized to be involved in disruption of male and

[1] British biologist and science writer, "The Time Before History: 5 Million Years of Human Impact", 1996, Scribner.

female reproduction and to induce breast and prostate cancer and cardiovascular disease [2–4].

In 1962, Rachel Carson's groundbreaking work *Silent Spring* argued that unexamined pesticide use was harming and even killing both animals and birds as well as humans. Although the book has received criticism and generated controversy, there is no doubt that it played a central role in initiating today's environmental movement and increasing awareness of EDs. Since then, there has been constantly growing concern about the considerable health threat posed to humans and our environment by these ubiquitous products [5, 6].

In the last 50, and particularly 30, years, clinical observational studies have highlighted the toxicity of EDs and the perils they represent for public health [7–9], with all endocrine systems being impacted by them due to similarities of the hormone receptors with components of these compounds. Among the various endocrine systems, most particularly the thyroid—together with the reproductive system—is exposed to industrial chemicals, this vital organ being highly vulnerable to and variably affected by EDs. The latter is due to the fact that the health of every body organ and tissue requires a euthyroid state together with an optimally functioning hypothalamic-pituitary-thyroid axis. A disruption of thyroid activity will, therefore, have a highly negative impact both on neural and physical development in children and, in the entire population, on whole-organism homeostasis.

The goal of this review is to provide an update on the mechanisms by which EDs affect thyroid action and interfere with thyroid hormone (TH) signaling. Emphasis has been placed on the experimental and clinical studies reporting, mainly over the last few years, on industrial chemicals, pesticides and plastics and their impact on the thyroid. Drugs which may affect thyroid function and natural chemicals have not been considered as it is beyond the scope of this article. Another aim of the present review is to contribute to raising awareness among the authorities, industries, and the general public of the dangers inherent in the "chemical contamination" of today's world and, specifically, of the impact of EDs upon the thyroid, which is giving rise to a host of disorders and diseases worldwide.

Endocrine disruptors affecting the thyroid

Today, a very large number of industrial chemicals flood our environment. Those that exert an effect on thyroid function have been categorized according to their propensity to act upon this vital organ as well as extensively discussed in reviews spanning the past two and a half decades [10–12].

Table 1 Endocrine disruptors that affect thyroid function

Industrial chemicals and byproducts (solvents/lubricants)
Polychlorinated dioxins and -furans (PCDD/FsDioxins), Perchlorate
Polychlorinated biphenyls (PCBs)
Polybrominated biphenyls (PBBs)
Plastics and plasticizers
Bisphenol A (BPA), tetrabromobisphenol A (TBBPA) and Phthalates
Pesticides
Alachlor, dicamba, carbamate, chlorpyrifos,
Dichlorodiphenyltrichloroethane (DDT), Fibronil
Endosulfan, heptachlor, lindane, toxaphene
Fungicides
Amitriole, vinclozolin, mancozeb
Sunscreen-Cosmetics
Benzophenone2 & Benzophenone3
Homosalate (HMS), 2-ethylhexyl 4-dimethylaminobenzoate
(OD-PABA) and 4-aminobenzoic acid (PABA).
Heavy metals
Cadmium, mercury, lead
Polyphenols
Isoflavones (soy), Flavonoids (catechin, quercetin)

It is of especial note that the various classes of EDs, though not characterized by any structural similarity other than a small molecular mass of about 1,000 Daltons, may variably act as either TH receptor agonists or antagonists, thus making it difficult to predict which chemical may exert thyroid-disrupting activity [13]. Furthermore, many industrial chemicals and their derivatives, such as dioxin, polychlorinated biphenyls (PCBs) and its hydroxylated form (OH-PCB), polybrominated biphenyls (PBBs), polybrominated diphenylethers (PBDEs), perchlorate, thiocyanate, plastics and lasticizers, and cosmetics and sunscreen such as benzophenones, may induce considerable abnormalities in thyroid function (Table 1). Chemical pesticides, including carbamate, dichlorodiphenyl-trichloroethane (DDT), endosulfan and fipronil, fungicides, but also natural substances such as polyphenols (soy and catechins) exert similar thyroid disrupting effects [14, 15]. When assessing all blood metals, mercury was associated with decreases in T3 and T4, while cadmium was associated with decreased TSH [16] (Table 1).

It is noteworthy, that iodine deficiency predisposes the thyroid gland to the adverse effects of EDs, especially during phases of vulnerability such as development and adaptive challenges during diseases [17].

The disruptive effects are often exerted non-linearly, i.e., in a U-shaped or inverted-U manner [18]. Therefore, a minimal dose of EDs may cause reproductive or developmental abnormalities, while, apparently paradoxically,

low-dose exposure can in certain cases be more harmful than higher doses [19]. Vandenberg's recent and most comprehensive review stated that small amounts of EDs are capable of causing adverse effects that cannot be predicted by their effects at much higher doses, thereby re-introducing the "low-dose-hypothesis" and the concept of non-monotonic dose response curves defined as a nonlinear relationship between dose and effect [20]. However, not only is there difficulty in predicting the point of change on the slope of the curve, even when it remains within the range of doses examined [20], but full clarification of the circumstances and dose–response curve of many chemicals is as yet lacking.

EDs may affect the thyroid by different means depending both on the class of chemicals and on dose and duration of exposure. Nevertheless, what is evident is the extreme importance of ensuring or rectifying the integrity of the hypothalamic-pituitary thyroid (HPT) axis, the properties of thyroxine (T4) and the metabolism of TH whenever EDs activity on the thyroid is suspected.

Thyroid hormone regulation, metabolism, and disruption

The thyroid is regulated by the hypothalamic-pituitary unit. Thyrotropin-releasing hormone (TRH), secreted via hypophysiotropic neurons located in the medial and periventricular parvocellular subdivisions of the hypothalamic paraventricular nucleus, controls the synthesis and secretion of thyrotropin (TSH) from the pituitary gland [21]. TSH in turn stimulates the production and release of thyroid hormones, which subsequently exert a negative feedback on both pituitary and hypothalamus levels [22].

Serum T4 in humans has a half-life of 7–10 days at a serum concentration of about 10 μγ/dl. It is tightly bound to specific binding proteins, thyroxin-binding globulin (TBG), transthyretin (TTR), and albumin. Due to this avid binding to the serum proteins, T4 possesses a much longer half-life than Triiodothyronine (T3). T3 is mainly produced locally from T4 conversion by the 3 types of iodothyronine deiodinases (DIOs) which thus play a critical role in modulating the physiological effects of TH. TH is transported across the plasma membrane by highly specific transporters, namely monocarboxylate transporter 8 (MCT8), MCT10, and organic anion-transporting polypeptide 1c1 (OATP 1c1), which latter is important for TH transport across the blood brain barrier [23]. Since elimination of TH occurs following a process of glucuronidation and sulfation, its conjugation with glucuronic acid forms the chief metabolic pathway of TH metabolism [25]. On entering the cell, TH binds to the thyroid receptor (TR). Nuclear TR, a transcription factor that binds to a specific nucleotide sequence known as the TH-responsive element (TRE), acting as a homodimer or heterodimer with the retinoid X receptor (RXR), binds to a series of proteins termed co-activators or co-repressors in a ligand-dependent manner thus regulating the transcription of target genes [24, 25].

Over the past decade, it has been clearly demonstrated that TH receptors are unintended targets of industrial chemicals [26]. EDs have the capacity to affect TH metabolism and thyroid function at various sites and by various pathways (Fig. 1).

Industrial chemicals, particularly PCB153, may centrally decrease TH by suppressing TRH–TSH secretion via the JNK pathway [27], via TSH receptor internalization [28] and by affecting its biosynthesis and biotransformation [29]. Combined exposure to PCB153 and *p,p′*-DDE, a metabolite of the pesticide DDT, serum T4, Free T4, T3, TSH, NIS, TPO, Tg, and TTR levels were significantly decreased, while free triiodothyronine (FT3) and TRH were not affected [30]. Following combined exposure mRNA expression of DIO2 was also suppressed, while DIO1 and DIO3 levels were not significantly affected. In contrast, PCB153 and *p,p′*-DDE increased the hepatic enzymes UDPGTs, CYP1A1, CYP2B1, and CYP3A1 mRNA expressions [30]. Thus, there are data indicating that PCB and congener(s) combined with metabolites of pesticide may disrupt TH homeostasis by interacting at various levels, influencing synthesis-associated proteins (NIS, TPO, and Tg), DIOs activity, receptors (TSHr and TRHr), and hepatic enzymes that increase the clearance of TH. However, due to wide physiological interindividual variations, it is naturally unfeasible to undertake lifelong examination of individuals, who are exposed to a vast medley of chemicals acting at low doses in numerous environments. Further complicating the matter is increasing evidence that genetic predisposition modifies the susceptibility to the adverse effects of toxic chemicals [31]. In addition, susceptibility to EDs may vary according to genetic polymorphisms. Several epigenetic mechanisms, including DNA methylation, histone modifications and microRNA expression, can impact genome function under exogenous influences, while there are indications that epigenetic alterations mediate the toxicity of environmental chemicals [31]. Future prospective investigations are needed to determine whether epigenetic alterations induced by chemical exposure over time increases the risk of disease and to determine whether environmental epigenetic changes are transmitted transgenerationally [32].

Endocrine disruptors and the developing brain

There is at present much debate as to whether EDs exert adverse effects on the developing brain, possibly causing

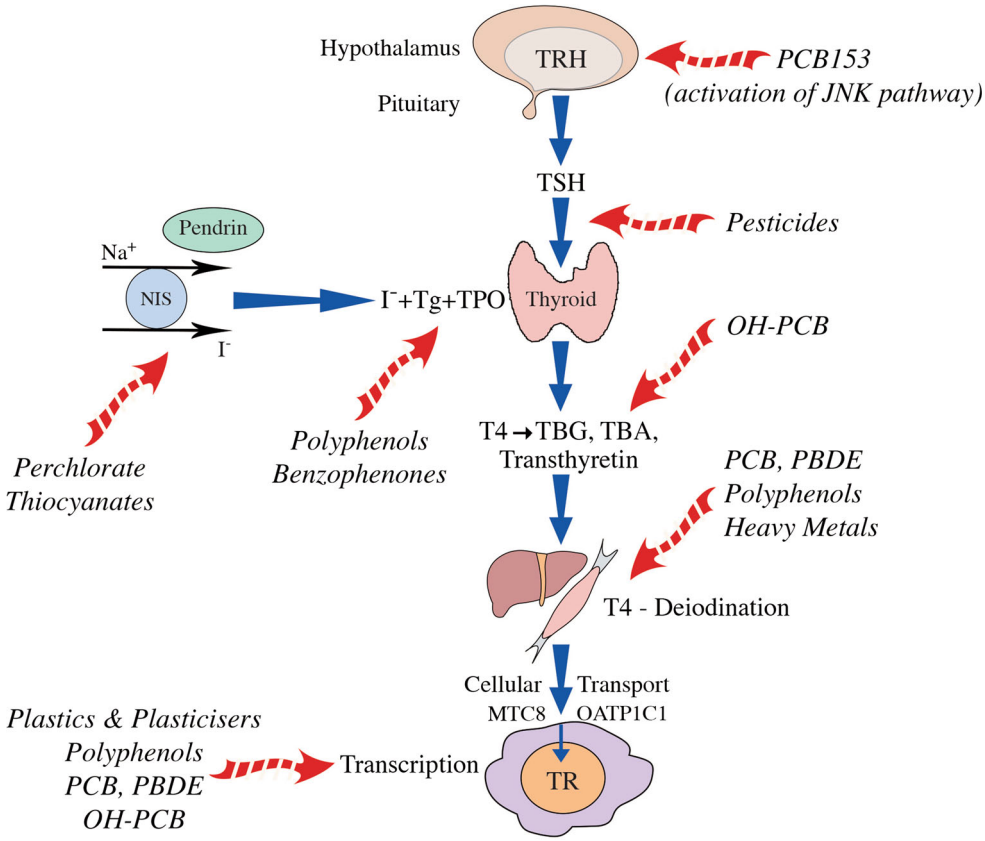

Fig. 1 The various classes of chemicals that interfere with different steps of thyroid hormone synthesis, secretion and metabolism, thereby disrupting thyroid function and action. The effects are variable according to the dose and duration of exposure

prenatal hypothyroidism and neurodevelopmental diseases such as autism and attention-deficit-hyperactive disorder, all today on the rise. Since neurological development is to a great extent dependent on normal TH homeostasis, it is highly likely to be particularly sensitive to EDs derangement of the thyroid axis via mechanisms that are directly or indirectly related to the transcriptional activity of the TH receptors [33].

In a recent experimental study, early-weaned male rats were treated with a single dose of 2,3,6-2′,5′-pentachlorinated biphenyl (PCB 95; 32 mg/kg per day, by i.p. injection) for two consecutive days and sacrificed 24 or 48 h after the administration of the last dose [34]. Compared with the control group, administration of PCB 95 induced a reduction ($P < 0.01$) in serum concentrations of T4, T3, and GH and an increase ($P < 0.01$) in serum TSH level [34]. In addition, leptin, adiponectin, and tumor necrosis factor were elevated, while serum concentrations of IGF1 and insulin on both postnatal days were decreased compared with the control group. It is thus clear that, at least in rats, PCB95, by disrupting the developing hypothalamic-pituitary-thyroid axis, is capable of inducing hypothyroidism, while it also impairs the adipokine axis and fat metabolism.

However, PCBs may interfere with TH signaling solely by reducing circulating levels of TH, or they may exert direct effects on TH receptors (TRs). A study on exposure of rats to A1254, a PCB mixture, revealed significantly reduced circulating levels of T3 and T4 in pregnant rats but an increased expression of several TH-responsive genes in the fetal cortex, consistent with a direct action of PCBs on TRs [35].

Recently, the effects of DE71 (a PBDE mixture) on TH-mediated developments in the cerebellum were investigated in primary cerebellar culture from newborn rats [36]. Low-dose DE71 significantly suppressed TH-mediated Purkinje cell dendrite arborization and impaired neurite extension of granule cells, suggesting that DE71, by suppressing TH-mediated neuronal development in the cerebellum, interferes with brain growth and function [36].

A common mechanism for a wide variety of PCBs is interference with TH signaling in the developing brain, through alteration of intracellular TH availability or by interacting directly at the level of the TH receptors; meanwhile, the gene expression in the cortex and cerebellum discloses both hypothyroid- and hyperthyroid-like effects [37].

Turning now to humans, prenatal exposure to PCBs and polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs), whose actions are known to considerably disrupt TH homeostasis, may have an impact on infant

neurobehavioral development. However, in the birth cohort study in Duisburg, including 232 healthy mother-infant pairs, dioxins, dioxin-like PCBs, and six indicator PCBs were analyzed in maternal blood during pregnancy and in maternal milk [38]. A multiple regression analysis did not show any decrease of thyroid hormones in blood and milk of mothers and their newborns, nor were any associations observed between exposure and neurological and developmental measures, thus indicating no consistent influence of PCDD/Fs and PCBs on thyroid status and neurodevelopment at environmental background levels [38].

On the other hand, placental PCDD/Fs levels have been linked to decreased FT4 and TSH levels in neonates [39]. In a follow-up study of 200 subjects, 136 and 149 were observed at year 2 and year 5, respectively. Height, weight, FT4, TSH, and TTR at year 2, and height, T3 and IGF-1 at year 5 differed significantly in accordance with PCDD/Fs level. In females, height, weight, chronological age, and thyroid hormones were significantly higher at year 2. In males, FT4, TSH at year 2 and IGF-1 at year 5 were significantly higher in the high PCDD/Fs exposed group. However, epidemiological studies carried out in environments with lower background levels of contamination than those of 10 years previously reveal no consistent influence of PCDD/Fs and PCBs on thyroid status and neurodevelopment, suggesting that the effects may resolve with decreasing exposure to these compounds [39].

In utero prenatal exposure to PBCs was associated with lower verbal IQ scores after adjustment for potential confounding variables in 213 children recruited as newborns and controlled at 11 years old [40]. The strongest effects were related to memory and attention. These findings suggest that developing fetal brain is particularly sensitive to PBCs and in utero exposure to these compounds in concentrations slightly higher than those in the general population can have a long-term impact on intellectual function [40].

The effects on TH of low-level background exposure to PCBs and PCCD/DF were studied in a prospective study including 395 primiparous women from the Uppsala region in Sweden [41]. A serum sample was obtained from 325 mothers in late pregnancy and breast milk was obtained from 211 women 3 weeks after delivery. Babies were sampled for blood at 3 weeks ($n = 150$) and 3 months ($n = 115$) after birth. Levels of low (tri- to penta-) chlorinated PCB, di-ortho PCB, p,p'-DDE, (mono-ortho) PCB TEQ, and PCDD/DF TEQ were monitored in breast milk and in mother's blood (not PCDD/DF). The results demonstrated normal levels for measured TSH, FT4, and T3 in mothers and children. In simple regression analysis, some significant associations were noted between PCB exposures and TH levels in mother and/or child. Following adjustment for important confounding factors, the significant associations mostly disappeared. However, significantly decreasing T3 levels with increasing prenatal low-chlorinated PCB exposure were still seen in 3-week old children and in T3 in mothers exposed to PCDD/DF [41]. These results clearly reveal the significance of adjustment for important confounding factors in comparison of analyses between PCBs exposure and hormonal effects.

Industrial chemicals, byproducts and the thyroid

PCBs, polychlorinated dioxins and -furans (PCDD/Fs), PBBs are environmental toxicants that have been proven to influence TH metabolism both in animal studies and in humans [42]. PCB residues in environmental media and human tissues may not be similar to commercial PCB mixtures, depending on the source of exposure, bioaccumulation and weathering of PCBs in the environment, while current analytic techniques have shown that different classes of PCB congeners have different profiles of toxicity [43]. Since the chemical structures of these compounds vary greatly, their mechanism of action is also variable. Therefore, evaluations should be carried out on a population basis to determine the degree of thyroid disruption leading to abnormal TH levels, this possibly representing a biomarker of disruption and adverse outcome [44].

Persistent polyhalogenated (PHA) compounds are organic pollutants that are increasingly building up worldwide in numerous environments and along the food chain. PHA aromatic hydrocarbons (PHAHs), alter TH homeostasis and cause thyroid dysfunction. They became widely known following the 1968 mass poisoning by PCBs of 2,000 people in Kyushu, Japan and 14,000 in central Taiwan (named "Yusho" disease and "Yu-Cheng" disease, respectively, both meaning "oil symptoms"), the disorders manifesting with dermal lesions, ocular symptoms, and increased autoimmunity [45]. Coplanar PCB and related congeners, e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxins, induce gene expression mainly via a ligand-dependent transactivating factor, the aryl hydrocarbon receptor (AhR). Toxicity of coplanar PCBs and mono-ortho-PCBs is similar to that of dioxin and is mediated via binding and abnormal activation of AhR, the latter altering gene transcription and disrupting cell function [46]. The significance of AhR was clearly shown in mice in which exposure to PHA compounds resulted in a marked reduction of T4 and FT4 levels in the serum of AhR ± mice, while no effects were observed in AhR-/- mice [47].

Concerning polybrominated diphenyl ethers (PBDE), which are very similar to PCBs, these are synthesized chemicals essential to retard flames and minimize deaths from fire-outbreaks; they are used worldwide and both persist in the environment and bioaccumulate. Together with PCBs and dioxins, PBDE are prototypic thyroid-

disrupting chemicals (TDCs), which have been shown to alter TH homeostasis, primarily by up-regulating hepatic catabolism of thyroid hormones, and to affect serum T4 concentrations in a dose-additive manner [48]. However, hydroxylated PCBs and PBDEs do not bind to AhR, while their binding capacity to TTR and TBG is even stronger, respectively, than to T4 [49]. What is more, as their environmental levels rise and their bioaccumulation capability correspondingly increases, PBDEs have the potential to disrupt thyroid homeostasis, by competitive binding with TH transport proteins, while they also disturb the thyroid by inhibiting TH transporters [49].

Due to the structural similarity between PCB and TH, the former can affect T4/T3 and induced transcriptional activation of the TH receptor. The molecular mechanism is not as yet completely understood, but presumably partial dissociation of the TR/retinoid X receptor heterodimer complex from the TRE occurs in the suppression of transcription induced by PCB [50].

In a recent study investigating the relationship between exposure to several PHCs and thyroid homeostasis in 41 Inuit adults from Nunavik, Canada, among 623 contaminated with a measure of dioxin-like compounds, serum concentrations of T3 and TBG were found statistically significantly decreased and increased, respectively [51]. These findings indicate that PHCs may inhibit T4-deiodination and influence TBG synthesis, possibly via an estrogen-like mechanism.

In another study conducted in a heavily polluted area in Slovakia, the prevalence of TPOAb in both men and women was significantly higher in the polluted area, suggesting that PHA may trigger thyroid autoimmunity [52].

In a study in Catalonia, *p,p*'-DDT, *p,p*'-DDE, and various PCBs congeners, including hexachlorobenzene (HCB) and beta-hexachlorocyclohexane (beta-HCH), were detected in more than 85 % of the subjects ($n = 919$), though the levels were relatively low in the majority of the individuals [53]. However, these and other studies revealing the exposure of a very large proportion of the European population to these harmful compounds underscores the necessity of a general policy to register PHA levels across Europe as a whole [54].

Perchlorate, extensively employed in the production of missiles, explosives, fireworks, as well as sometimes in bleach and fertilizers, and thus very widespread in the environment (it has been determined that traces of it can be found in the bloodstream of virtually every human being on earth), is known to be a competitive inhibitor of the sodium/iodide symporter (NIS) [55]. Meanwhile, thiocyanate is a common cofactor in the multifactorial etiology of goiter [56]. However, though nitrate and thiocyanate intake, via drinking-water or food, are stronger inhibitors of iodine uptake than perchlorate, the latter has attracted more interest because of the considerable health risks it poses [57]. Thus, although in a Boston-area study, a generally iodine sufficient region, exposure to perchlorate and thiocyanate in mothers and their breastfed infants was not seen to affect infant thyroid function [58], there is nevertheless ample evidence that it can disrupt the process of normal growth and development and is additionally suspected to be a human carcinogen [58]. In the 2001–2002 NHANES, in women with urinary iodine concentration <100 μg/l, urinary perchlorate was associated with significant changes in TSH and T4 [59]. TPO antibodies were significant predictors of FT4 among non-pregnant women, though only when urinary perchlorate, nitrate, or thiocyanate was detected [59].

The results of this analysis indicate that risk assessment for perchlorate exposure should evaluate co-exposure to nitrate and thiocyanate.

Accumulating data on early biological changes from chemical exposures require new interpretation tools to guide decision-making [60], while combining analysis of chemical exposures and biological perturbations (PCBs and FT4 of downstream overt effects (FT4 and IQ) has recently been proposed as an approach for effect prediction [60].

Pesticides

An association between hypothyroidism and insecticides, herbicides and fumigants/fungicides was recently found among 22,246 male pesticide applicators in the Agricultural Health Study [61]. An exposure–response analysis exhibited increasing hypothyroidism with increasing levels of exposure for the herbicides alachlor and 2,4-D and the insecticides aldrin, chlordane, DDT, lindane, and parathion [62]. Early exposure to pesticides interferes with neonatal TH status, though the pattern of interference is not clearly elucidated as yet. Based on analysis of data derived from the 2001–2002 National Health and Nutrition Examination Survey, an evaluation was made of the impact of exposure to selected organochlorine pesticides (OCPs) on T4 and TSH [63]. The data demonstrated that TSH and T4 levels were lowest for 20–39 year-olds and highest for 60 + year-olds and also that TSH and T4 levels for iodine deficient males and females were dependent on ethnicity, age, and smoking. In a cross-sectional study conducted in a contaminated area in Brazil in 608 men and women, it was shown that OCPs can affect the thyroid system through gender-specific mechanisms that may differ among compounds [64]. A positive association was observed between exposure to methoxychlor in males and presence of TPOAb, but no association with TPOAb was found in women.

Another widely used pesticide, fipronil, an active ingredient of Frontline® acaricide, a phenyl-pyrazolic

derivative, disorganizes follicular structure, and depletes colloid from its protein content [65]. Furthermore, there were indications from microarray screening in the liver of rats that fipronil may interact with hepatic gene expression with the participation of other nuclear receptors e.g., pregnane X and constitutive androstane receptor, these augmenting the impact of fipronil on hepatic gene expression linked to TH metabolism [66].

Organochlorine pesticides and dioxins may activate hepatic enzymes, resulting in decrease of serum T4 half-life [67, 68].

Mancozeb, a widely applied pesticide, reduces T4 levels in dams and it may, therefore, be a thyroid disruptor in humans. Exposure to mancozeb during pregnancy it may adversely affect the developing brain [69].

Sunscreen-cosmetics

Topical application of sunscreens containing ultraviolet-filters (UV-filters) is today widely recommended, though their protective effects against melanoma are less conclusive as is also protection against adverse effects of ultraviolet radiation [70]. Overall, benzophenones (BPs), PAHs and POPs slightly alter TPO activity at low doses [71]. However, while benzophenone, benzhydrol, 3-methylchloranthracene, pyrene, benzo(k)fluoranthene, benzo(e)pyrene, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and heptachlor decreased TPO activity, 2,4-dihydroxy BP, 2,2'-dihydroxy-4-methoxy BP, and dibenzo(a,h)anthracene increased TPO activity [72].

In another study investigating the effects of octyl-methoxycinnamate (OMC), one of the most frequently used UV-filters in sunscreens, on the hypothalamic-pituitary-thyroid axis in rats, it was shown that TRH expression remained unaltered in contrast to the increased expression of the TSH receptor in the thyroid [73]. NIS and TPO were unaffected by OMC, demonstrating a non-estrogenic interference of OMC within the rodent HPT-axis: disrupted feedback response to deranged TH levels was noted, this effect highlighted by decreased serum TH and hepatic deiodinase 1 (DO1) levels. Hence, sunscreen-cosmetics, and most potently BP2 and OMC, are likely to derange TH homeostasis by inhibiting or increasing TPO and also by suppressing DO1 activity.

Bisphenol A

Bisphenol A (BPA) is a high volume chemical, an essential compound of polycarbonate plastic, that is widely used for food storage and is likely to be harmful to animal and human life, most particularly after contact with hot liquids [74, 75]. An altered expression of the genes involved in TH synthesis and of thyroid specific transcriptional factors was detected in a vivo and vitro model (zebrafish) investigating dose and time effects of BPA on TH synthesis [76]. BPA may exert a direct effect on thyroid follicular cells although these effects are complex and to date not well clarified [77].

It was also revealed that BPA inhibits TR-mediated transcription by acting as an antagonist. In transient gene expression experiments, BPA suppressed transcriptional activity which is stimulated by physiological concentrations of T3 in a dose-dependent manner [78]. BPA may disrupt the function of various types of nuclear hormone receptors and, consequently, internal hormonal homeostasis.

There are as yet limited studies in humans. Recently, BPA levels were evaluated in the urine samples of 335 women during the second half of pregnancy in participants of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), California, USA, and TH levels in blood samples taken from the mothers during pregnancy and from the newborns within a few days of birth [79]. They found that for each doubling of BPA levels, there was an associated decrease of 0.13 mcg/dL total thyroxine in mothers during pregnancy, which suggests a hypothyroid effect. In contrast, in newborn boys, each doubling of BPA levels was linked with a 9.9 % decrease in thyroid-stimulating hormone, indicating a hyperthyroid effect [79]. It is of particular interest that this association was found in newborn boys but not among newborn girls.

In a cross-sectional study from Thailand, the Thai National Health Examination Survey IV 2009, investigating the relationship between BPA exposure and thyroid function, in 2,340 subjects 18–94 years old [80], BPA was detected in 52.8 % of serum samples (median concentration of 0.33; range 0–66.91 ng/ml). The analysis showed a significantly negative correlation between serum BPA and FT4 levels in males only, while no association was registered with TSH in either gender [80]. According to the authors, this gender-related association could possibly be related to androgen-dependent differences in the metabolism of BPA.

In another cross-sectional study from the NHANES 2007–2008, the relationship between urinary phthalate and BPA with serum TH and TSH concentrations were analyzed [81]. While inverse relationships were noted in adults between urinary BPA and total T4 and TSH, significant positive relationships were observed between phthalates metabolites and total T3 among adolescents. Although these study results are not suggestive of any causal conclusion, a thyroid disruptive effect of BPA can be postulated. This effect may be directly suppressive on thyroid follicular cells and could also be gender and androgen

dependent. The findings in any case point to the pressing need to conduct more studies in order to elucidate the mechanisms as well as the extent of BPA disrupting action on endocrine and, particularly, on thyroid function.

Heavy metals

Cadmium (Cd), which is among the 126 priority pollutants, has strong tendency to accumulate in various organs, including the thyroid gland [82]. Cd blood concentration correlates positively with its accumulation in the thyroid gland, while women of fertile age have higher Cd blood and urine concentrations than men. Cd promotes oxidative stress and damage to the tissue by indirect mechanisms, mitochondria having been considered the main intracellular targets for Cd toxicity [82]. Cd exposure in rats significantly increased thyroid weight, intra-thyroid Cd concentration, and serum TSH levels, whereas serum T4 level was decreased compared to control rats [83]. Selenium treatment alone, in the form of selenite, partially protected from the Cd-induced decrease in serum T4 level, while the combined administration with zinc protected against Cd-induced thyroid dysfunction by maintaining normal thyroid weight and by decreasing Cd concentration in the thyroid [83].

A subanalysis from the NHANES 2007-2010, including 6,231 participants aged 20 and older, investigated whether whole blood Cd and lead concentrations are associated with serum thyroid hormones levels. The results suggested that thyroid function may be disrupted by both Cd and lead exposures in the general population and that the specific effects of Cd and lead exposure on the thyroid axis may differ by gender [84].

In another analysis of samples of 1,109 adolescents (12–19 years of age) and 4,409 adults from the NHANES 2007–2008 study, blood mercury (Hg) was inversely related and urinary Cd was positively associated with T4, T3, FT3, and Tg, but there were no associations with lead (Pb) [85]. Associations were relatively weak at an individual level. These studies indicate the damaging effect of heavy metals on thyroid dysfunction and the need for further studies to elucidate the mechanism of action.

Notably, PHA can amplify the neurotoxic effects of other environmental pollutants, such as heavy metals, further increasing their adverse impact on human and animal neurodevelopment [37].

Polyphenols

Soy consumption has been associated with hypothyroidism, goiter, and autoimmune thyroid disease (ATD), though the exact anti-thyroid components as well as the molecular mechanisms involved are not thus far well-defined [14].

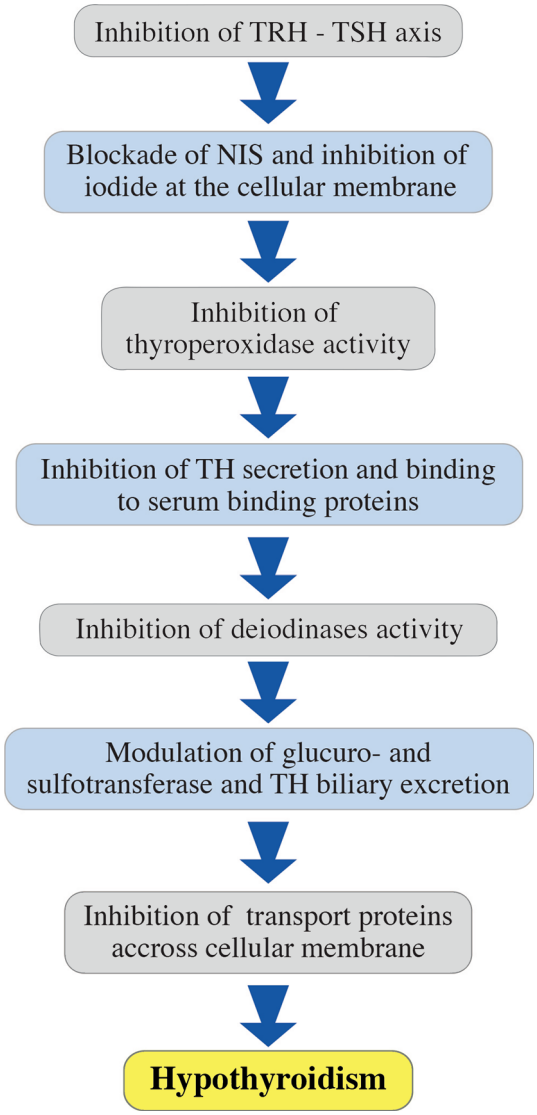

Fig. 2 Chemicals which, by inhibiting the hypothalamic-pituitary thyroid axis and various pathways of thyroid hormone metabolism, may lead to a hypothyroid state

Recently, a study examined the effects of soy isoflavones (ISF) on iodide uptake and expression of thyroglobulin (Tg) and sodium/iodide symporter (NIS) in thyrocytes. This study demonstrated that the alcohol soluble component(s) in soy significantly inhibited iodide uptake in the FRTL cells and that soy ISF, particularly genistein, may increase the incidence of ATD, which is reported in soy infant formula-fed children, by inducing the production of P40, a strong autoimmunogen [86].

In a Canadian study, T4, T3, and TSH were investigated in relation to serum organochlorines (OCs), bioindicators of mercury (Hg), and blood lead (Pb) in 211 freshwater fish

consumers [87]. Stratified analysis serum T3 levels were negatively related to serum concentrations of PCB 138, PCB 153 and the non-coplanar congeners, Arochlor 1260, SigmaPCB, and *p,p*'-DDE in women. No relations were observed between T4 or any of the chemicals measured, but TSH was negatively related to blood Pb. In men, serum T4 was inversely related to PCB 138, non-ortho-substituted (dioxin-like), while TSH was positively related to different PCB congeners (PCB 138, PCB 180, non-coplanar congeners, mono-ortho coplanar congeners, dioxin-like PCBs) [87]. These findings indicate that even at low concentrations these environmental contaminants may disrupt thyroid function, the effects differing by gender.

There is some evidence indicating that soy foods, by inhibiting absorption, are likely to elevate the dose of TH required by hypothyroid patients. There are also indications that in individuals who have compromised thyroid function and/or marginal iodine intake, soy foods may augment the risk of developing clinical hypothyroidism [88]. Therefore, it is important that soy food consumers should ensure that their intake of iodine is adequate.

It can thus be seen that different chemicals, by interfering with the various pathways of TH and by inhibiting the HPT-axis, may lead to a hypothyroid-like state (Fig. 2).

Conclusions

The various classes of EDs may variably affect thyroid function, although few studies have as yet been carried out in humans. These chemicals, by inhibiting TRH or TSH secretion or else NIS activity, by displacement of T4 from binding globulin or from TTR and by affecting DIOs activity inside the cell can lead to decreased availability of TH to various tissues and can consequently induce hypothyroidism. On the other hand, diagnosis in an individual of a state of hypothyroidism could well be a case of late detection; moreover, the problem could be an organ-limited one and be reversible once exposure has ceased. Nevertheless, since this might concern an organ-restricted case, depending on length of exposure, age of occurrence, and mechanistic action of the chemical, a prompt diagnosis might not be feasible.

There are also indications that certain chemicals might facilitate the manifestation of or aggravate preexisting thyroid autoimmunity. This could also be due to duration of exposure, the now longtime presence of these chemicals in numerous parts of our world thus likely accounting for today's rising global incidence of autoimmunity. If this is so, action must certainly be taken to prevent further such adverse impacts on humans and their multiple environments.

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References

1. International Programme for Chemical Safety (IPCS) in Global assessment of the state-of-the-science of endocrine disruptors. Chapter 1, Executive Summary, 1–3. http://www.who.int/ipcs/publications/en/ch1.pdf (2010)
2. E. Diamanti-Kandarakis, J.P. Bourguignon, L.C. Giudice, R. Hauser, G.S. Prins, A.M. Soto, R.T. Zoeller, A.C. Gore, Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr. Rev. **30**, 293–342 (2009)
3. G.G. Kuiper, J.G. Lemmen, B. Carlsson, J.C. Corton, S.H. Safe, P.T. van der Saag, B. van der Burg, J.A. Gustafsson, Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology **139**, 4252–4263 (1998)
4. P. Alonso-Magdalena, I. Quesada, A. Nadal, Endocrine disruptors in the etiology of type 2 diabetes mellitus. Nat. Rev. Endocrinol. **7**, 346–353 (2011). doi:10.1038/nrendo.2011.56
5. L. Patrick, Thyroid disruption: Mechanisms and clinical implications in human health. Altern. Med. Rev. **14**, 326–346 (2009)
6. G. Mastorakos, E.I. Karoutsou, M. Mizamtsidi, G. Creatsas, The menace of endocrine disruptors on thyroid hormone physiology and their impact on intrauterine development. Endocrine **31**, 219–237 (2007)
7. T.K. Woodruff, C.L. Walker, Fetal and early postnatal environmental exposures and reproductive health effects in the female. Fertil. Steril. **89**, e47–e51 (2008)
8. D.H. Lee, I.K. Lee, S.H. Jin, M. Steffes, D.R. Jacobs Jr, Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. Diabetes Care **30**, 622–628 (2007)
9. D. Crews, J.A. McLachlan, Epigenetics, evolution, endocrine disruption, health, and disease. Endocrinology **147**, S4–S10 (2006)
10. F. Brucker-Davis, Effects of environmental synthetic chemicals on thyroid function. Thyroid **8**, 827–856 (1998)
11. K.L. Howdeshell, A model of the development of the brain as a construct of the thyroid system. Environ. Health Perspect. **110**(Suppl 3), 337–348 (2002)
12. R.T. Zoller, Environmental chemicals impacting the thyroid: targets and consequences. Thyroid **17**, 811–817 (2007)
13. D.T. Szabo, V.M. Richardson, D.G. Ross, J.J. Diliberto, R.P.S. Kdavanti, L.S. Birnbaum, Effects of perinatal PBDE exposure on hepatic phase I, phase II, phase III, and deiodinase 1 gene expression involved in thyroid hormone metabolism in male rat pups. Toxicol. Sci. **107**, 27–39 (2009)
14. M.C. de Souza Dos Santos, C.F. Gonçalves, M. Vaisman, A.C. Ferreira, D.P. de Carvalho, Impact of flavonoids on thyroid function. Food Chem. Toxicol. **49**, 2495–2502 (2011). doi:10.1016/j.fct.2011.06.074
15. T. Sathyapalan, A.M. Manuchehri, N.J. Thatcher, A.S. Rigby, T. Chapman, E.S. Kilpatrick, S.L. Atkin, The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study. J. Clin. Endocrinol. Metab. **96**, 1442–1449 (2011). doi:10.1210/jc.2010-2255
16. K.L. Yorita, Christensen, Metals in blood and urine, and thyroid function among adults in the United States 2007–2008. Int. J. Hyg. Environ. Health **216**, 624–632 (2013). doi:10.1016/j.ijheh.2012.08.005
17. J. Köhrle, Environment and endocrinology: the case of thyroidology. Ann. Endocrinol. (Paris) **69**, 116–122 (2008). doi:10.1016/j.ando.2008.02.008
18. F.S. vom Saal, W.V. Welshons, Large effects from small exposures. II. The importance of positive controls in low-dose research on bisphenol A. Environ. Res. **100**, 50–76 (2006)

19. W.V. Welshons, K.A. Thayer, B.M. Judy, J.A. Taylor, E.M. Curran, F.S. vom Saal, Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ. Health Perspect. **111**, 994–1006 (2003)
20. L.N. Vandenberg, T. Colborn, T.B. Hayes, J.J. Heindel, D.R. Jacobs, D.-H. Lee Jr, T. Shioda, A.M. Soto, F.S. vom Saal, W.V. Welshons, R.T. Zoeller, J.P. Myers, Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr. Rev. **33**, 378–455 (2012)
21. R.M. Lechan, C. Fekete, The TRH neuron: a hypothalamic integrator of energy metabolism. Prog. Brain Res. **153**, 209–235 (2006)
22. L.H. Duntas, C. Emerson, On the fortieth anniversary of thyrotropin-releasing hormone: the hormone that launched a new era. Thyroid **19**, 1299–1301 (2009). doi:10.1089/thy.2009.1610
23. W.E. Visser, E.C. Friesema, J. Jansen, T.J. Visser, Thyroid hormone transport in and out of cells. Trends Endocrinol. Metab. **19**, 50–56 (2008). doi:10.106/j.tem.2007.11.003
24. N. Koibuchi, Mechanism of chemical disruptors of thyroid function. Hot Thyroidology **12** (2010)
25. M.A. Lazar, Thyroid hormone receptors: multiple forms, multiple possibilities. Endocr. Rev. **14**, 184–193 (1993)
26. R.T. Zoeller, Environmental chemicals as thyroid hormone analogues: new studies indicate that thyroid hormone receptors are targets of industrial chemicals? Mol. Cell. Endocrinol. **242**, 10–15 (2005)
27. C. Liu, M. Ha, Y. Cui, C. Wang, M. Yan, W. Fu, C. Quan, J. Zhou, K. Yang, JNK pathway decreases thyroid hormones via TRH receptor: a novel mechanism for disturbance of thyroid hormone homeostasis by PCB153. Toxicology **302**, 68–76 (2012). doi:10.1016/j.tox.2012.07.016
28. S. Picchietti, M. Belardinelli, A.R. Taddei, A.M. Fausto, M. Pellegrino, R. Maggio, M. Rossi, F. Giorgi, Thyroid disruptor 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane (DDT) prevents internalization of TSH receptor. Cell Tissue Res. **336**, 31–40 (2009)
29. C. Liu, C. Wang, M. Yan, C. Quan, J. Zhou, K. Yang, PCB153 disrupts thyroid hormone homeostasis by affecting its biosynthesis, biotransformation, feedback regulation, and metabolism. Horm. Metab. Res. **44**, 662–669 (2012). doi:10.1055/s-0032-1311569
30. C. Liu, M. Ha, L. Li, K. Yang, PCB153 and *p,p′*-DDE disorder thyroid hormones via thyroglobulin, deiodinase 2, transthyretin, hepatic enzymes and receptors. Environ. Sci. Pollut. Res. Int. **21**(19), 11361–11369 (2014). doi:10.1007/s11356-014-3093-3
31. L.J. Brokken, Y.L. Giwercman, Gene-environment interactions in male reproductive health: special reference to the aryl hydrocarbon receptor signaling pathway. Asian J Androl. **16**, 89–96 (2014). doi:10.4103/1008-682X.122193
32. A. Baccarelli, V. Bollati, Epigenetics and environmental chemicals. Curr. Opin. Pediatr. **12**, 243–251 (2009)
33. M.L. Jugan, Y. Levi, J.P. Blondeau, Endocrine disruptors and thyroid hormone physiology. Biochem. Pharmacol. **79**, 939–947 (2010)
34. R.G. Ahmed, Early weaning PCB 95 exposure alters the neonatal endocrine system: thyroid adipokine dysfunction. J Endocrinol. **219**, 205–215 (2013). doi:10.1530/JOE-13-0302
35. K.J. Gauger, Y. Kato, K. Haraguchi, H.J. Lehmler, L.W. Robertson, R. Bansal, R.T. Zoeller, Polychlorinated biphenyls (PCBs) exert thyroid hormone-like effects in the fetal rat brain but do not bind to thyroid hormone receptors. Environ. Health Perspect. **112**, 516–523 (2004)
36. K. Ibhazehiebo, T. Iwasaki, J. Kimura-Kuroda, W. Miyazaki, N. Shimokawa, N. Koibuchi, Disruption of thyroid hormone receptor-mediated transcription and thyroid hormone-induced Purkinje cell dendrite arborization by polybrominated diphenyl ethers. Environ. Health Perspect. **119**, 168–175 (2011). doi:10.1289/ehp.1002065
37. V.M. Darras, Endocrine disrupting polyhalogenated organic pollutants interfere with thyroid hormone signaling in the developing brain. Cerebellum **7**, 26–37 (2008). doi:10.1007/s12311-008-0004-5
38. M. Wilhelm, J. Wittsiepe, F. Lemm, U. Ranft, U. Krämer, P. Fürst, S.C. Röseler, M. Greshake, M. Imöhl, G. Eberwein, K. Rauchfuss, M. Kraft, G. Winneke, The Duisburg birth cohort study: influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. Mutat. Res. **659**, 83–92 (2008)
39. P.H. Su, J.Y. Chen, J.W. Chen, S.L. Wang, Growth and thyroid function in children with in utero exposure to dioxin: a 5-year follow-up study. Pediatr. Res. **67**, 205–210 (2010). doi:10.1203/PDR.0b013e3181c8f04b
40. J.L. Jacobson, S.W. Jacobson, Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N. Engl. J. Med. **335**, 783–789 (1996)
41. P.O. Darnerud, S. Lignell, A. Glyn, M. Aune, A. Törnkvist, M. Stridsberg, POP levels in breast milk and maternal serum and thyroid hormone levels in mother-child pairs from Uppsala. Swed. Environ Int. **36**, 180–187 (2010). doi:10.1016/j.envint.2009.11.001
42. M. Boas, U. Feldt-Rasmussen, K.M. Main, Thyroid effects of endocrine disrupting chemicals. Mol. Cell. Endocrinol. **355**, 240–248 (2012). doi:10.1016/j.mce.2011.09.005
43. S.L. Schantz, J.J. Widholm, D.C. Rice, Effects of PCB exposure on neuropsychological function in children. Environ. Health Perspect. **111**, 357–376 (2003)
44. M.D. Miller, K.M. Crofton, D.C. Rice, R.T. Zoeller, Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. Environ. Health Perspect. **117**, 1033–1041 (2009). doi:10.1289/ehp.0800247
45. Y. Aoki, Polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans as endocrine disrupters–what we have learned from Yusho disease. Environ. Res. **86**, 2–11 (2001)
46. F. Bogazzi, F. Raggi, F. Ultimieri, D. Russo, A. Campomori, J.D. McKinney, A. Pinchera, L. Bartalena, E. Martino, Effects of a mixture of polychlorinated biphenyls (Aroclor 1254) on the transcriptional activity of thyroid hormone receptor. J. Endocrinol. Invest. **26**, 972–978 (2003)
47. N. Nishimura, J. Yonemoto, Y. Miyabara, Y. Fujii-Kuriyama, C. Tohyama, Altered thyroxin and retinoid metabolic response to 2,3,7,8-tetrachlorodibenzo-p-dioxin in aryl hydrocarbon receptor-null mice. Arch. Toxicol. **79**, 260–267 (2005)
48. K.M. Crofton, E.S. Craft, J.M. Hedge, C. Gennings, J.E. Simmons, R.A. Carchman, W.H. Carter Jr, M.J. De Vito, Thyroid-hormone-disrupting chemicals: evidence for dose-dependent additivity or synergism. Environ. Health Perspect. **113**, 1549–1554 (2005)
49. X.M. Ren, L.H. Guo, Assessment of the binding of hydroxylated polybrominated diphenyl ethers to thyroid hormone transport proteins using a site-specific fluorescence probe. Environ. Sci. Technol. **46**, 4633–4640 (2012). doi:10.1021/es2046074
50. W. Miyazaki, T. Iwasaki, A. Takeshita, Y. Kuroda, N. Koibuchi, Polychlorinated biphenyls suppress thyroid hormone receptor-mediated transcription through a novel mechanism. J. Biol. Chem. **279**, 18195–18202 (2004)
51. S. Dallaire, E. Dewailly, D. Pereg, S. Dery, P. Ayotte, Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults. Environ. Health Perspect. **117**, 1380–1386 (2009). doi:10.1289/ehp.0900633
52. Z. Rádiková, M. Tajtáková, A. Kocan, T. Trnovec, E. Seböková, I. Klimes, P. Langer, Possible effects of environmental nitrates

and toxic organochlorines on human thyroid in highly polluted areas in Slovakia. Thyroid **18**, 353–362 (2008). doi:10.1089/thy.2007.0182
53. M. Porta, M. Gasull, E. Puigdomènech, M. Garí, M.B. de Basea, M. Guillén, T. López, E. Bigas, J. Pumarega, X. Llebaria, J.O. Grimalt, R. Tresserras, Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Catalonia. Environ. Int. **36**, 655–664 (2010)
54. M. Porta, E. Puigdomènech, F. Ballester, J. Selva, N. Ribas-Fitó, S. Llop, T. López, Monitoring concentrations of persistent organic pollutants in the general population: the international experience. Environ. Int. **34**, 546–561 (2008)
55. B. De Groef, B.R. Decallonne, S. Van der Geyten, V.M. Darras, R. Bouillon, Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects. Eur. J. Endocrinol. **155**, 17–25 (2006)
56. V.F. Brauer, H. Below, A. Kramer, D. Führer, R. Paschke, The role of thiocyanate in the etiology of goiter in an industrial metropolitan area. Eur. J. Endocrinol. **154**, 229–235 (2006)
57. A.M. Leung, X. He, E.N. Pearce, L.E. Braverman, Perchlorate Concentrations in Boston's Charles River after the July 4th Fireworks Spectacular. Thyroid **23**, 378–379 (2013). doi:10.1089/thy.2012.0410
58. A.M. Leung, L.E. Braverman, X. He, K.E. Schuller, A. Roussilhes, K.A. Jahreis, E.N. Pearce, Environmental perchlorate and thiocyanate exposures and infant serum thyroid function. Thyroid **22**, 938–943 (2012). doi:10.1089/thy.2012.0058
59. M. Suh, L. Abraham, J.G.Hixon, D.M. Proctor. The effects of perchlorate, nitrate, and thiocyanate on free thyroxine for potentially sensitive subpopulations of the 2001–2002 and 2007–2008 National Health and Nutrition Examination Surveys. J Expo Sci Environ Epidemiol. **23,** (2013). doi: 10.1038/jes.2013.67
60. A. Wise, F. Parham, D.A. Axelrad, K.Z. Guyton, C. Portier, L. Zeise, R.T. Zoeller, T.J. Woodruff, Upstream adverse effects in risk assessment: a model of polychlorinated biphenyls, thyroid hormone disruption and neurological outcomes in humans. Environ. Res. **117**, 90–99 (2012). doi:10.1016/j.envres.2012.05.013
61. W.S. Goldner, D.P. Sandler, F. Yu, V. Shostrom, J.A. Hoppin, F. Kamel, T.D. LeVan, Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study. J. Occup. Environ. Med. **55**, 1171–1178 (2013). doi:10.1097/JOM.0b013e31829b290b
62. C. Freire, M.J. Lopez-Espinoza, M. Fernández, J.M. Molina-Molina, R. Prada, N. Olea, Prenatal exposure to organochlorine pesticides and TSH status in newborns from Southern Spain. Sci. Total Environ. **409**, 3281–3287 (2011)
63. R.B. Jain, Association between thyroid function and selected organochlorine pesticides: data from NHANES 2001–2002. Sci. Total Environ. **1**(466–467), 706–715 (2014). doi:10.1016/j.scitotenv.2013.07.087
64. C. Freire, R.J. Koifman, P.N. Sarcinelli, A.C. Simões Rosa, R. Clapauch, S. Koifman, Long-term exposure to organochlorine pesticides and thyroid status in adults in a heavily contaminated area in Brazil. Environ. Res. **127**, 7–15 (2013). doi:10.1016/j.envres.2013.09.001
65. B.B. Roques, J. Leghait, M.Z. Lacroix, F. Lasserre, T. Pineau, C. Viguié, P.G. Martin, The nuclear receptors pregnane X receptor and constitutive androstane receptor contribute to the impact of fipronil on hepatic gene expression linked to thyroid hormone metabolism. Biochem. Pharmacol. **86**, 997–1039 (2013)
66. M. Ferreira, P.R. De Oliveira, S.E. Denardi, G.H. Bechara, M.I. Mathias, Fipronil (active ingredient of acaricide frontline®) acting on the mice thyroid. Microsc. Res. Tech. **75**, 265–270 (2012)
67. E.N. Pearce, L.E. Braverman, Environmental pollutants and the thyroid. Best Pract. Res. Clin. Endocrinol. Metab. **23**, 801–813 (2009). doi:10.1016/j.beem.2009.06.003
68. J. Leghait, V. Gayrard, N. Picard-Hagen, M. Camp, E. Perdu, P.-L. Toutain, C. Viguié, Fipronil induced disruption of thyroid function in rats is mediated by increased total and free thyroxine clearances concomitantly to increased activity of hepatic enzymes. Toxicology **255**, 38–44 (2009)
69. M. Axelstad, J. Boberg, C. Nellemann, M. Kiersgaard, P.R. Jacobsen, S. Christiansen, K.S. Hougaard, U. Hass, Exposure to the widely used fungicide mancozeb causes thyroid hormone disruption in rat dams but no behavioral effects in the offspring. Toxicol. Sci. **120**, 439–446 (2011)
70. M. Krause, A. Klit, M. Blomberg-Jensen, T. Søeborg, H. Frederiksen, M. Schlumpf, W. Lichtensteiger, N.E. Skakkebaek, K.T. Drzewiecki, Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. Int. J. Androl. **35**, 424–436 (2012). doi:10.1111/j.1365-2605.2012.01280
71. M. Song, Y.J. Kim, Y.K. Park, J.C. Ryu, Changes in thyroid peroxidase activity in response to various chemicals. J. Environ. Monit. **14**, 2121–2126 (2012). doi:10.1039/c2em30106g
72. C. Schmutzler, A. Bacinski, I. Gotthardt, K. Huhne, P. Ambrugger, H. Klammer, C. Schlecht, C. Hoang-Vu, A. Grüters, W. Wuttke, H. Jarry, J. Köhrle, The ultraviolet filter benzophenone 2 interferes with the thyroid hormone axis in rat and is a potent in vitro inhibitor of human recombinant thyroid peroxidase. Endocrinology **148**, 2835–2844 (2007)
73. H. Klammer, C. Schlecht, W. Wuttke, C. Schmutzler, I. Gotthardt, J. Köhrle, H. Jarry, Effects of a 5-day treatment with the UV-filter octyl-methoxycinnamate (OMC) on the function of the hypothalamo-pituitary-thyroid function in rats. Toxicology **238**, 192–199 (2007)
74. J.R. Rochester, Bisphenol A and human health: a review of the literature. Reprod. Toxicol. **42**, 132–155 (2013). doi:10.1016/j.reprotox.2013.08.008
75. B.S. Rubin, Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J. Steroid Biochem. Mol. Biol. **127**, 27–34 (2011). doi:10.1016/j.jsbmb.2011.05.002
76. S. Soriano, P. Alonso-Magdalena, M. García-Arévalo, A. Novials, S.J. Muhammed, A. Salehi, J.A. Gustafsson, I. Quesada, A. Nadal, Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor β. PLoS ONE **7**, e31109 (2012). doi:10.1371/journal.pone.0031109
77. D. Gentilcore, I. Porreca, F. Rizzo, E. Ganbaatar, E. Carchia, M. Mallardo, M. De Felice, C. Ambrosino, Bisphenol A interferes with thyroid specific gene expression. Toxicology **304**, 21–31 (2013)
78. Z.G. Sheng, Y. Tang, Y.X. Liu, Y. Yuan, B.Q. Zhao, X.J. Chao, B.Z. Zhu, Low concentrations of bisphenol a suppress thyroid hormone receptor transcription through a nongenomic mechanism. Toxicol. Appl. Pharmacol. **259**, 133–142 (2012)
79. J. Chevrier, R.B. Gunier, A. Bradman, N.T. Holland, A.M. Calafat, B. Eskenazi, K.G. Harley, Maternal urinary bisphenol a during pregnancy and maternal and neonatal thyroid function in the CHAMACOS study. Environ. Health Perspect. **121**, 138–144 (2013). doi:10.1289/ehp.1205092
80. C. Sriphrapradang, L.O. Chailurkit, W. Aekplakorn, B. Ongphiphadhanakul, Association between bisphenol A and abnormal free thyroxine level in men. Endocrine **44**, 441–447 (2013). doi:10.1007/s12020-013-9889-y
81. J.D. Meeker, K.K. Ferguson, Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007–2008.

Environ. Health Perspect. **119**, 1396–1402 (2011). doi:10.1289/ehp.1103582
82. S.A. Jancic, B.Z. Stosic, Cadmium effects on the thyroid gland. Vitam. Horm. **94**, 391–425 (2014). doi:10.1016/B978-0-12-800095-3.00014-6
83. F. Hammouda, I. Messaoudi, J. El Hani, T. Baat, K. Saïd, A. Kerkeni, Reversal of cadmium-induced thyroid dysfunction by selenium, zinc, or their combination in rat. Biol. Trace Elem. Res. **126**, 194–203 (2008). doi:10.1007/s12011-008-8194-8
84. J. Luo, M. Hendryx, Relationship between blood cadmium, lead, and serum thyroid measures in US adults–the National Health and Nutrition Examination Survey (NHANES) 2007–2010. Int J Environ Health Res. **24**, 125–136 (2014). doi:10.1080/09603123.2013.800962
85. A. Chen, S.S. Kim, E. Chung, K.N. Dietrich, Thyroid hormones in relation to lead, mercury, and cadmium exposure in the National Health and Nutrition Examination Survey, 2007–2008. Environ. Health Perspect. **121**, 181–186 (2013). doi:10.1289/ehp.1205239
86. L. Tran, M. Hammuda, C. Wood, C.W. Xiao, Soy extracts suppressed iodine uptake and stimulated the production of autoimmunogen in rat thyrocytes. Exp. Biol. Med. **238**, 623–630 (2013). doi:10.1177/1535370213489488
87. N. Abdelouahab, D. Mergler, L. Takser, C. Vanier, M. St-Jean, M. Baldwin, P.A. Spear, H.M. Chan, Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada). Environ. Res. **107**, 380–392 (2008). doi:10.1016/j.envres.2008.01.006
88. M. Messina, G. Redmond, Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid **16**, 249–258 (2008)