Environmental chemicals and thyroid function: an update

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Purpose of review
To overview the effects of endocrine disrupters on thyroid function.
Recent findings
Studies in recent years have revealed thyroid-disrupting properties of many environmentally abundant chemicals. Of special concern is the exposure of pregnant women and infants, as thyroid disruption of the developing fetus may have deleterious effects on neurological outcome. Evidence is reviewed for the following groups of chemicals: polychlorinated biphenyls, dioxins, flame retardants, pesticides, perfluorinated chemicals, phthalates, bisphenol A and ultraviolet filters. Chemicals may exert thyroid effects through a variety of mechanisms of action, and some publications have focused on elucidating the mechanisms of specific (groups of) chemicals.
Summary
A large variety of ubiquitous chemicals have been shown to have thyroid-disrupting properties, and the combination of mechanistic, epidemiological and exposure studies indicates that the ubiquitous human and environmental exposure to industrial chemicals may impose a serious threat to human and wildlife thyroid homeostasis. Currently, available evidence suggests that authorities need to regulate exposure to thyroid-disrupting chemicals of pregnant women, neonates and small children in order to avoid potential impairment of brain development. Future studies will indicate whether adults also are at risk of thyroid damage due to these chemicals.

Keywords
brain development, endocrine disrupters, polychlorinated biphenyls, thyroid, thyroxine

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Introduction

A large number of studies of the thyroid-disrupting properties of environmentally abundant chemicals have appeared in recent years. These indicate that the regular human and environmental exposure to such industrial source chemicals may pose a serious threat to human and wildlife thyroid homeostasis. We have earlier reviewed the literature in this field [1], and the present review will update the current knowledge. In recent years, several 'new' groups of chemicals have been suspected to have thyroid-disrupting properties [perfluorinated chemicals (PFCs), phthalates, bisphenol A (BPA) and ultraviolet (UV) filters], and evidence for these groups is included.

Chemicals may exert thyroid effects through a variety of mechanisms of action, and some publications have focused on elucidating the mechanisms of specific (groups of) chemicals.

Overview of evidence for effects from different types of compounds

In the following, we will give an overview of the evidence of thyroid-disrupting properties of different groups of chemicals.

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) comprise a group of highly persistent lipophilic chemicals, which can be detected in samples from human and wildlife populations, although banned for decades in most countries. PCBs, especially the hydroxylated metabolites, which are also biologically active, have a high degree of structural resemblance to thyroxine (T4).

The negative effect of PCB exposure on peripheral thyroid hormone levels is well documented by studies in laboratory animals. Thus, PCB exposure decreased the levels of circulating thyroid hormones, especially T4

[2–4]. Monkeys exposed orally to PCB for 18–23 weeks showed a significant dose-dependent reduction of T4, free T4 (FT4), triiodothyronine (T3) and an increase in thyroid-stimulating hormone (TSH) [5]. There is substantial evidence that perinatal exposure to PCBs and their hydroxylated metabolites decreases thyroid hormones in the offspring [6–14]. Studies have demonstrated accumulation of hydroxylated metabolites in the fetal compartment [8].

Similar relationships between serum levels of organochlorine pollutants and thyroid hormones are reported from wild animals [15–17].

Multiple studies [18,19,20•,21,22•] of PCB exposure and effects have been carried out in human populations, the majority of which raise concern that environmental levels of PCBs may reduce peripheral thyroid hormone levels. A few studies [22•,23] also demonstrated a positive correlation between PCB exposure and TSH. Furthermore, in young adults, levels of persistent PCBs and dichlorodiphenyldichloroethylene (DDE) were associated with elevated levels of antibodies against thyroid peroxidase (TPOAb) [24•]. The volume of the thyroid gland is another endpoint for thyroid function but is rarely used in human toxicological studies; in adults from a PCB-polluted area, the thyroid volume assessed by ultrasound was found to be significantly larger than in 'nonexposed' individuals [25].

Alterations in fetal and infant thyroid homeostasis due to environmental exposures are of special concern, as it is well known that normal thyroid function is crucial for neurological development. In recent years, several studies have aimed at elucidating potential toxic effects of environmental levels of PCBs on human thyroid function in developmentally important age groups. Thus, environmental levels of PCBs are associated with reduced thyroid hormone levels and/or positive associations with TSH in pregnant women in several studies [26,27] but not in all [28].

In 1994, a study of 105 mother–infant pairs showed that PCB and dioxin-like toxicants in breast milk were significantly correlated with lower maternal thyroid hormones in late pregnancy and postpartum. PCB levels were significantly associated with higher TSH in infants at 2 weeks and 3 months of age but not with thyroid hormones [29]. Recent studies of newborns have confirmed this association [30] and found additional negative associations with FT4 [31]. However, not all studies of newborns found significant associations between PCB exposure and infant thyroid hormone levels [28,32–34], which may be due to the evaluation of infant thyroid hormone levels in cord blood or in dried blood spots obtained shortly after birth. These may not be optimal endpoints, as many factors related to pregnancy, delivery and perinatal health are affecting the levels of thyroid hormones in newborns [31]. There could also be differences in methodology for measuring both the thyroid function-related variables and the chemical substances as explanations for different results and conclusions.

In summary, human and wildlife observations point towards subtle, but significant, effects of low-dose PCB exposure on human thyroid function.

Dioxins

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are widespread, persistent and highly toxic environmental pollutants from industrial burning processes or production of herbicides.

A single dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) dose-dependently decreased T4 and FT4 [35] and increased TSH [36] in adult rats. Given to pregnant dams, TCDD decreased T4 and increased TSH in male offspring [37]. Human studies are scarce, but in a large study of Vietnam War veterans, the group with the highest exposure to TCDD had significantly higher TSH levels [38].

Flame retardants

The use of some flame retardants is abundant, and this group of chemicals is found in different products such as electronic equipments, plastics, paints and synthetic textiles. During recent years, an extensive amount of publications have focused on the possible thyroid-disrupting qualities of flame retardants, which comprise chemicals such as tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs). TBBPA and PBDEs show even closer structural relationship with T4 than PCBs.

In rats, several PBDEs as well as commercial mixtures decrease the levels of circulating thyroid hormones [3,39–41]. Furthermore, one study [42] indicated that marginal hypovitaminosis A might enhance the susceptibility to thyroid disruption. Perinatal maternal exposure of rats to different mixtures and congeners of PBDE reduced thyroid hormones prenatally and postnatally in both dams and fetuses [43]. Studies of other species have shown similar results, as total T4 was decreased in fish after exposure to PBDE [44] and 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) [45]. Similarly, exposure of kestrels before and after hatching to different PBDE congeners decreased T4 levels in the offspring [46]. Exposure of minks to the technical penta-BDE mixture DE-71 reduced T3 in a dose-dependent manner in both dams and offspring [47].

Recently, several studies have proved that even low doses of PBDEs, comparable to levels of environmental human exposure, may similarly disrupt thyroid homeostasis. Thus, a single low dose of BDE-99 in pregnant rats reduced T4 in dams at the beginning of lactation and in offspring 3 weeks postpartum [48]. Accordingly, low doses of BDE-47 in pregnant sheep significantly reduced T4 and T3 levels in the cord blood of exposed lambs [49••].

Mechanistic studies indicated that PBDEs might act by induction of hepatic enzymes involved in glucuronidation [3] or by downregulating the transport protein transthyretin (TTR) and transmembranal thyroid hormone transport [50]. Similarly, TBBPA has been documented to interfere with binding proteins [51]. Furthermore, TBBPA binds thyroid hormone receptor directly and impairs thyroid hormone-dependent metamorphosis in amphibian models [52–54] and acts antagonistically in a competition assay [55•].

Few human studies exist regarding flame retardants and thyroid function. However, recently, a large study [56•] of consumers of fish from the Great Lakes reported negative associations between concentrations of PBDE congeners in serum and serum levels of T3 and TSH, as well as a positive relation with T4. However, a previous study [57] of men exposed through Baltic fish consumption showed negative associations between TSH and PBDE. Thus, our current knowledge on the effect of flame retardants on human thyroid function is very limited.

Pesticides

Several hundreds, if not thousands, of different chemicals are used as pesticides and are as such part of potentially widespread human exposure. Of these, the persistent chemicals such as dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB) and nonylphenol 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.

A large number of animal and toxicological studies suggest that multiple pesticides may have thyroid-disrupting properties, but an overview of thyroid-disrupting effects of specific pesticides is beyond the scope of the present review.

Perfluorinated chemicals

Perfluorinated chemicals (PFCs) are widely used in industrial and consumer products due to their surface protection properties; the latter are exploited not only in products as stain and oil-resistant coatings but also in floor polishes and insecticide formulations. The group comprises several chemicals, for example, perfluorooctanoic acid (PFOA) as well as perfluorooctane sulfonate (PFOS), which is also the metabolic end-product of other PFCs. PFCs are extremely persistent in the environment.

Several animal studies found decreased levels of T4 after both long-term [58•] and short-term exposure [59,60] to PFOS and both in pregnant dams [61] and in pups [62,63]. Similarly, PFOA decreased levels of T3 [59]. However, single-dose exposure to PFOS resulted in transiently increased FT4 and decreased TSH, followed by a decrease in T4 and T3 [64]. Accordingly, a study [65] of monkeys showed a reduction of total T3 after exposure to PFOS. In-vitro studies of exposed rat tissues showed upregulation of hepatic glucuronidation enzymes and deiodinases in the thyroid gland [58•]. A large study of employees in a PFC manufacturer company showed negative associations between PFOA and FT4 [66], but epidemiological human studies of effects of environmental PFC levels are lacking.

Phthalates

Phthalates are widely used as plastic emollients and additives in various industrial and consumer products, and exposure to phthalates is inevitable. For certain groups such as hospitalized neonates, exposure may be massive. In these patients, changes in thyroid hormone levels as a result of exposure to phthalates may be transient, but could nonetheless have permanent effects on the development of the central nervous system, if changes occur in a developmentally critical phase.

Studies on thyroid-disrupting effects of phthalates and their monoester metabolites are scarce. In rats, di-*n*-butyl phthalate (DBP) decreased T3 and T4 in a dose-dependent manner [67], and several studies [68,69] have shown histopathological changes in the thyroid after exposure to phthalates. A recent study [55•] based on a newly developed reporter gene assay showed DBP to act antagonistically in a competition assay in a T3 reporter gene screening assay.

In human populations, negative associations between di(2-ethylhexyl) phthalate (DEHP) exposure and FT4 and T3 have been reported in men recruited from a fertility clinic [70]. In pregnant women, a significant negative association was found between DBP exposure and T4 and FT4 [71]. Studies [72,73] of smaller populations did not find any relationships, probably due to lack of statistical power.

Bisphenol A

BPA (4,4′-isopropylidenediphenol) is widely used to manufacture numerous plastic products, including

food-can linings and clear plastic bottles, and several population studies [74,75] have reported a high degree of human exposure.

BPA fed to pregnant rats was associated with a significant increase of total T4 in the pups 15 days postpartum compatible with thyroid resistance syndrome [76]. However, other studies [77–79] have found no or contrasting effects on thyroid hormone levels after BPA exposure, and human data are lacking. In mechanistic studies [80,81], BPA has been found to bind to the thyroid hormone receptor and act as an antagonist to T3 at thyroid hormone receptor, thus inhibiting thyroid hormone receptor-mediated transcriptional activity. Furthermore, BPA was shown to inhibit human recombinant TPO [82]. Accordingly, studies have shown BPA to block T3-induced metamorphism of tadpoles [83] and differentiation of mouse oligodendrocytes [84].

Ultraviolet filters

Certain ultraviolet (UV) filters, which are produced in high amounts and used not only in sunscreens but also in other cosmetic products, are suspected to have thyroid-disrupting properties. This applies to 4-methylbenzylidene-camphor (4-MBC), octyl-methoxycinnamate (OMC), and benzophenone 2 and benzophenone 3 (BP2 and BP3). Rat studies have shown significant reductions of T4 as well as increased TSH levels by 4-MBC [85] and reductions of both T4 and T3 but decreased TSH levels after exposure to OMC [86]. Furthermore, OMC was shown to reduce hepatic deiodinase activity [86,87]. BP2 was shown *in vivo* to reduce thyroid hormone levels in rats [82,88] and to be a potent inhibitor of human recombinant TPO [82]. Thus, evidence from animal and in-vitro studies indicates that several frequently used UV filters may have thyroid-disrupting properties.

Future perspectives

Evidence reviewed above indicates that many different groups of chemicals, to which human and wildlife populations are exposed ubiquitously, may interfere with thyroid hormonal homeostasis. This holds true in all age groups but may be of special concern in developmentally critical periods of life, that is, fetal life and early childhood when normal levels of thyroid hormones are crucial to growth and neurological development [89]. The hypothalamus–pituitary–thyroid axis is closely regulated by a feedback mechanism, and peripheral thyroid hormone effects are regulated both by thyroid hormone transporters and deiodinases, which are different in different organs. Both thyroid hormone levels and thyroid gland volume and capacity are dynamic entities changing according to current needs. Therefore, it is difficult to establish reliable endpoints in human epidemiological studies of thyroid function. Alterations in thyroid hormone levels can be due to current influences from measurable chemical exposure but may be transient, and normal thyroid hormone levels may thus not reveal permanent deleterious effects of previous exposures. Permanent biomarkers of thyroid disruption in humans are yet to be determined. Furthermore, reference ranges of normal thyroid function are wide, but as individual variations are known to be narrower [90], even small alterations in the individual may be of importance. Thus, a marginally low T4 level in a pregnant women may give rise to offspring with six intelligence quotient (IQ) points lower than those of mothers with higher T4 concentrations [91,92]. Other aspects, which remain to be elucidated, are whether susceptibility to endocrine disrupters may be influenced by iodine intake and sex.

Human and wildlife populations are exposed not just to the single group of chemicals that are ordinarily the subjects of reports. The environmental mixtures of various groups of chemicals may have additive or synergistic effects, which result in more serious consequences than predicted by studies of single substances [93]. Large epidemiological studies evaluating the total exposure burden from various groups of chemicals on thyroid function are needed.

Conclusion

A large variety of ubiquitously present chemicals have been shown to have thyroid-disrupting properties. A combination of mechanistic, epidemiological and exposure studies indicates that human and wildlife health is at risk from these chemicals. Currently, available evidence suggests that governing agencies need to regulate the use of thyroid-disrupting chemicals, particularly as such uses relate exposures of pregnant women, neonates and small children to the agents. A specific concern is avoidance of effects on brain development. In the authors' country, recommendations to pregnant women from the health authorities include avoidance of exposure to endocrine-disrupting chemicals. This is just a first step that should be pursued further globally. Given the long half-life of some environmental chemicals, measures may be needed that also minimize exposures before pregnancy. Apart from that, future studies will indicate whether also adults are at risk of thyroid damage due to these chemicals.

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- •• of outstanding interest

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