REVIEW

Thyroid function disruptors: from nature to chemicals

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Abstract

The modern concept of thyroid disruptors includes synthetic chemicals and bioactive compounds from food that interfere with any aspect of the hypothalamus–pituitary–thyroid axis, thyroid hormone biosynthesis and secretion, blood and transmembrane transport, metabolism and local actions of thyroid hormones. This review highlights relevant disruptors that affect populations through their diet: directly from food itself (fish oil and polyunsaturated fatty acids, pepper, coffee, cinnamon and resveratrol/grapes), through vegetable cultivation (pesticides) and from containers for food storage and cooking (bisphenol A, phthalates and polybrominated diphenyl ethers). Due to the vital role of thyroid hormones during every stage of life, we review effects from the gestational period to adulthood, including evidence from *in vitro* studies, rodent models, human trials and epidemiological studies.

Key Words

- ▶ bioactive food compounds
- ▶ chemical disruptors
- ▶ TSH
- ▶ thyroid hormones

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Introduction: temporal description, definitions, basic concepts

Although the terms endocrine disruption and endocrine disruptors were coined at the Wingspread Conference in 1991, the concept of endocrine alterations caused by synthetic chemicals has followed the larger context of the environmental movement that has had various influences on science since the 1960s and 1970s (Schug *et al.* 2016). Several factors have guided this journey, such as Rachel Carson's 1962 book *Silent Spring*; several wildlife studies showing reproductive alterations in birds, alligators and fish (Gilbertson & Reynolds 1972, Aulerich *et al.* 1973, Aulerich & Ringer 1977, Semenza *et al.* 1997, Jobling *et al.*

2002); and the disastrous use of an estrogen analog, diethylstilbestrol, which was used by millions of women during pregnancy to reduce the risk of miscarriage: later this use was linked to the occurrence of unusual cancers and reproductive system malformations for those exposed *in utero* (McLachlan *et al.* 1980, Newbold *et al.* 1985). Dietary phytoestrogens, which are phytochemicals that are structurally similar to estrogens, are able to bind and activate estrogen receptors (ERs), mimicking or interfering with endogenous estrogen pathways. Therefore, these plant-derived compounds can induce many health

benefits but can also cause harmful effects, such as an elevated breast cancer risk and premature puberty (Sauve & Desrosiers 2014).

In 2012, the Endocrine Society published (Zoeller *et al.* 2012, Schug *et al.* 2016) a statement of principles and used the following definition to describe endocrine-disrupting chemicals (EDCs): chemicals, or mixtures of chemicals, which interfere with any aspect of hormone action (Patisaul & Jefferson 2010, Bode & Dong 2015). There are a great variety of agents that have been reported to have endocrine-related effects, including more than 1000 chemicals from several chemical classes (Diamanti-Kandarakis *et al.* 2009). These chemicals are not identified by their chemical structure or by a specific type of usage but rather by their mechanisms of action and ability to alter endocrine system function. In this context, there are a large number of chemicals with different structures present in food, and many of them have biological properties, including endocrine-disrupting-related effects (Gore *et al.* 2015), which extends the concept of endocrine disruptors beyond man-made chemicals. Several reviews have explored the effects of chemicals and bioactive compounds in food on the reproductive system. In addition to effects on the reproductive system, endocrine disruptors also affect different endocrine glands, including the thyroid, a fundamental gland for neural development. Thyroid hormones (THs) are released under the regulation of the hypothalamus–pituitary–thyroid (HPT, Fig. 1) axis and other factors that control the mechanism of action of THs (Fig. 2), which have been extensively reviewed elsewhere (Ortiga-Carvalho *et al.* 2014, 2016, Bernal *et al.* 2015). Importantly, endocrine disruptors may act at any level of this regulation. In this review, we explore the effects of natural and artificial compounds on thyroid function and regulation.

Bioactive food compounds as thyroid-disrupting factors

Some vegetables, such as cabbage, broccoli and cassava, are a source of antithyroid compounds, such as thiocyanate and thioamides, which are well-characterized goitrogens (Gaitan 1990, Felker *et al.* 2016, Willemin & Lumen 2017). However, the consumption of other foods and food-related compounds, such as soy protein and soybean isoflavones, as well as other flavonoids, may interfere with thyroid function. These effects of those compounds have been reviewed recently by several authors (Doerge & Chang 2002, Messina & Redmond 2006, Xiao 2008, de Souza Dos Santos *et al.* 2011). Here, we focus on reviewing

the thyroid-disrupting properties of other less well-known bioactive food compounds.

Fish oil and polyunsaturated fatty acids

Essential fatty acids play important roles in plasma membrane integrity and function, energy production and as precursors of bioactive lipids at all stages of life. The long chain *n*–3 polyunsaturated fatty acid (*n*–3 PUFA) docosahexaenoic acid (22:6n-3; DHA) is especially important to brain development during gestation and infancy (Chilton *et al.* 2017). Male rat pups supplemented with DHA during the first 6 weeks of life exhibited higher serum thyroid-stimulating hormone (TSH) levels without changes in other pituitary hormones (Clandinin *et al.* 1998), which suggests that DHA interferes in the HPT axis (Fig. 1). However, other authors (Souza *et al.* 2010) studying rats supplemented with fish oil, which is enriched in *n*–3 PUFAs, from lactation until 11 weeks of age found no alterations in serum TSH or TH concentrations. The authors detected higher levels of the TH receptor β (THR β) protein in the liver, accompanied by increased mitochondrial glycerophosphate dehydrogenase (mGPD) activity; mGPD is a THR β -mediated triiodothyronine (T3) target, suggesting that fish oil increases TH sensitivity in this tissue. However, deiodinase type 1 (D1, DIO1) activity, another recognized marker of TH action in the liver (Fig. 2), was not changed, suggesting that the *n*–3 PUFAs present in fish oil might interfere with T3 action in a target-specific manner (Souza *et al.* 2011). Another study showed that hepatocytes treated with T3 and eicosapentaenoic acid (20:5n-3; EPA) showed a reduction of 70% in the effect of T3 on thyroid hormone responsive spot 14 (*Thsrp*) gene transcription (Jump *et al.* 1993). However, the authors showed that the *Thsrp* TH-response element (TRE) was not directly sensitive to EPA inhibition. The PUFA-responsive element was found to be located in a region that potentiates T3-mediated activation of *Thsrp* gene transcription.

In hypothyroid patients, higher levels of free fatty acids were associated with lower symptom severity, along with lower serum TSH and higher thyroxine (T4) and T3 levels, than in patients with low levels of plasma free fatty acids (Makino *et al.* 2001). These authors also showed, in methimazole-induced hypothyroid rats, that chronic EPA supplementation for 28 days reduced the methimazole-induced drop in TH levels and the consequent increase in serum TSH levels (Makino *et al.* 2001). This study suggests that EPA exerts a direct stimulatory effect on the thyroid.

Figure 1

Simple scheme of the hypothalamus-pituitary-thyroid axis. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release thyrotropin (thyroid-stimulating hormone, TSH). TSH is released in circulation and stimulates the thyroid gland to produce thyroid hormones (THs) (Ortiga-Carvalho *et al.* 2014). The thyroid produces the main THs, thyroxine (T4) and triiodothyronine (T3). TSH stimulates all the steps of TH biosynthesis and release, as well as the expression and activity of several proteins: the solute carrier family 5A (also known as sodium-iodide symporter (NIS)), pendrin (PDS), dual oxidase type 2 (DUOX), thyroid peroxidase (TPO), thyroglobulin (Agic *et al.* 2007) and deiodinases type 1 (D1, DIO1), 2 (D2, DIO2) and 3 (D3, DIO3). In physiologic balance, T4 and T3 (3) regulate their own concentrations in the blood by negative feedback acting at the hypothalamic (1) and pituitary (2) levels (Ortiga-Carvalho *et al.* 2016). BPA, bisphenol A; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PBDE, polybrominated diphenyl ether.

Pepper and piperine

Piperine is the main alkaloid found in the fruit *Piper nigrum*, which is also known as black pepper. Studies have shown that piperine enhances the bioavailability of several drugs and nutraceuticals and possesses important pharmacological effects, including anticancer, anti-inflammatory and antimicrobial activities (Chavarria *et al.* 2016). Although there is no evidence for the effects of piperine in humans, studies conducted in rodents point to a thyroid-disrupting effect of pepper and isolated

piperine. Two different preparations of the *Piper* fruit were tested in mice. A water extract induced a reduction in serum T3 and T4 levels after 15 days of treatment. An ethanolic extract had the opposite effect and induced an elevation in TH levels (Panda & Kar 2003b). The study did not evaluate the chemical composition of the extracts to identify the bioactive component responsible for the different effects observed. Another study investigated the effect of isolated piperine administered orally for 15 days to mice. This study found suppressed hepatic D1 activity in the groups receiving high or low doses of piperine, with

Figure 2

Schematic local action of thyroid hormones (THs). (1) Thyroxine (T4) and triiodothyronine (T3) reach the cytoplasm by transport through the plasma membrane. There are several proteins able to transport T4 and T3; however, monocarboxylate transporter 8 (MCT-8, *Slc16a2*) is the most specific (Bernal *et al.* 2015). (2) T4 and T3 are activated or inactivated by deiodinases type 1 (D1, DIO1), 2 (D2, DIO2) and 3 (D3, DIO3) (Ortiga-Carvalho *et al.* 2016). (3) T3 is the TH able to bind TH receptors (THRs) that are encoded by two different genes (*Thra* and *Thrb*), which encode 3 main isoforms of these receptors: THR α 1 and THR β 1 and THR β 2. THRs bind to DNA at the TRE, modulating specific gene expression patterns (Ortiga-Carvalho *et al.* 2014). BPA, bisphenol A; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GPDm, mitochondrial glycerophosphate dehydrogenase; PBDEs, polybrominated diphenyl ethers; T2, 3,5-diiodo-L-thyronine; THR, thyroid hormone receptor.

the former showing reduced serum T3 and T4 levels and the latter only showing reduced serum T3 levels (Panda & Kar 2003a). These authors suggested that piperine has a direct suppressive effect on the thyroid at higher doses, but at lower doses, it directly inhibits the peripheral metabolism of THs mediated by the D1 in the liver.

Coffee and caffeine

Coffee contains over a thousand components, including many with biological activity, such as caffeine, diterpene alcohols and chlorogenic acid, which are potential nutraceuticals. Although the biological effects of coffee are not restricted to caffeine, this is the most studied component of coffee (O'Keefe *et al.* 2013). The effects of caffeine on thyroid function in animal models are inconclusive due to variations in the species, ages and doses studied. Caffeine has been used for more than 40 years as a prescribed drug in neonatal medicine, mostly for apnea treatment, but the overall effect of caffeine exposure at this age is poorly understood (Kreutzer & Bassler 2014). In newborn rats, a single administration of caffeine induced a biphasic response, with plasma T4 levels elevated after 4 h and then reduced 24 h after administration (Clozel *et al.* 1983). These authors suggested that the decrease in T4 concentration was a direct effect of caffeine on the thyroid gland since no significant change in thyrotropin-releasing

hormone (TRH)-stimulated TSH levels were observed at the same point. However, after 10 days of caffeine administration, basal serum TSH and T4 concentrations were increased, but after TRH stimulation, TSH levels were attenuated by caffeine, suggesting that chronic exposure to caffeine may lead to exhaustion of the pituitary reserve (Clozel *et al.* 1983). A study performed in preterm infants showed that caffeine was negatively associated with TSH levels at the 7th postnatal day (PND) but was positively associated with TSH levels at the 14th day, and caffeine showed no correlation at the 28th day. The reverse T3 (rT3) level was negatively correlated with caffeine exposure at the 7th PND. Therefore, these authors suggested a mild and transitory effect of caffeine on thyroid function in newborn humans (Williams *et al.* 2005). In adult rats, an acute injection of caffeine induced a decrease in TSH levels after 1–6 h, followed by a reduction in T3 and T4 levels after 4 h. An injection of anti-somatostatin antiserum blocked the inhibitory effect of caffeine on TSH secretion, and the incubation of an isolated pituitary gland with caffeine did not elicit changes in TSH release, suggesting that the effect of caffeine on TSH release appears to be mediated by hypothalamus-derived somatostatin (Spindel *et al.* 1984). The chronic exposure to caffeine associated with regular intake induces tolerance related to hemodynamic and humoral effects (O'Keefe *et al.* 2013), and this seems to extend to the effects on thyroid function as well.

Spindel *et al.* (1984) observed that an acute injection of caffeine induced an inhibitory effect on serum TSH; however, a 7-day treatment with caffeine induced tolerance to its effect on serum TSH. A possible tolerance-inducing effect on thyroid function was also observed in Syrian golden hamsters treated for 90 days with caffeine. After 3 days of treatment, the authors observed a transient increase in serum T3 levels, without changes in T4 levels. After 90 days of treatment, no changes in serum T3 and T4 levels or in thyroid histopathology were identified (Bartsch *et al.* 1996). Evidence in humans is complex but also points to a transitory effect and a possible tolerance-related outcome. The acute intake of caffeine did not promote any changes in serum TSH or T3 levels over 4 h in healthy adults who normally drank one to three cups of coffee a day (Spindel *et al.* 1984). In a study conducted by Friedrich *et al.* (2017), a strong positive correlation between the levels of free T4 (FT4) and urinary trigonelline, a urinary marker of coffee consumption in humans (Lang *et al.* 2011), was observed in cross-sectional analyses. However, this positive association was lost in longitudinal analyses, and higher trigonelline levels in urine samples were related to a greater decline in FT4.

Grape and resveratrol

Resveratrol is a natural polyphenol stilbene found in foods such as grapes, berries and peanuts, as well as in red wine, which is the main source of resveratrol in the Mediterranean diet (Gambini *et al.* 2015). *In vitro* resveratrol incubation of the rat thyroid cell line FRTL-5 induced a rapid and transient stimulatory effect of iodide trapping, with the highest effect occurring between 6 h and 12 h, and after 24 h, no changes were observed. The stimulatory effect was dose dependent and associated with increased levels of the solute carrier family 5A (also known as sodium-iodide symporter or NIS) protein. In addition, the effect of resveratrol on iodide uptake after 6 h of incubation was additive to the effect TSH stimulation and was mediated by a cAMP-independent pathway (Sebai *et al.* 2010). Interestingly, after 48 h of incubation, the effect of resveratrol on FRTL-5 cells was the opposite: it induced a reduction in iodide uptake accompanied by the reduced expression of NIS and the gene that encodes this transporter, *Slc5a5* (Giuliani *et al.* 2014). At this time point, resveratrol also downregulated the expression of TSH receptor (*Tshr*), thyroid peroxidase (*Tpo*), thyroglobulin (Agić *et al.* 2007) and the related transcriptional factors NK2 homeobox 1

(*Nkx2-1*), forkhead box E1 (*Foxe1*) and paired box 8 (*Pax8*) mRNAs in FRTL-5 cells (Giuliani *et al.* 2017). *In vivo*, resveratrol administered to adult male rats for 14 days induced lower NIS protein expression levels and reduced radioiodine uptake by the thyroid, with no significant effects on thyroid growth or TSH and TH concentrations (Giuliani *et al.* 2014). In a chronic study, the treatment of adult male rats with resveratrol for 60 days promoted increased thyroid mass and higher serum TSH levels, without altering the serum concentration of THs, and the histological analyses showed an increased number of follicles, with lower thyroglobulin concentrations in the colloid (Giuliani *et al.* 2017). Therefore, these data suggest that resveratrol elicits a direct antithyroid effect and a mild goitrogenic effect when administered chronically. The thyroid-related effects of resveratrol can be different in females, as showed previously (Bottner *et al.* 2006). Ovariectomized female rats treated chronically with resveratrol for 3 months showed higher levels of serum T3, without changes in serum T4 or TSH levels, pituitary TSH beta subunit (*Tshb*) mRNA expression, thyroid weight or the gross morphology of the thyroid. In addition, resveratrol had no effect on TRH-stimulated TSH secretion from isolated pituitary cells (Bottner *et al.* 2006). These authors pointed out that the higher T3 levels observed in their study cannot be related to the estrogenic action of resveratrol since 17 β -estradiol treatment of ovariectomized rats did not promote any change in the concentration of T3. In addition, the authors suggested that the higher T3 levels should be related to increased D1 activity or altered levels of T3-binding proteins such as thyroxine-binding protein (TBG) (Bottner *et al.* 2006). Resveratrol administration for 26 weeks to female rats fed a high-fat diet (HFD) attenuated the increase in total serum T4 levels and the reduction in total serum T3 levels induced by a HFD, while this treatment increased the levels of free T4 and T3 in HFD-fed mice. Resveratrol also increased levels of the *Dio1* mRNA in the hearts of HFD-fed mice, restoring expression levels to those observed in rats fed a normolipid diet, and resveratrol decreased TR α 1 (*Thra*) mRNA expression in the hearts of HFD-fed rats. These results indicate that resveratrol can affect the peripheral metabolism and actions of THs (Cheserek *et al.* 2016).

Human studies concerning the effects of grapes or resveratrol on thyroid function are scarce, and they do not point to a thyroid-disrupting effect; these studies have only explored a few parameters related to the thyroid physiology (Tome-Carneiro *et al.* 2012, 2013).

Cinnamon

Cinnamon is a common spice that is used worldwide and has been widely studied as a nutraceutical for the management of insulin resistance, obesity and dyslipidemia (Rafehi *et al.* 2012, Medagama 2015). According to the results of human, animal or *in vitro* studies, cinnamon and its active biological compounds interfere with the biosynthesis or action of many hormones, such as insulin, glucagon-like peptide-1 (GLP1), ghrelin and leptin (Hlebowicz *et al.* 2009, Rafehi *et al.* 2012, Camacho *et al.* 2015, Lopes *et al.* 2015, Medagama 2015, Bento-Bernardes *et al.* 2017). In this context, a study showed that rats supplemented with a water extract of cinnamon exhibited lower serum T3 levels accompanied by unaltered serum T4 and TSH levels. Cinnamon did not seem to impact pituitary or liver TH signaling or metabolism since *Thrb* or *Dio* expression in these tissues was similar to that in controls. However, cinnamon-treated rats showed a strong reduction of *Thra* and *THR α* expression in the cardiac ventricle, with important consequences for the expression of calcium handling proteins (Gaique *et al.* 2016).

Chemicals as thyroid-disrupting factors

Due to the need to increase the productivity of agriculture and industry, thousands of different chemicals have been developed. Many of these artificial chemicals (such as hexachlorobenzene (HCB) and dichlorodiphenyltrichloroethane (DDT)) have been used as pesticides to improve agricultural efficiency. Plastic components and additives, such as bisphenol A (BPA), phthalates and benzo(a)pyrene diol epoxide (BPDE), are frequently used in products that people use daily to improve industrial processes. The present manuscript will concentrate on describing published data for pesticides that are directly involved in food contamination and chemicals that contaminate food due to their presence in plastic containers (BPA, phthalates and BPDEs) to present a more comprehensive review of selected chemicals. However, several other substances have already been shown to disrupt thyroid function, such as perchlorate, thiocyanate, nitrate, polychlorinated biphenyls, triclosan, dioxins and furans, styrenes, sunscreens and lead. Some of these substances can also reach humans and other animals through food contamination (Pearce & Braverman 2009).

Pesticides are chemical agents that are known to act as endocrine disruptors. For example, in 2014, the European Food Safety Authority reported that of 287 pesticides

tested, more than a third of them (103) had thyroid-disrupting properties (Sugiyama *et al.* 2005, Pearce & Braverman 2009, Bellanger *et al.* 2015, Leung *et al.* 2016).

Plasticizers

Plastic items are produced and used intensely worldwide, generating several environmental concerns associated with not only individual plastic use but also related to contamination due to leakage of plastic components into the environment. Two important substances used in the plastics industry that are correlated with endocrine disruption, particularly HPT axis disruption, are BPA and phthalates (Talsness *et al.* 2009). Humans can ingest these components because they can leach from food cans, microwave containers and polycarbonate bottles.

BPA was shown to interfere with the binding of T3 to its receptor by acting as an antagonist, both *in vitro* (Moriyama *et al.* 2002, Gayathri *et al.* 2004) and *in vivo* (Zoeller *et al.* 2005), particularly to the beta isoform of THR (THR β), mainly disrupting the negative feedback of THs in the pituitary (Zoeller *et al.* 2005). It was also shown, *in vitro*, that BPA suppressed expression of the gene encoding RXR gamma, which forms heterodimers with THR (Iwamuro *et al.* 2006). Similarly, several phthalate metabolites that act as THR antagonists were detected in Chinese rivers (Ibhazehiebo & Koibuchi 2011, Shi *et al.* 2011, Hu *et al.* 2013, Li *et al.* 2014), which was corroborated by a transient transfection study with low phthalate doses (Hansen *et al.* 2016).

The capacity of BPA to interfere with THR transcription activity has been analyzed by several studies, with some of them showing interference at the nuclear transcriptional level, particularly for T3-related genes (Xu *et al.* 2007, Heimeier *et al.* 2009, Hansen *et al.* 2016, Jiang *et al.* 2016), and one study demonstrated interference at a nongenomic level (Sheng *et al.* 2012). BPA and several BPA analogs that have recently been introduced in the plastics industry were tested on different TH-responsive cell lines (GH3, FRTL-5 and rat cerebellar cells), and the results showed that they interfered with the expression of genes involved in TH synthesis (*Slc5*, *Tg* and *Tpo*), thyroid cell activity/proliferation (*Tshr*, *Tshb*, *Thrb*, *Thra*, *Dio1* and *Dio2*) and thyroid transcriptional regulation (*Pax8*, *Nkx2-1* and *FoxE1*) (Gentilcore *et al.* 2013, Lee *et al.* 2017). From these results, one can presume that BPA and BPA analogs may affect thyroid function even at low doses, with a possible mechanism being through NF- κ B and RAR/RXR pathways (Ghisari & Bonefeld-Jorgensen 2005, Okada *et al.* 2007, Somogyi *et al.* 2016). Phthalate metabolites could affect

iodine uptake through the regulation of NIS and of *Slc5a5* mRNA expression (Breous *et al.* 2005, Wenzel *et al.* 2005) and by modulating hormone sulfation (Turan *et al.* 2005).

Several studies using animal models were controversial in demonstrating disruption of thyroid function after BPA exposure using different doses and windows of exposure. Zoeller *et al.* showed that there was an increase in serum concentrations of total T4 in pups after perinatal exposure, as early as PND 15, with no difference in TSH levels compared to levels in animals not exposed to BPA (Zoeller *et al.* 2005). However, another group did not detect any difference in the F1 generation of rats exposed to BPA prenatally (Kobayashi *et al.* 2005). Pregnant female rats exposed to BPA experienced transient hypothyroidism, while their male pups underwent transient hyperthyroidism, followed by hypothyroidism (Xu *et al.* 2007). Infant rats exposed during the neonatal period did not present any alterations, but the adult female animals developed a TH status similar to hypothyroidism, and evidence in a primary pituitary cell line showed that BPA alters TSH release through direct action on the pituitary (Fernandez *et al.* 2018). Studies with pregnant ewes, which have a gestational period more comparable to that of humans, that were exposed to BPA both subcutaneously and by dietary exposure demonstrated lower levels of THs in pregnant females and newborns, and those females showed evidence of a modified deiodination balance (Viguie *et al.* 2013, Guignard *et al.* 2017). In analyzing other windows of exposure, mice exposed to BPA during puberty have been shown to have lower free T4 levels (Jiang *et al.* 2016).

Animal studies of phthalates exposure have shown similar discrepancies; earlier studies suggested that phthalate metabolites could show thyromimetic effect (Price *et al.* 1988, Badr 1992, Gayathri *et al.* 2004). However, later studies were more consistent in showing a thyroid antagonistic effect, causing reductions in TH levels and signs of multigenerational and persistent effects (Pereira *et al.* 2007, Erkekoglu *et al.* 2012, Liu *et al.* 2015, Dong *et al.* 2017, Mahaboob Basha & Radha 2017, Sun *et al.* 2018). Evidence shows disruption of the TSH/TSHR pathway, with involvement of the hypothalamus (Dong *et al.* 2017, Sun *et al.* 2018), and of the TH synthesis machinery (downregulation of NIS, TPO, D1s and transthyretin), as well as increased TH metabolism caused by increased expression of hepatic enzymes (Liu *et al.* 2015). Phthalates, particularly di-n-butyl phthalate (DBP), might also exacerbate chronic lymphocytic thyroiditis by inducing oxidative stress and changes in serum TBG levels and thyroid interleukin-7 (IL-7) levels (Johns *et al.* 2016).

In humans, the available data are even more controversial; two prospective studies, CHAMACOS (Chevrier *et al.* 2013) and HOME, have evaluated the possible associations of BPA with THs during pregnancy and in neonates, and the results are somewhat similar regarding neonatal thyroid profiles, with a negative correlation between BPA exposure and TSH levels only in male newborns in the CHAMACOS study and in female newborns in the HOME study, with the strongest association found when exposure occurred later in pregnancy (Chevrier *et al.* 2013, Romano *et al.* 2015). Only the CHAMACOS study observed an inverse association between BPA exposure and total T4 levels in pregnant women (Chevrier *et al.* 2013).

Regarding possible interference from phthalates during pregnancy, the majority of studies have reported a negative correlation between levels of several metabolites and THs, particularly free and total T4 and free T3 levels, and a positive correlation with TSH levels, and these effects may depend on the timing of exposure during gestation (Huang *et al.* 2007, 2016, Johns *et al.* 2015, Yao *et al.* 2016, Gao *et al.* 2017). However, other studies have shown very different results, with an inverse association with TSH and a positive association with free and total T4 levels (Huang *et al.* 2007, 2016, Johns *et al.* 2015, 2016, Yao *et al.* 2016, Gao *et al.* 2017). Regarding phthalate exposure and neonatal thyroid status, some studies have shown a correlation between phthalate levels and TH levels in newborns; a Dutch prospective cohort detected changes in free T4 levels in girls but not in boys (de Cock *et al.* 2014), and a study in Taiwan found an association of phthalate exposure with reduced levels of THs in young children (Huang *et al.* 2017a,b).

No evidence of an association between phthalate exposure and changes in TH levels was detected in children exposed during the use of extracorporeal oxygenation or after using DEHP-tainted foodstuffs (illegal use of DEHP in food from Taiwan); however, in the second group, a reduction in TSH levels was detected just after exposure (Rais-Bahrami *et al.* 2004, Wu *et al.* 2013, Tsai *et al.* 2016a,b). There is evidence in the literature of changes in TH levels, with a negative association of phthalate exposure with serum levels of THs, primarily in girls (Boas *et al.* 2010, Morgenstern *et al.* 2017). By contrast, another study showed a different thyroid profile, with sex-specific and metabolite-specific positive changes in TH levels (Weng *et al.* 2017).

Results from epidemiological cross-sectional studies vary for the different populations analyzed. In the National Health and Nutrition Examination Survey

(NHANES) 2007–2008, BPA and several other chemicals such as perchlorate and phthalates were correlated with reductions in T4 levels in males, but when BPA was analyzed individually, there was no association with TH fluctuation, while phthalate metabolites such as DEHP and DBP presented negative correlations with free and total T4, total T3 and thyroglobulin levels and a positive correlation with TSH levels, suggesting that these metabolites share a similar source and that there are sex-based differences in how the thyroid responds to phthalates (Meeker & Ferguson 2011, Mendez & Eftim 2012, Kim *et al.* 2017, Przybyla *et al.* 2018). Similar results for phthalates were found in the Korean National Environmental Health Survey (KoNEHS) 2012–2014, but BPA presented a negative association with TSH (Park *et al.* 2017). However, in a similar health cross-sectional study in Thailand, the Thai National Health Examination Survey IV 2009, a negative correlation between BPA and free T4 was detected in males, without changes in TSH levels (Sriphrapradang *et al.* 2013), and in this same group, BPA was also associated with thyroid autoimmunity, with an increase in TPO antibody positivity (Chailurkit *et al.* 2016). The Taiwan Environmental Survey for Toxicants (TEST) 2013 showed negative associations between free and total T4 levels and some phthalate metabolites in adults; however, a positive association with free T4 levels was found in children (Huang *et al.* 2017a,b). Other studies, with different population segments, such as Chinese adults, workers with occupational BPA exposure, men from a fertility clinic, and women with polycystic ovary syndrome all showed similar thyroid profiles, with increased TH levels and/or reduced TSH levels linked to BPA exposure (Meeker *et al.* 2010, Wang *et al.* 2012, 2013, Vahedi *et al.* 2016). By contrast, other studies showed positive correlations between urinary BPA and TSH levels (Geens *et al.* 2015, Andrianou *et al.* 2016). There is no consensus in the literature regarding phthalate exposure in male populations, with studies showing an inverse association between MEHP and free T4 and T3 levels (Geens *et al.* 2015, Andrianou *et al.* 2016) (Meeker *et al.* 2007) and another showing no disruption of TH levels in young males exposed to MEP and MBP (Janjua *et al.* 2007).

Since the incidence of thyroid cancer is increasing and environmental carcinogen exposure is a probable cause (Pellegriti *et al.* 2013), BPA seems to be a good candidate for having a role in this process based on different studies of cancer (Shafei *et al.* 2018). Animal models present contradictory evidence; Takagi *et al.* did not find any effect of BPA in promoting thyroid carcinogenesis (Takagi *et al.* 2002). However, other studies, both with animal models

and humans, demonstrated that BPA could influence thyroid carcinogenesis, particularly through an association with excess iodine (Zhang *et al.* 2017a, Zhou *et al.* 2017). One proposed mechanisms for this process includes interference with the action of ERs, particularly the alpha isoform (Zhang *et al.* 2017a,b). Additionally, a recent study based on microarray experiments, showed that BPA exposure impairs cellular defense against DNA damage, resulting in follicular cells being more likely to die or develop a genetic impairment (Porreca *et al.* 2017).

Pesticides

Many toxic effects of thyroid-disrupting pesticides have been recognized at various stages of development in various adult animal models and in humans. The effects on humans have mainly focused on somatic changes, as well as changes that can be inherited by subsequent generations through epigenetic mechanisms of transgenerational inheritance (Tabb & Blumberg 2006, Andersen *et al.* 2008, Schug *et al.* 2011).

Human epidemiological studies have shown that genetic nucleotide polymorphisms in the enzyme paraoxonase 1 (*PON1*) gene, which encodes a serum enzyme with antioxidant and detoxification properties (Furlong *et al.* 2005, Eskenazi *et al.* 2014), can alter the activity of the enzyme and may determine the level of sensitivity to pesticide toxicity (Furlong *et al.* 2010). Changes in serum lipid and lipoprotein concentrations occur frequently in thyroid dysfunction; in addition, a significant reduction in PON1 activity was observed in both hyperthyroid and hypothyroid patients (Azizi *et al.* 2003). This supports the idea that pesticides act as thyroid disruptors in humans, and their potential detrimental effects are more pronounced in individuals who are genetically more susceptible to thyroid dysfunction (Lacasana *et al.* 2010).

Some pesticides have long been banned in many countries but are still present in the environment, such as DDT, HCB and chlorpyrifos (CPF), and many of these have been examined and investigated for their thyroid-disrupting abilities (Pearce & Braverman 2009). *In vitro* studies on DDT exposure showed that DDT inhibits TSH release, mainly by affecting cAMP production at the post-receptor step (Santini *et al.* 2003), and DDT can inhibit the activity of TSHR (Rossi *et al.* 2007, 2009, 2018). In addition, it has been demonstrated that, in rats, a low dose of DDT increases the concentration of T3 and reduces the level of TSH (Yaglova & Yaglov 2014). Furthermore, the stable metabolite of DDT, p,p'-DDE, has also been investigated as a thyroid

disruptor in a study of male Mexican floriculture workers who presented with low serum levels of THs and no significant changes in TSH levels (Blanco-Munoz *et al.* 2016).

In a study of prenatal HCB exposure, the effect of HCB depended on the genotype of the gene encoding the D1 (*Dio1*) enzyme, suggesting that D1s play a role in the disruption of THs following exposure to HCB (Llop *et al.* 2017). Similar studies have shown that diminished T3 levels caused by HCB exposure during pregnancy can interfere with the TH levels in early newborns and affect neurodevelopment (Takser *et al.* 2005, Maervoet *et al.* 2007, Berg *et al.* 2017).

CPF is an organochlorine pesticide commonly used in households and agriculture in the United States. CPF can cross the placental barrier and mainly acts by inhibiting acetylcholinesterase. Even at low doses, this chemical can cause endocrine disruption related to neurodevelopmental defects, resulting in decreased IQ scores and impaired memory skills in children (Crumpton *et al.* 2000), as well as reductions in serum T4 levels (De Angelis *et al.* 2009, Zhang *et al.* 2013).

A cross-sectional study of spray paint workers showed that TSH levels were elevated in this group of workers and that T4 levels were suppressed, while T3 levels were not altered (Zaidi *et al.* 2006). Furthermore, the evaluation of serum samples from greenhouse workers exposed to pesticides between spring and the fall showed reductions in free T4 and free T3 levels and an increase in TSH levels (Toft *et al.* 2006).

Glyphosate-based herbicides (GBHs) are among the most widely used pesticides in the world, and they cause several types of endocrine disruption (Toft *et al.* 2006, Bai & Ogbourne 2016). de Souza demonstrated that glyphosate could also disrupt the HPT axis (Fig. 1) (de Souza *et al.* 2017). The hormonal profiles of the exposed group showed decreased TSH concentrations, with no variation in the levels of THs. In addition, hypothalamic gene expression analysis of the exposed group revealed that there was a reduction in the expression of genes encoding DI 2 (*Dio2*) and 3 (*DIO3*), and TH transporters *Slc1c1* (formerly *Oatp1c1*) and *Slc16a2* (formerly *Mct8*). On the other hand, in the pituitary of the exposed group, *Dio2*, *Thr* (*Thra1* and *Thrb1*), and *Slc16a2* genes were expressed at higher levels. Thus, the role of GBH exposure on HPT axis disruption should be considered in populations exposed to these herbicides (de Souza *et al.* 2017).

Dimethoate is an organophosphate insecticide used to kill mites and aphids and is applied to crops such as citrus, cotton, fruit, olives, potatoes, tea, tobacco and vegetables.

Dimethoate was classified as an endocrine disruptor after studies showed that the treatment of lactating rats with the insecticide resulted in reduced TH secretion in pups, as well as increased plasma T3 and T4 levels and reduced iodine uptake (Mahjoubi-Samet *et al.* 2005).

Fipronil is used worldwide as an insecticide. It is most commonly applied to crops such as corn, sunflowers, apples, rice and beans and is also used for household and veterinary pest control (Tingle *et al.* 2003). It accumulates in adipose tissue and the brain (Hainzl & Casida 1996, Simon-Delso *et al.* 2015). An *in vitro* study using fipronil and its metabolites showed that fipronil sulfone had anti-THR alpha activity (Lu *et al.* 2015). It also has been associated with an increase in the incidence of thyroid tumors in rats, decreased plasma T4 concentrations and increased T4 clearance in the rat liver, but these effects have not been observed in occupationally exposed humans (Takagi *et al.* 2002, Blair *et al.* 2005, Leghait *et al.* 2009, Herin *et al.* 2011). These different results might be related to the exposure dosage of the toxicant and the metabolites present in different environments (Leghait *et al.* 2010).

Ioxynil (IOX) is an iodine-containing herbicide used for the control of weeds (Takahashi *et al.* 2010). Ioxynil has been shown to bind to the TH transporter protein TBPA, in different species (Ogilvie & Ramsden 1988, Akiyoshi *et al.* 2012). It has also been shown to cause epigenetic changes in DNA, resulting in post-receptor changes (Otsuka *et al.* 2014).

Mancozeb is an agricultural fungicide that, at different oral doses, shows the ability to reduce iodine uptake and reduce serum T4 levels in dams and adult rats (Kackar *et al.* 1997, Axelstad *et al.* 2011). In addition, a study of the thyroid axis using adult male birds exposed to Mancozeb for 30 days showed an increase in thyroid size, an increase in plasma TSH levels and a decrease in T4 and T3 levels, mainly during the breeding phase (Pandey & Mohanty 2015).

Other widely used pesticides as acetochlor, amitrole and cyhalothrin have been tested in zebrafish and amphibian models and have been shown to affect the development and metamorphosis (Crump *et al.* 2002, Helbing *et al.* 2006, Pan *et al.* 2011, Tu *et al.* 2016), as well as the expression of a large group of genes that could affect HPT axis and thyroid function (Li *et al.* 2009, Pan *et al.* 2011, Tu *et al.* 2016, Yang *et al.* 2016, Chang *et al.* 2018). However, studies in mammals and humans are necessary to further study the impact of the use of these pesticides.

Thus far, compelling evidence has been presented on pesticides as endocrine disruptors; however, more

toxicology screening is needed to identify the toxicity levels and elucidate the mechanisms underlying the effects of these pesticides.

Polybrominated diphenyl ethers

There are over 200 brominated flame retardant (BFR) compounds that are used in many industrial applications (de Wit 2002, de Wit *et al.* 2006, Kabir *et al.* 2015). Polybrominated diphenyl ethers (PBDEs) are the most common chemicals used BFRs (Mazdai *et al.* 2003, Streets *et al.* 2006, de Wit *et al.* 2010, Covaci *et al.* 2011). As a consequence, PBDEs are present in plastics, paints, textiles, furniture and other items. In general, they are commercially available in mixtures classified as pentaBDE, octaBDE and decaBDE (Talsness 2008). The compound 2,2',4,4',5-pentaBDE (BDE-99) is one of the most prevalent congeners found in humans, and the presence of PBDEs in pregnant women, the accumulation and transfer of this compound from the mother to the infant through the placenta and breast milk has been a concern of society for more than 10 years (Gomara *et al.* 2007, Schuhmacher *et al.* 2009).

Several published studies have shown a correlation between PBDE levels and changes in thyroid function to different degrees (Turyk *et al.* 2008, Chevrier *et al.* 2010, 2011, Zhang *et al.* 2010, Lin *et al.* 2011, Zota *et al.* 2011). How PBDE affect thyroid function is still unclear. It has been suggested that due to the chemical nature of PBDEs, this chemical could bind directly to THR and affect the expression of T3 target genes (Fig. 2). In an *in vitro* study, Ren demonstrated that lower-brominated OH-PBDEs bind the inner side of the THR-binding pocket, acting as agonists (Ren *et al.* 2013). Additionally, as hydroxylated metabolites of PBDE, OH-PBDEs are structurally similar to T3 and can compete to bind to THR (Kojima *et al.* 2009, Schreiber *et al.* 2010). However, the relationship between PBDEs and thyroid function was suggested based on the cognitive alterations, as many studies showed cognitive alterations associated with impaired TH function (Bowers *et al.* 2015). Single doses of 2,2',4,4'-terabDE (BDE-47) on PND 10 (Dingemans *et al.* 2007) or chronic administration of decaBDE (BDE 209) during rat gestation (Xing *et al.* 2009) caused reductions in levels of a key factor in learning and memory, brain-derived neurotrophic factor (BDNF), which is regulated by THs (Koibuchi *et al.* 1999, Gilbert & Lasley 2013, Shulga & Rivera 2013). Blanco and collaborators treated pregnant rats from embryonic day 6 (E6) to PND 21 and observed a delay in the spatial learning task in the water maze concomitant with decreased BDNF

levels in the hippocampus (Blanco *et al.* 2013). Effects on cognitive function, a downregulation of BDNF and a concomitant decrease in TH serum levels have been reported in several papers (Kodavanti & Derr-Yellin 2002, Darnerud *et al.* 2007, Bowers *et al.* 2015).

However, there is controversy regarding the effect of the PBDEs on serum TH levels in animal models depending on the specific chemical, administration time and dose, as well as the hormone that is being evaluated. The majority of the papers found a decrease in total serum T4 levels (Stoker *et al.* 2004, Kuriyama *et al.* 2007, van der Ven *et al.* 2008, Blanco *et al.* 2013, Kim *et al.* 2013, Bowers *et al.* 2015) and total and free T3 levels (Stoker *et al.* 2004, van der Ven *et al.* 2008, Blanco *et al.* 2013, Bowers *et al.* 2015). A few papers have shown an increase in TH level (Reverte *et al.* 2014) or no correlation at all (Huang *et al.* 2014).

The decrease of serum TH levels could be explained by impaired TH biosynthesis impairment (Fig. 2). However, very few studies have found changes in the thyroid. Rats exposed to BDE-47 showed a significant increase in the presence of cellular debris in the follicular lumen (+71%), together with a decrease in iodide uptake (Maranghi *et al.* 2013, Wu *et al.* 2016). However, no effect on TPO activity was observed (Wu *et al.* 2016).

As discussed before, the effects of THs may be affected by cellular metabolism of T4 and T3, as well as interactions with THR (Fig. 2). Several papers studied alterations in D1 activity and THR expression in different animal models, such as birds, zebrafish and others organisms (Butt *et al.* 2011, Butt & Stapleton 2013, Francois & Verreault 2018). However, few studies have addressed these points in rodent models.

In vitro, PBDEs decreased DIO1 activity in liver cells (Butt *et al.* 2011) and DIO2 activity in cultured human glial cells (Roberts *et al.* 2015). The possible mechanism for this inhibition was suggested by Marsan and Baise who showed that OH-PBDEs compete with THR through D1s (Marsan & Bayse 2017).

Although PBDEs consistently cause a decrease in the serum levels of THs in rodent models, in humans, many epidemiological papers present inconsistent results (Turyk *et al.* 2008, Chevrier *et al.* 2010, 2011, Han *et al.* 2011, Lin *et al.* 2011, Kim *et al.* 2012, 2013, 2015). The differences in the evaluations of cause and effect from these contradictory results can be explained by the highly complex correlations that are possible with over 200 different PBDEs. For example, serum T3 levels were positively correlated with BDE-99 and BDE-209 and negatively correlated with BDE-17, BDE-28, BDE-47, BDE-183 and pentaPBDEs (Huang *et al.* 2014).

In a Canadian Study evaluating pregnant women, there was a negative association between PBDEs and serum total and free T3 levels (Abdelouhab *et al.* 2013). In contrast with these studies, Bloom and collaborators observed an increase of free T3 levels with an increase of PBDEs in older women (Bloom *et al.* 2014). On the other hand, Leonetti found no correlation between BRFs and THs in the placenta (Leonetti *et al.* 2016). However, a positive association with HO-tetraBDEs and TSH was found in thyroid cancer patients with a decrease in free T4 levels (Liu *et al.* 2017).

The explanation for low levels of THs could be decreases in biosynthesis and secretion by the thyroid caused by direct effects on the gland or a decrease in TSH stimulation of the thyroid (Fig. 1). However, there are once again many inconsistencies in the results. TSH was correlated with BDE-17, BDE-28, BDE-47 and BDE-183 and inversely correlated with BDE-99 (Huang *et al.* 2014). However, in cancer patients, Liu and collaborators showed a positive correlation of HO-tetraBDEs and TSH (Liu *et al.* 2017).

It is important to note that TH levels in blood are tightly regulated within an individual; hence, intra-individual variation would often be negligible compared to the inter-individual variation or the wide range of reference values. Therefore, it has been suggested by some authors that small changes in TH levels in response to exposure to environmental chemicals may not be easy to detect in small human population (Boas *et al.* 2012). Recently, to try to end this controversy, a meta-analysis was published, indicating that the effect of PBDEs on thyroid function depends on the PBDE exposure dose and its serum levels, suggesting a u-shaped curve (Zhao *et al.* 2015).

Take home message

Here, we reviewed a relevant group of thyroid disruptors to which the general population is exposed to daily. These compounds are present not just in industrialized food but also in fresh preparations. Controlling the consumption of natural bioactive compounds by a population is difficult so increase the population's awareness of their potential undesirable effects is fundamental. On the other hand, there is an enormous amount of data proving the deleterious effects of the chemicals, and as a consequence, several of them have already been banned from industrial processes or have an identified reference exposure dose. It is important to note that these reference exposures dose values are based on regulatory and often non-comprehensive tests that not

always take into account how the endocrine system works, especially the thyroid gland.

THs are vital for neurological development in the early stages of life (Bernal 2017), and several studies have shown that low doses of these chemicals, closer to the usual environmental contamination dose, have effects on the endocrine system, particularly in developmentally vulnerable windows (Vandenberg *et al.* 2012).

Thyroid function is essential during all stages of life as it affects growth, development, metabolism and the cardiovascular and immune systems, and the continuous exposure to natural and artificial thyroid disruptors will deeply affect quality of life.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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