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Review

Thyroid under Attack: The Adverse Impact of Plasticizers, Pesticides, and PFASs on Thyroid Function

Vinicius Gonçalves Rodrigues [1,2,†], Guilherme Henrique [1,2,†], Érica Kássia Sousa-Vidal [3], Rafaela Martins Miguel de Souza [1,2], Evelyn Franciny Cardoso Tavares [1,2], Nathana Mezzalira [1,2], Thacila de Oliveira Marques [1,2], Bruna Monteiro Alves [1,2], João Anthony Araújo Pinto [1,2], Luana Naomi Niwa Irikura [1,2], Renata Elen Costa da Silva [1], Kelly Cristina de Oliveira [1], Rui Monteiro de Barros Maciel [1], Gisele Giannocco [1,2] and Caroline Serrano-Nascimento [1,2,*]

[1] Laboratório de Endocrinologia Molecular e Translacional (LEMT), Departamento de Medicina, Escola Paulista de Medicina, Universidade Federal de São Paulo, Sao Paulo 04039-032, SP, Brazil
[2] Laboratório de Fisiologia e Fisiopatologia da Tireoide (LaFFT), Departamento de Ciências Biológicas, Instituto de Ciências Ambientais, Químicas e Farmacêuticas (ICAQF), Universidade Federal de São Paulo, Diadema 09972-270, SP, Brazil
[3] Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, Sao Paulo 05652-900, SP, Brazil
* Correspondence: caroline.serrano@unifesp.br
† These authors contributed equally to this work.

Abstract: Endocrine-disrupting chemicals (EDCs) are synthetic or natural compounds that interfere with the endocrine system, inducing harmful effects on organisms depending on the dose and period of exposure. Numerous studies have identified concerning amounts of EDCs in environmental and human samples. The thyroid gland is essential for thyroid hormone production and controls several body functions. Several EDCs have been classified as thyroid disruptors, impairing thyroid hormone production, synthesis, metabolism, transport, and/or actions. Notably, thyroid disorders are the second most prevalent endocrine disease worldwide, with incidence increasing significantly in recent years. Some studies have correlated this rise in thyroid dysfunctions and cancers with increased exposure to EDCs. Although many EDCs are linked to thyroid dysfunction, this review focuses on the deleterious effects of plasticizers, organochlorine pesticides, and per- and poly-fluoroalkyl substances on thyroid function. These contaminants are commonly found in food, water, and everyday products. Although the impact of human exposure to these EDCs is controversial, numerous epidemiological, in vivo, and in vitro studies have indicated their harmful effects on thyroid function. Given the critical role of thyroid function and hormone production in growth, metabolism, and development, this review summarizes the consequences of exposure to thyroid disruptors for human health.

Keywords: endocrine disruptors; thyroid; bisphenol A; phthalates; DDE; PFASs

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1. Introduction

Endocrine-disrupting chemicals (EDCs)—also known as endocrine disruptors, endocrine toxins, or xenohormones—are natural or synthetic substances that interfere with various aspects of endocrine function, causing adverse effects on growth, development, reproduction, and metabolism [1]. Human exposure to these chemicals has been related to systemic repercussions of varying severity, depending on the duration and the developmental stage at which the individual is exposed [2,3]. Indeed, in recent years, there has been a significant increase in epidemiological data and animal studies demonstrating the harmful health effects of EDC exposure. In this context, epidemiological studies indicate an increase in the incidence and prevalence of diseases associated with EDC exposure, such as breast, thyroid, prostate, and testicular cancers, diabetes, obesity, and decreased fertility over the past 50 years [4].

The most well-known mechanism of action of these compounds involves their binding to hormone receptors, such as estrogen, androgen, progesterone, and thyroid hormone (TH) receptors. Additionally, the actions of EDCs involve their binding to other nuclear receptors, membrane receptors, neurotransmitter receptors (such as serotonin, dopamine, and norepinephrine), and orphan receptors. Furthermore, EDCs trigger the activation/inactivation of enzymatic pathways involved in hormone metabolism and synthesis [5].

Unlike adults, newborns and children are more susceptible to the harmful actions of EDCs, primarily because the metabolizing pathways of these substances are immature in these individuals [6]. Moreover, embryos, fetuses, and newborns are adversely impacted by maternal exposure to these contaminants, which are transferred through the placenta and maternal milk [7]. Consequently, these individuals become more vulnerable to hormonal, immunological, and neurological alterations during critical stages of their development [8]. In agreement, studies have shown that EDC exposure during intrauterine and neonatal lives is related to several diseases during adulthood [9–11]. In this context, it is noteworthy that a growing number of studies emphasize the importance of the intrauterine period for the programming of genes that influence an organism's susceptibility to diseases in adulthood [12,13]. Therefore, several studies have highlighted the crucial role of epigenetic mechanisms in regulating gene expression during these critical developmental periods, when the organism is most vulnerable to environmental and nutritional stressors [14–16]. These regulatory mechanisms of gene expression include alterations in DNA methylation/demethylation, post-translational modifications of histones, and differential expression of noncoding RNAs [17–20]. Interestingly, studies have indicated that maternal exposure to EDCs during pregnancy triggers epigenetic modifications in the placenta and the fetus, altering gene expression and compromising fetal development [21–23]. These alterations can persist throughout an individual's life and may even affect gene expression and development in subsequent generations as multigenerational and transgenerational effects [24,25].

The thyroid gland is histologically organized into thyroid follicles, which are formed by a layer of cuboidal epithelial cells, the thyrocytes, that surround a luminal region filled with colloid, primarily composed of thyroglobulin (TG). TH synthesis depends on the expression and activity of several proteins [26]. The sodium–iodide symporter (NIS), located on the basolateral membrane of thyrocytes, mediates the uptake of iodide from the bloodstream, transporting it into the cell alongside two sodium ions [27]. Iodide is then transported to the luminal region via the activity of channels present in the apical membrane, such as pendrin and anoctamin-1 [28]. In the follicular lumen, iodide is oxidized to iodine by the activity of thyroid peroxidase (TPO) and incorporated into tyrosine residues of the TG molecule, forming diiodotyrosine and monoiodotyrosine. TPO is also responsible for coupling iodotyrosine to form iodothyronines, which are the actual THs: diiodothyronine (T2), triiodothyronine (T3), thyroxine (T4), and reverse T3 [29]. Upon secretion stimulation, colloid is endocytosed by the microvilli of the apical portion and processed in intracellular phagolysosomes. The T3 and T4 released from TG molecules are then secreted into circulation through the monocarboxylate transporter 8 (MCT8) [30] (Figure 1).

THs play a fundamental role in growth, metabolism, and fetal development and maturation, particularly in the central nervous system (CNS) [31]. TH actions are complex and rely on the expression of TH receptors, transporters, and deiodinases, which either activate or inactivate these hormones within target cells [32] (Figure 2).

It is worth noting that thyroid function is finely regulated by the hypothalamic–pituitary–thyroid (HPT) axis. Parvicellular neurons of the hypothalamus secrete the thyrotropin-releasing hormone (TRH) in the median eminence region, which reaches the anterior pituitary through the hypophyseal portal system. In thyrotropes, the TRH binds to membrane receptors and stimulates the synthesis and secretion of the thyroid-stimulating hormone or thyrotropin (TSH). Once released into circulation, the TSH reaches the thyroid, where, by binding to its receptor, TSHR, it stimulates all steps involved in the synthesis

and secretion of THs. THs, in turn, feedback to the system, inhibiting the synthesis and secretion of the TRH in the hypothalamus and the TSH in the pituitary, in a mechanism known as negative feedback [33].

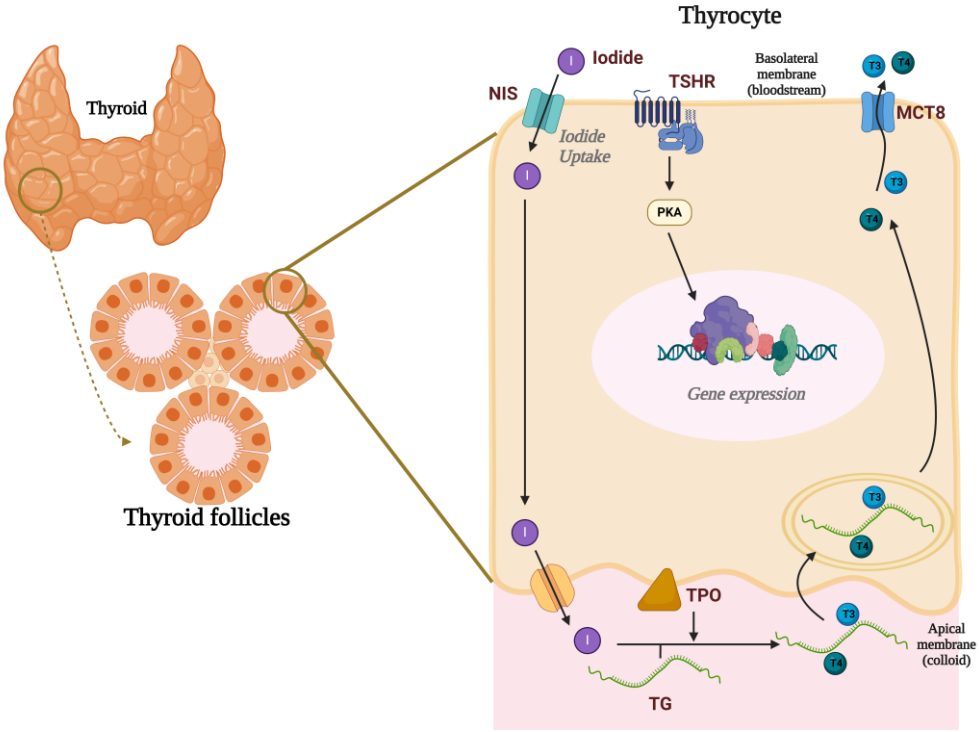

Figure 1. Thyroid gland and thyroid hormone synthesis. The thyroid gland is organized into thyroid follicles, which consist of a single layer of cuboidal epithelial cells known as thyrocytes surrounding a lumen filled with colloid. The uptake of iodide, mediated by the sodium–iodide symporter (NIS), is the first rate-limiting step in thyroid hormone (TH) synthesis. Iodide is then transported into the lumen via pendrin and anoctamin-1, where thyroid peroxidase (TPO) oxidizes iodide to iodine. TPO also catalyzes the incorporation of iodine into tyrosine residues on thyroglobulin and couples iodotyrosines to form the thyroid hormones T3 and T4. Upon stimulation by TSH, T3 and T4 are secreted into the bloodstream via the monocarboxylate transporter 8 (MCT8). Created with Biorender.com.

Interestingly, until the 12th–16th week of gestation, the fetus relies exclusively on THs produced by the mother, and even mild alterations in maternal TH levels during this period result in adverse consequences for fetal development [34]. The transfer of maternal THs to the fetus occurs through the placenta, due to the expression of specific thyroid transporters and deiodinases in the chorionic villi [35]. In addition to their direct role in fetal development, THs have important effects on the placenta's metabolism, differentiation, and development [36,37]. Therefore, TH transport across the placenta is a critical step for the adequate development and function of fetal and placental tissues. Accordingly, previous studies have shown an increased incidence of clinical complications during pregnancy associated with poor placentation in patients with untreated thyroid disorders [38,39].

More than 100 natural and synthetic compounds have been classified as thyroid disruptors [40,41] (Figure 3).

Importantly, a study conducted by the European Union indicated that the costs related to impaired neural development and IQ loss attributed to two thyroid disruptors (flame retardants and organophosphate pesticides) would exceed EUR 150 billion per year [42].

In this context, several studies have described the interfering effects of several EDCs such as phthalates, bisphenol A, organochlorine pesticides, and per- and poly-fluoroalkyl substances on thyroid function. This review will focus on those EDCs.

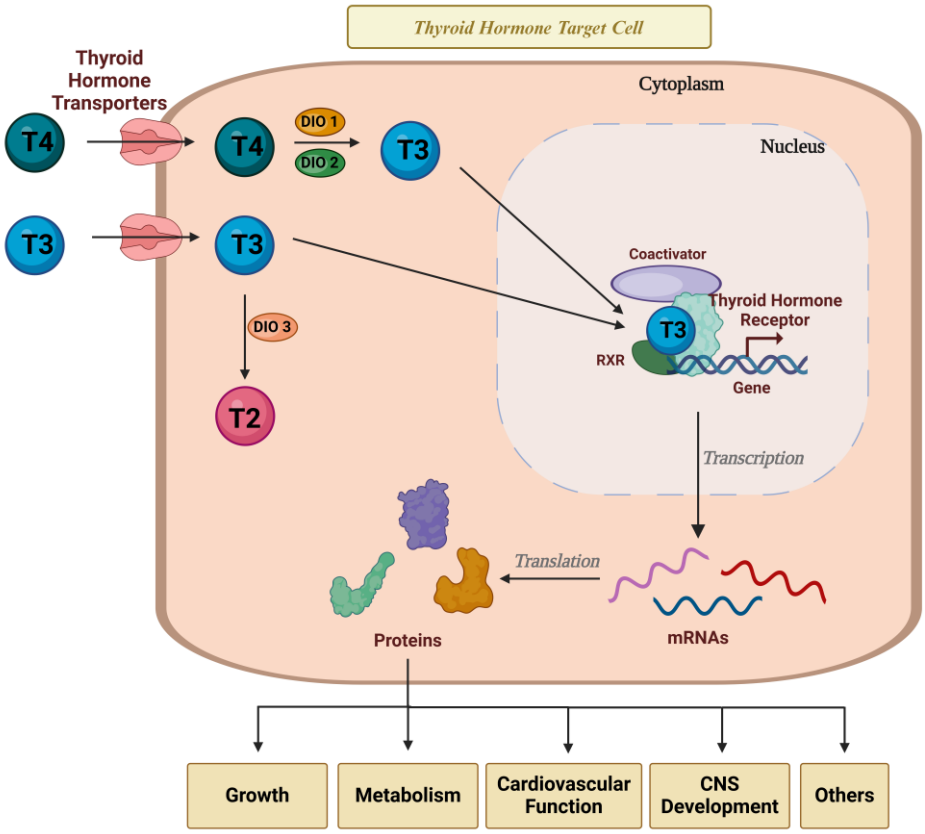

Figure 2. Thyroid hormone action in target cells. THs are essential for controlling the metabolism, growth, and development of several tissues in the body. TH action depends on the expression and activity of TH transporters, TH receptors, and deiodinases in the target cells. Created with Biorender.com.

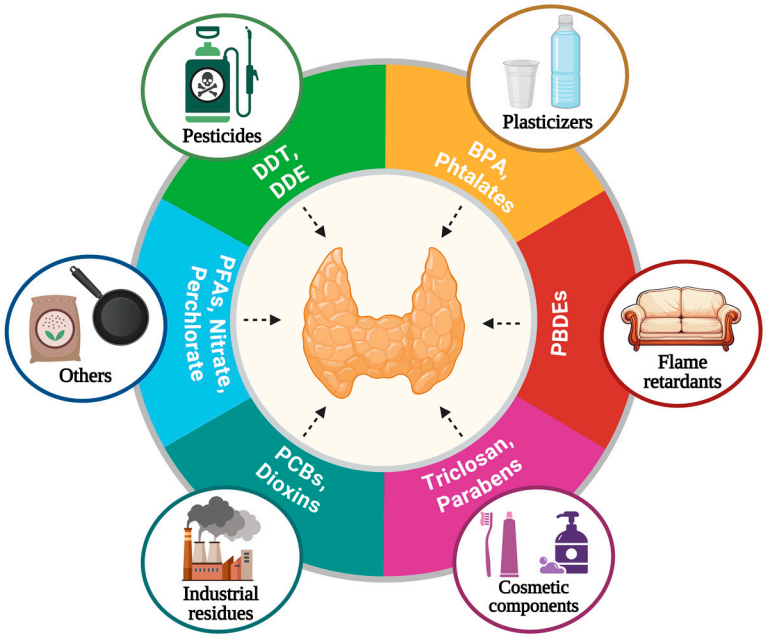

Figure 3. Thyroid disruptors. EDCs are found in food, water, and everyday products and several studies indicated that some of them interfere with the synthesis, secretion, transport, and action of thyroid hormones. BPA: bisphenol A., PBDEs: polybrominated diphenyl ethers, PCBs: polychlorinated biphenyls, PFASs: per- and polyfluoroalkyl substances, DDT: dichloro-diphenyl-trichloroethane, DDE: dichlorodiphenyldichloroethylene. Created with Biorender.com.

1.1. Phthalates

Plasticizers are essential compounds in the production of plastic products, enhancing flexibility, durability, and overall quality. Consequently, the demand for plasticizers continues to rise, with the plastic industry using approximately 8.23 million tons in 2020 and projected to reach up to 12.9 million tons by 2030 [43]. Due to their highly stable properties, phthalates are widely used to increase the flexibility of plastics in various commercial products such as toys, construction materials, personal care products, cosmetics, food preservation films, detergents, and medical devices [44,45].

Phthalates are a group of chemical compounds derived from phthalic acid, produced as diesters, and rapidly metabolized to monoesters upon entering the body [46]. The most used plasticizer is di(2-ethylhexyl) phthalate (DEHP). Human exposure to phthalates mainly occurs via ingestion, inhalation, and dermal routes. Numerous studies worldwide have detected DEHP metabolites in urine, blood, hair, amniotic fluid, and breast milk, confirming widespread human contamination of phthalates and their metabolites [47–51].

Phthalates Exposure and Thyroid Dysfunction

Several human studies have demonstrated associations between DEHP exposure and alterations in T3, T4, and TSH concentrations in pregnant women, newborns, and children [52–54]. Furthermore, in the general population, urinary concentrations of DEHP metabolites have shown a negative correlation with T4 and T3 levels [55–58].

In vivo and in vitro studies have explored the disruptive mechanisms induced by phthalates in the thyroid gland.

Indeed, chronically phthalate-exposed animals presented a significant reduction in T4 levels, and alterations in thyroid organelles morphology [59,60]. In agreement, di-n-butyl phthalate (DBP) administration caused a dose-dependent decrease in serum T3 and T4 concentrations at all studied doses. Nonetheless, DBP-treated animals have not presented alterations in TSH serum levels and thyroid weight [61]. Moreover, co-exposure to high iodine levels and DBP in an autoimmune thyroid disease model was linked to increased thyroid damage and a disruption of TH levels [62].

Furthermore, DEHP-exposed animals presented increased oxidative markers in serum, altered thyroid morphology with signs of necrosis, and the infiltration of inflammatory cells in the follicular epithelium [63–65]. In selenium-deficient conditions, DEHP altered the antioxidant status and induced oxidative stress in the thyroid gland of rats by increasing superoxide dismutase activity and thiobarbituric acid reactive substance levels [66,67]. In consonance, selenium and curcumin nanoparticles improved thyroid parameters and the redox status in DEHP-exposed animals [68].

Additionally, data indicated that the TH serum level reduction induced by phthalate exposure depends on the disruption of TH synthesis, transformation, transport, receptor levels, and peripheral metabolism [69–73]. In this regard, in vitro studies indicated that phthalate exposure significantly enhanced iodide uptake, altered TSHR expression, and interfered with TH actions in target cells [74–76].

Importantly, the disruption of the HPT axis caused by exposure to phthalates during critical developmental periods is particularly concerning. In this context, recent studies demonstrated that intrauterine and/or neonatal exposure to DEHP significantly increased the offspring's susceptibility to developing thyroid dysfunctions during life [77–81].

Finally, a pair-matching case–control study found a positive association between urinary phthalate metabolites and the risk of developing papillary thyroid cancer [82]. In this context, it has been demonstrated that DEHP-induced thyroid hyperplasia occurs through the eicosanoid-associated pathway and suggested that this exposure could be associated with thyroid cancer [83].

In summary, phthalates, particularly DEHP, have been linked to thyroid dysfunction and an increased risk of thyroid cancer in both humans and animal models. However, the molecular mechanisms underlying these disruptions are not yet fully understood, highlighting the need for further research to clarify them.

1.2. Bisphenols

Bisphenol A (BPA) is a ubiquitous industrial plasticizer compound used in polycarbonate plastics, epoxy resin, food can linings, and dental sealants [84,85]. BPA was consistently found in urine, and serum samples from humans, in both adults and newborns [86–88]. Besides its estrogenic properties, it is well described that BPA acts as an antagonist of THs by binding to their nuclear receptors in target cells [89,90]. In agreement, it has been demonstrated that BPA interacts with the TH receptor beta (THRB) and induces its translocation to the nucleus [91]. Furthermore, low concentrations of BPA (10^{-9} M) suppressed TH receptor transcription by disrupting the physiological concentrations of the T3/T4-mediated β3 integrin/c-Src/MAPK/TR-β1 pathway, offering novel insights into the molecular mechanisms involved in BPA-mediated TH disruption [92].

1.2.1. BPA Effects in Pregnant Women and Their Progeny

Epidemiological studies have demonstrated inconclusive data about BPA exposure and thyroid function in newborns, children, adolescents, and adults.

A study found a suggestive inverse relationship between urinary BPA and total T4 and TSH in samples of U.S. adults and adolescents [93]. Another study indicated a negative correlation between serum BPA and free T4 levels in men, but not in women. Additionally, no associations were found between BPA and TSH levels in either gender [94]. A recent systematic review and meta-analysis found that the BPA concentration was negatively correlated with free T4 and TSH in males, while in females, it was positively correlated with free T4 [95].

This gender-specific response was also found in the CHAMACOS study that associated intrauterine exposure to BPA with reduced T4 in pregnant women and decreased the TSH in male neonates, but not in female ones [96]. Conversely, the HOME study indicated a negative correlation between maternal BPA exposure and the TSH in newborn girls, but not in newborn boys, especially in iodine-deficient mothers [97]. In a Korean study, BPA exposure was negatively associated with TSH levels, but no significant associations were found in TH levels [98]. In agreement, BPA cord blood levels were not associated with TH serum concentrations in newborns in two other studies [99,100]. Interestingly, maternal exposure to BPA, during the first trimester, and to bisphenol S (BPS), throughout all three trimesters, was associated with increased TSH levels in newborns [101].

BPA exposure was also associated with TPOAb positivity in both men and women. However, the mechanisms involved in the development of autoimmune thyroid disease in BPA-exposed individuals need to be further explored [102].

1.2.2. BPA Exposure and Thyroid Cancer

Regarding thyroid cancer, the exposure to environmentally significant concentrations of BPA synergizes with the BRAFV600E mutation, promoting epithelial–mesenchymal transition through the activation of the ERK signaling pathway in the human thyroid follicular epithelial cell line Nthy-ori 3-1 [103].

In a DMD-induced cancer protocol, BPA exposure alone increased the incidence of thyroid tumors in female rats, and co-exposure with DEHP enhanced the effect of BPA on cancer promotion. In vitro data of the same study indicated that the HDAC6/PTEN/AKT pathway is involved in BPA-MEHP enhanced proliferation and the migration of human thyroid cancer cells BCPAP [104].

In humans, the data about thyroid cancer and BPA are still inconsistent. In this regard, elevated urinary levels of BPA and BPS were associated with increased urinary levels of oxidative stress biomarkers and an enhanced risk of thyroid cancer. Furthermore, BPA exposure in overweight and obese individuals was significantly associated with higher TSH levels, suggesting it may be a risk factor for developing thyroid nodules [105]. Nevertheless, a recent meta-analysis study did not find a significant association between BPA exposure and thyroid cancer [106].

1.2.3. BPA Exposure Effects in Animal Models and In Vitro Studies

The results of BPA exposure during critical development periods in animal models are controversial.

Perinatal exposure to BPA (0, 4, or 40 mg/kg body weight per day) did not alter T4 serum levels or thyroid gland response to the TSH in the offspring rats [107]. Conversely, pregnant rats exposed to BPA (20 or 40 µg/kg body weight) from GD1-20 showed reduced T4 and T3 serum levels and elevated TSHs in the dams and their offspring. In addition, histopathological changes were observed in the thyroid of BPA-exposed animals, such as fibroblast proliferation, follicular hyperplasia, degeneration, and luminal obliteration [108]. In female Sprague–Dawley rats exposed to BPA injections during the neonatal period, TSH levels remained unchanged until PND13. However, these animals exhibited reduced T4 levels and increased TSH levels during adulthood [109]. Moreover, maternal exposure to low doses of BPA during intrauterine and neonatal periods did not alter TH levels in the dams. However, it reduced serum T4 levels in male and female offspring rats during adulthood, particularly at the lowest treatment dose (10 µg/kg/day) [110].

Another study indicated that BPA exposure led to a 30% decrease in total and free T4 levels in pregnant ewes and their newborns and that BPA exposure in long-gestation species can be linked to hypothyroidism in newborns, posing a potential risk for human BPA exposure [111]. Consistently, a study from the same group showed that exposing pregnant ewes to BPA at concentrations similar to those reported in epidemiological studies decreased TH levels without significantly altering TSH [112].

Additionally, BPA decelerated T4-induced changes, reduced the expression of TH receptors, and inhibited the expression of T3-regulated genes in animals that depend on THs for metamorphosis processes [113–115]. A recent study has shown that besides the reduction in whole-body T4 levels in zebrafish (*Danio rerio*), BPA exposure up to 8 days post-fertilization altered retinal layering, decreased motility across varying light conditions, and impaired responsiveness to red light, suggesting compromised neurodevelopment [116].

Even though the effects of BPA exposure on thyroid function have been extensively described in the literature, the molecular mechanisms involved in BPA-induced thyroid dysfunction are not completely comprehended. In vitro studies have shown that BPA interferes with the synthesis of THs by decreasing the expression of genes related to thyroid differentiation and function, such as NIS, TPO, TSHR, and TG, and increasing the expression of genes related to cell death and DNA damage [117–119]. Moreover, data from in vivo and in vitro studies demonstrated that BPA exposure increased thyroid production of reactive oxygen species, which could be related to thyroid damage [120].

1.2.4. Bisphenol Analogs and Thyroid Dysfunction

It is worth noting that BPA analogs, such as BPS, tetrabromobisphenol A (TBBPA), tetrabromobisphenol S (TBBPS), and bisphenol F (BPF), have also been associated with thyroid function disruption.

In this regard, both in vivo and in vitro studies have shown that BPS and BPF disrupt the TH signaling pathway by activating TH-controlled gene transcription in the absence of T3 and displaying both agonistic and antagonistic actions in the presence of this hormone [121]. In accordance, it has been shown that using a T3-induced metamorphosis assay that high concentrations of BPF (100–10,000 nM) antagonizes T3-controlled gene transcription and morphological changes. On the contrary, BPF, at low doses, stimulates T3-induced metamorphosis while inhibiting T3-induced gene transcription [122].

Interestingly, an in silico study suggested that BPA and BPS interact with thyroid transcription factors NKX2.1 and PAX8, elucidating part of the molecular mechanisms involved in BPA-elicited thyroid disruption [123].

Finally, mice exposed to TBBPS and BPS presented increased levels of TSH, altered thyroid morphology, and reduced expression of the proteins involved in TH synthesis, but showed no significant alterations in T3 and T4 levels [124].

Therefore, the data strongly indicate that BPA and its analogs are significant disruptors of thyroid function, with far-reaching implications for both human and other animals' health. BPA's ability to bind to TH receptors and thyroid transcription factors highlights its potent role in altering thyroid signaling pathways and gene expression. Despite the extensive data about BPA effects, particularly about thyroid dysfunction and cancer, the underlying molecular mechanisms remain incompletely understood. Moreover, inconsistent findings in epidemiological studies, particularly regarding gender-specific responses and the impact on thyroid function in various populations, underscore the complexity of BPA effects. Additionally, the emerging evidence of BPA analogs, such as BPS and BPF, disrupting thyroid function further amplifies this concern. These analogs not only mimic the actions of BPA but also exhibit unique disruptive properties, suggesting a broader environmental and public health challenge. Future research should prioritize unraveling the precise molecular pathways involved in BPA and its analogs' thyroid-disruptive effects, particularly focusing on vulnerable populations like pregnant women and developing fetuses, to better inform regulatory policies and protective measures.

1.3. Organochloride Pesticides (OCPs)

OCPs, such as dichlorodiphenylotrichloroethane (DDT), widely used during World War II, were banned in developed countries in the 1970s, but are still used in several developing countries to combat disease vectors [125]. The main metabolite generated from DDT is DDE (dichlorodiphenyldichloroethylene). Both are highly stable, persistent in the environment and accumulate in the fatty tissue of humans and other animals [126,127]. Human exposure to these pesticides occurs mainly through consuming contaminated food and water [128,129].

DDT and DDE have a similar chemical structure to THs [130]. For this reason, they are described as potential disruptors of TH synthesis, action, and metabolism. Consistently, it has been suggested that OCPs affect serum TH levels by interacting with specific hormone-binding proteins, such as thyroxine-binding globulin (TBG) and transthyretin (TTR) [131,132].

1.3.1. OCP Exposure and Thyroid Dysfunction in Humans

DDT and its metabolites cross the placenta and have been found in breast milk samples [133,134]. Moreover, it has been reported that maternal exposure to DDT increased the methylation of the DIO3 and MCT8 genes in the placenta of humans in a sexually dimorphic manner, potentially compromising TH metabolism and action in placental and fetal tissues [135]. Interestingly, paternal exposure to DDT is also associated with disruptions in placental growth and function, affecting metabolic parameters in male offspring but not in females [136].

Previous studies have demonstrated a negative association between free T4 concentrations and serum levels of DDE in pregnant women and newborns [137,138]. Analyses of umbilical cord samples reinforced that high levels of OCPs correlate with low serum TH concentrations, especially T4, in newborns [139,140]. Conversely, it has been shown that intrauterine exposure to DDT influences fetal growth without interfering with maternal TH levels [141,142]. In addition, TSH levels were positively associated with pregnancy exposure to DDT [143,144].

Postnatal deleterious effects of OCP exposure on thyroid function have also been reported. Consistently, a negative correlation between maternal DDE/DDT exposure and birth weight, head circumference, and gestation time was observed in a Bolivian cohort [145]. In addition, newborns whose mothers had detectable levels of OCPs in serum presented decreased TH and GH levels in their umbilical cord blood samples.

Furthermore, it was suggested that the consumption of DDE-contaminated breast milk negatively affects the cognitive development of 10–12-month-old newborns [146]. Finally, detectable OCP levels in the peripheral blood of 4-year-old children reinforced the negative association between DDT exposure and total T3 serum levels [147].

The data about DDE exposure on adult human thyroid function are inconsistent. Some studies have not found any correlation between DDT/DDE contamination and thyroid disruption [148,149]. Contrarily, other studies have reported a negative correlation between DDE exposure and TH serum levels in adult individuals and a positive correlation between DDE contaminant and TSH levels [150–152]. In addition, in another study, DDT exposure was positively associated with T3 levels, and negatively associated with the TSH [153]. The inconsistency in data regarding DDE exposure and thyroid function in adults highlights the need for further research to clarify its true impact on thyroid health.

1.3.2. OCP Exposure and Thyroid Dysfunction in Animal Models

The exposure of zebrafish embryos/larvae to DDT and DDE increased malformations during embryonic development, altered the expression of genes involved in TH biosynthesis, and significantly reduced the total T3 content and the T3/T4 ratio in these animals [154].

Similarly, the chronic exposure of rats to DDE resulted in increased thyroid weight, reduced T3 and T4, and increased TSH serum levels [61,155]. Furthermore, rats exposed solely to DDE or DDE combined with PCB153 exhibited a significant reduction in total and free T4 levels, reduced TTR serum levels, and an increased expression of enzymes involved in the hepatic degradation of THs. Therefore, these data suggest impaired TH transport and peripheral metabolism in DDE-exposed animals [131,156].

Finally, rats exposed to DDE presented thyroid follicles with smaller lumens, various alterations in different organelles of thyrocytes, and the disrupted expression of enzymes involved in TH synthesis [157–160].

In summary, the evidence shows that OCPs, particularly DDT and its metabolite DDE, disrupt thyroid function in both humans and other animals. Although banned in many developed countries, DDT remains a concern due to its persistence and continued use in certain regions. While data in adults are inconsistent, DDE exposure has been linked to altered thyroid function, especially during pregnancy and early development, with potential long-term effects on cognitive development. Animal studies reinforce these findings, demonstrating significant changes in thyroid morphology and TH levels. These findings underscore the ongoing risks that OCP exposure poses to thyroid health.

1.4. Per- and Poly-Fluoroalkyl Substances (PFASs)

PFASs are a class of human-made chemicals characterized by the presence of at least one perfluoromethyl group (-CF3) or perfluoromethylene group (-CF2). PFASs are pollutants, highly persistent, odorless, colorless, and indestructible due to their thermal and chemical stability. They are globally used as surfactants in industrial production and are found in various consumer products, including packaging, non-stick cookware, waterproof makeup, clothing, adhesives, personal hygiene products, etc. Indeed, mixtures of PFASs are commonly found in drinking water, and serum PFASs are detected in up to 99% of the population [161,162]. The constant exposure of humans and animals to these EDCs raises serious concerns within the scientific community, given that their removal from the body can take years. Numerous studies indicate adverse health effects associated with this exposure, including thyroid dysfunctions, metabolic diseases, reproductive toxicity, and neurodevelopmental disorders [163,164].

Different generations of PFASs have been produced, and it has been demonstrated that each class triggers specific disruptive effects. Indeed, PFOA (perfluorooctanoic acid) is an older, long-chain PFAS that is listed as possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer [165,166].

1.4.1. PFASs Exposure and Thyroid Dysfunction in Humans

A possible link between exposure to some older-generation PFASs and thyroid disruption has been reported in several studies; however, data are still inconsistent.

Pregnant women exposed to different PFASs, especially perfluorooctane sulfonate (PFOS), presented slightly increased levels of TSHs [167]. In another study, only perfluorohexanesulfonic acid (PFHxS) concentrations were positively associated with maternal TSH serum levels. Moreover, higher levels of perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) were associated with reduced T4 levels in maternal and cord blood samples [168]. Conversely, in a study with 157 paired maternal and cord serum samples, the most prevalent PFASs, PFOS and PFOA, were negatively associated with maternal TSH levels, but no significant alterations were found in TH serum concentrations [169].

Results from the SELMA study indicated that, in 2008 pregnant women in the first trimester of gestation, PFAS exposure was not associated with alterations in the TSH. However, higher PFNA, PFDA, PFHpA, and PFOA levels were associated with increased free T4 and lower total T3 levels. In addition, higher PFUnDA levels were associated with lower free T3 and total T4 levels, and an inverted U-shaped curve association was described for PFOS exposure and total T4 levels [170].

Interestingly, PFAS mixture was not associated with maternal T4 or TSH levels in the Project Viva Cohort. However, isolated analysis revealed that PFOS was positively associated with T4 levels, and PFHxS demonstrated a non-linear effect on TSH levels [171]. In addition, in a study on 300 mother–infant pairs from the Shanghai-Minhang Birth Cohort Study, higher PFAS mixture concentrations were associated with increased T3 concentrations and high levels of PFNA and PFOA were associated with a decrease or increase in TSH concentrations, respectively [172].

A sex-dimorphic effect was observed in PFAS-exposed neonates as prenatal PFOS, PFOA, and PFHxS exposure was inversely associated with T4 levels in male neonates, but this association was not observed in female neonates [173]. Consistent with this dimorphic response, results from the Hokkaido Study revealed that maternal PFAS exposure was linked to higher TSH and lower free T3 levels in male neonates, whereas in female neonates, PFAS contamination was associated with lower TSH and higher free T3 levels [174].

As previously described, THs are essential for CNS development, and PFBS and PFHxS prenatal exposures were negatively associated with TSH and FT4 levels, and early neurodevelopment [175]. In agreement, prenatal exposure to PFASs was negatively associated with the IQ of school-aged children [176]. Moreover, PFAS levels were found to be significantly higher in infants with congenital hypothyroidism compared to those in the control group [177].

In the general population, PFAS exposure was detected in almost 99% of the samples in different studies, but few statistically significant associations were found between PFASs and TH levels in U.S. adults. PFASs were only associated with thyroid disruption in adults with high TPOAb and a low iodine status, which are commonly considered a vulnerable group for thyroid dysfunctions [178]. In agreement, a study conducted in a highly contaminated area did not find an association between TSHs and PFASs in adolescents or women [179].

Conversely, in female adolescents, serum PFOA and PFAS mixtures were associated with lower free T4 and higher free T3 levels. In male adolescents, PFOA was associated with lower free T4 levels and PFAS mixture was associated with higher TSH and a lower FT4/TSH ratio [180]. In the elderly, high levels of PFAS contamination were detected and associated with decreased TSH and free T4 levels, alongside increased total T4 and T3 levels [181].

It is important to reinforce that the inconsistent data about the consequences of human exposure to PFASs on the disruption of thyroid function may be associated with sample size, region, sample type, body mass index, and exposure period [182].

1.4.2. PFAS Exposure and Thyroid Dysfunction in Animal Models

In rodent models, PFAS exposure has been shown to alter circulating TH levels [183,184].

Interestingly, although PFOS exposure reduced TH levels and altered the expression of enzymes involved in TH clearance and metabolism, it was not associated with changes in TH-responsive genes in the rat liver [185]. Similarly, rats exposed for 7 days to 3 mg PFOS/kg/day presented differentially expressed genes in the hypothalamus, pituitary, thyroid, and liver in comparison to the control group, but none of them aligned with TH regulating genes [186].

In addition, in an ex vivo model, the exposure of fetal thyroid explants to low concentrations of PFOS reduced the expression of *Pax8* and cadherin-16, which control the apical–basal polarization of thyroid epithelial cells, suggesting that thyroid follicle organization may be disrupted by PFAS exposure during critical developmental periods [187].

Zebrafish exposed to PFASs also displayed alterations in TH levels [188,189]. In agreement, a study demonstrated that PFAS-exposed zebrafish embryos/larvae presented reduced T3 and T4 levels and altered expression of genes involved in the synthesis, regulation, and action of THs [190].

Conversely, although the exposure to some PFASs induced concentration-dependent developmental toxicity in *Xenopus laevis* embryos and larvae, no alterations were observed in thyroid endpoints [191]. Moreover, in rabbits, the exposure of dams to an environmentally relevant PFAS mixture did not alter T3 and T4 levels either in the dams or in the offspring [192].

1.4.3. PFAS Exposure and Thyroid Dysfunction in In Vitro Studies

In vitro studies demonstrated that PFOS acutely and reversibly inhibited NIS-mediated iodide uptake by FRTL-5 thyrocytes but did not alter iodide efflux in these cells. PFOA exposure did not change both parameters [193]. On the contrary, another study reported that PFOA, but not C6O4 or PFOS, impaired the TSH-mediated signaling pathway in thyrocytes. This impairment reduced intracellular cAMP production, decreased NIS and TPO gene expression, and diminished NIS-mediated iodide uptake. Interestingly, the same study demonstrated that PFOA, C6O4, and PFOS possibly interact with TSHR through computational analyses [194].

In a high-throughput screening assay, 38 of 149 evaluated PFAS chemicals inhibited iodide uptake in a stably transduced human NIS cell line. PFOS and PFHxS were found to be the most potent NIS inhibitors [195]. Moreover, PFOS and PFOA significantly reduced the activity of TPO in human follicular thyroid carcinoma cells stably transfected with human recombinant TPO [196]. Interestingly, despite the disruptive effect in the activity of two key proteins involved in TH synthesis, previous studies demonstrated that short-chain PFASs (PFBS, PFBA, PFPA, and PFPEA) did not significantly decrease the stimulation of cAMP induced by TSHs [197].

Regarding new-generation, short-chain PFASs, limited literature data support the hypothesis that they are less toxic, although results are still controversial [198].

For instance, a study on GenX, a new-generation PFOA substitute, demonstrated greater toxicity than PFOA and PFOS by causing cellular damage and activating the PPARα signaling pathway in mouse liver cell lines [199] In agreement, FRTL-5 cells exposed to GenX doses commonly found in human plasma presented reduced proliferation rates, DNA fragmentation, and genotoxicity, and altered the expression of thyroid transcription factors and the NIS [200]. These results agree with previously reported data that indicated reduced viability and proliferation rates due to increased cell death in PFOA and PFOS-exposed FRTL5 cells [201]. Accordingly, GenX exposure reduced cell viability and altered the expression of NKX2.1, PAX8, TSHR, and NIS in FRTL5 and primary normal human thyroid cells. Remarkably, these effects were not observed in cells exposed to another PFOS alternative, 4,8-dioxa-3H-perfluorononanoate (ADONA) [202]. C6O4, another new-generation PFAS, did not alter ROS production and cell viability, or induce apoptosis/necrosis in thyroid cells, as demonstrated for PFOS and PFOA [203]. Additionally, it has been shown that these new-generation short-chain PFASs are more efficient at crossing the placenta than their long-chain counterparts, increasing the risk of prenatal exposure [204].

1.4.4. PFAS Exposure and Thyroid Cancer

Concerning thyroid cancer, PFAS exposure has been previously associated with an increased risk of papillary thyroid tumor development in humans [166,205,206]. The carcinogenesis associated with PFAS exposure has been related to changes in epigenetic mechanisms, immunosuppression, increased oxidative stress/inflammation, alterations in hormonal/metabolic pathways, and the activation of epithelial–mesenchymal transition [207].

Indeed, studies have suggested that alterations in epigenetic events induced by PFAS exposure could synergistically amplify tumorigenicity and cancer progression, leading to a poorer prognosis [166,208,209]. In accordance, it has been shown that exposure to C6O4, PFHxA, and PFOA stimulated the secretion of the pro-tumorigenic chemokine CXCL8 and the expression of epithelial–mesenchymal transition genes in primary normal thyroid cells, in adherent and spheroid cultures. It is worth noting that the modulation of CXCL8 has clinical relevance to the tumor environment since it attracts immune system cells, which facilitate the metastatic process of tumor cells [165,210].

In conclusion, several studies suggest a potential link between older-generation PFAS exposure and thyroid disruption, but the data remain controversial in pregnant women, neonates, and adults. Additionally, prenatal PFAS exposure has been associated with adverse effects on neurodevelopment and cognitive outcomes in children. Animal models and in vitro studies further corroborate the thyroid-disrupting potential of PFASs, highlighting alterations in thyrocyte physiology and the expression of proteins involved in TH synthesis. These findings underscore the need for continued research to clarify the risks of PFAS exposure on thyroid health and its broader implications for human health.

1.5. Concluding Remarks: Gaps and Perspectives

In summary, the thyroid disruptors described herein alter several pathways involved in the negative feedback loops that control the HPT axis function and impair thyrocytes' cellular physiology and gene expression (Figure 4). Nonetheless, future studies need to further explore the molecular mechanisms involved in these disruptions, as understanding these mechanisms is crucial for developing targeted interventions and regulatory actions to mitigate adverse effects on thyroid health.

Additionally, for a long time, most studies on the disruptive effects of EDCs have focused on the reproductive system, as many of these compounds interfere with androgenic or estrogenic actions [211,212]. However, TH receptors are expressed in virtually all tissues, including in the gonads, significantly expanding the range of actions of these hormones in the body. Therefore, it is crucial to emphasize that thyroid function disruption extends beyond impairing TH synthesis, as these hormones influence virtually all organs and systems in the body (Figure 5).

Consistently, studies demonstrate an association between thyroid dysfunction and cardiovascular, metabolic, reproductive, neurological, behavioral, and fetal development disorders [213–215]. Therefore, given the importance of TH in maintaining homeostasis, chemicals that impair thyroid function are potentially deleterious, especially in vulnerable periods of development. Despite the progress in obtaining evidence about new thyroid disruptors in the last few years, the molecular mechanisms of these contaminants remain unclear. Epidemiological data are particularly controversial, and the impact of exposure to these thyroid disruptors on human health is inconclusive. These discrepancies may rely on variations in methodologies used to detect contaminants, TH and TSH levels, and differences in the exposure periods assessed. Furthermore, although data on the effects of specific and isolated classes of EDCs on thyroid function are extremely relevant, there is still a lack of studies on the impact of human and other animals' exposure to mixtures, which would more accurately reflect the exposure to these contaminants. Moreover, studies on the programming-induced effects of thyroid disruptors in human progeny in later life are still missing. Hence, further research is needed to clarify the effects of thyroid disruptors on systems and organs beyond the hypothalamus–pituitary–thyroid axis.

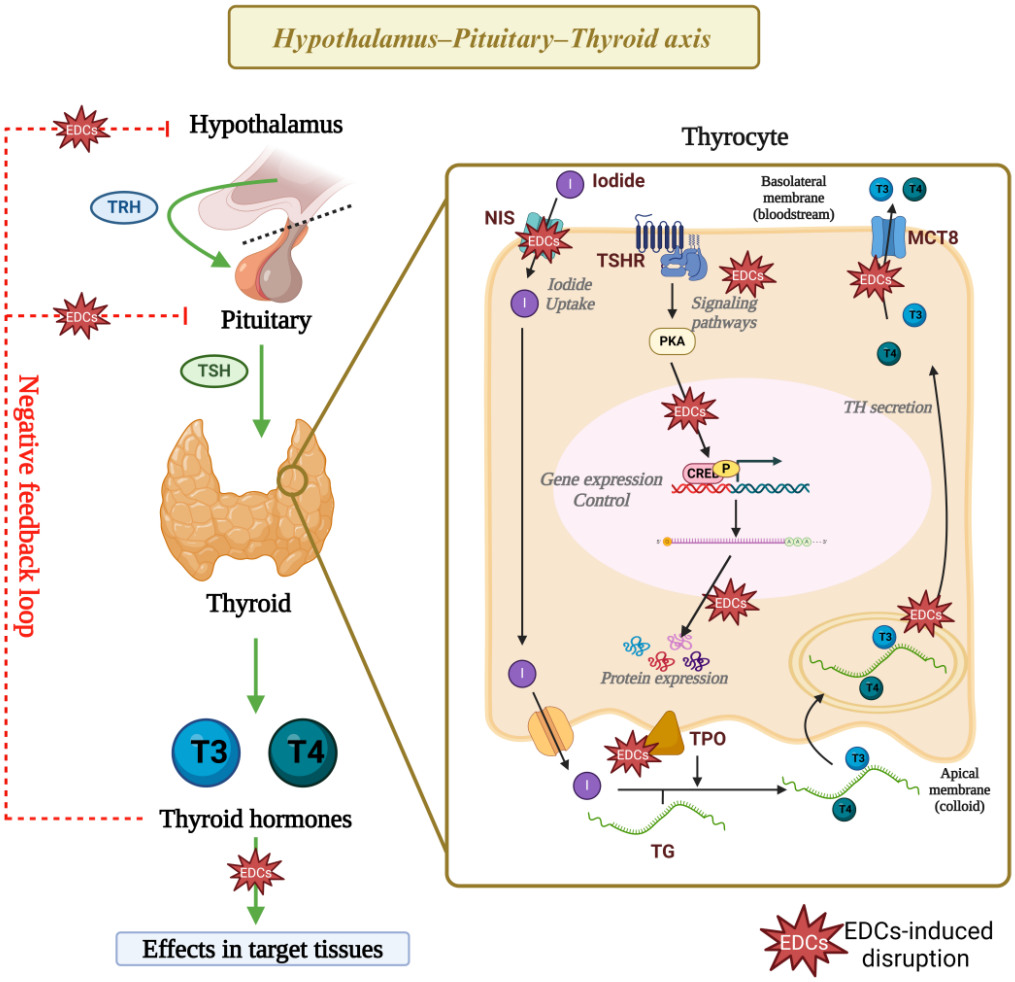

Figure 4. Mechanism of action of thyroid disruptors. Exposure to phthalates, bisphenols, DDT, and PFASs has been linked to disruptions in the function of the hypothalamus–pituitary–thyroid axis, as well as in the cellular physiology and gene expression of thyrocytes. Research indicates that these EDCs impair the activity and expression of proteins critical for thyroid hormone synthesis. Additionally, findings suggest that these EDCs possibly alter signaling pathways and epigenetic mechanisms that regulate gene expression in thyrocytes, but these mechanisms need to be further explored. EDCs: endocrine-disrupting chemicals, TRH: thyrotropin-releasing hormone, TSH: thyrotropin, NIS: sodium–iodide symporter, TSHR: thyrotropin receptor, TPO: thyroid peroxidase, TG: thyroglobulin, T3: triiodothyronine, T4: thyroxine, CREB: cAMP-response element binding protein. Created with Biorender.com.

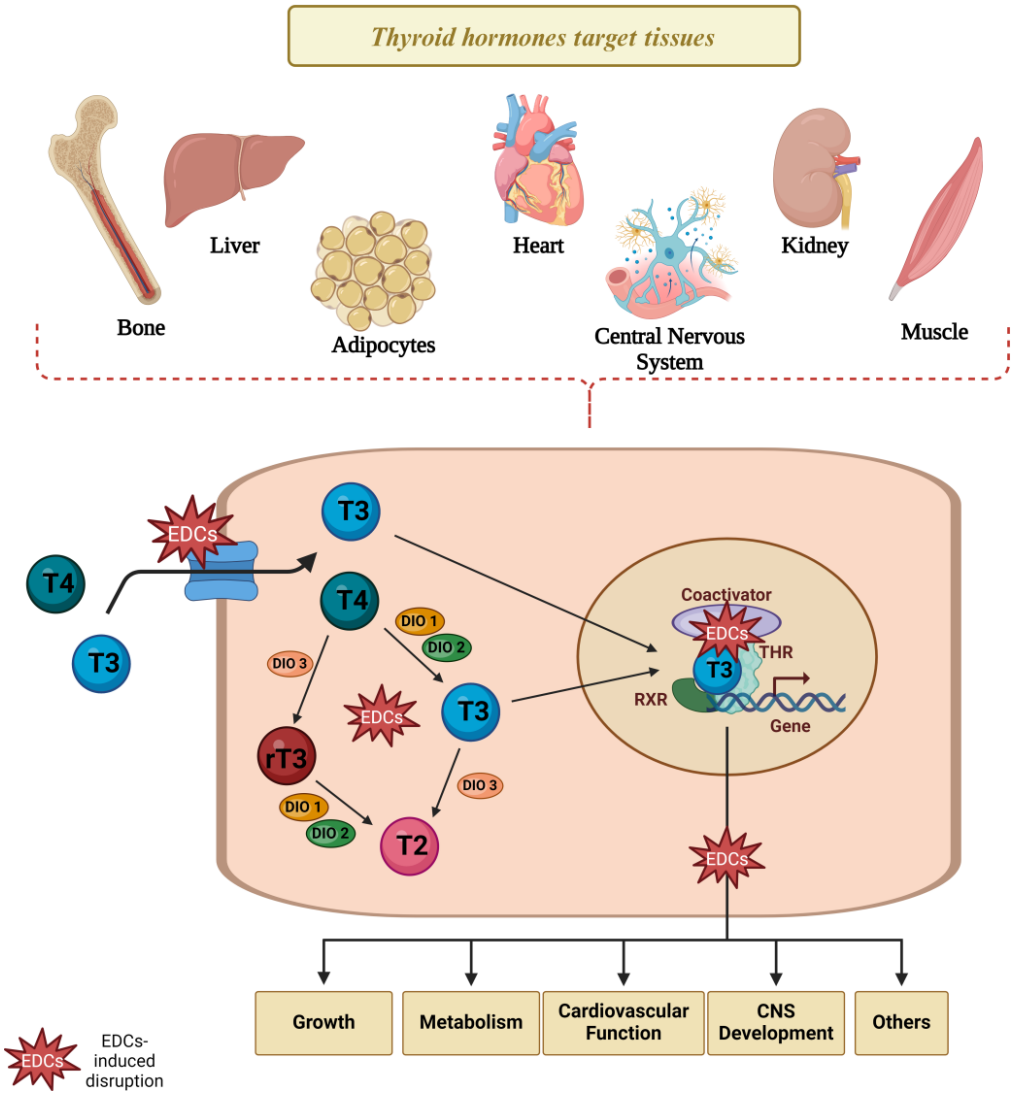

Figure 5. Thyroid disruptors and TH signaling in target cells. Several studies suggest that the TH-induced signaling pathways and TH action in target cells are compromised in animals and cells exposed to thyroid disruptors, possibly through the impairment disruption in several steps involved in TH transport, metabolism, and action in target cells. EDCs: endocrine-disrupting chemicals, T2: diiodothyronine, T3: triiodothyronine, T4: thyroxine, rT3: reverse triiodothyronine, THR: thyroid hormone receptor; DIO1: deiodinase type 1; DIO2: deiodinase type 2; DIO3: deiodinase type 3. Created with Biorender.com.

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Abbreviations

AKT	protein kinase B
BPA	bisphenol A.
BPF	bisphenol F
BPS	bisphenol S
CNS	central nervous system
DBP	di-n-butyl phthalate
DDE	dichlorodiphenyldichloroethylene
DDT	dichloro-diphenyl-trichloroethane
DEHP	di(2-ethylhexyl) phthalate
DIO1	deiodinase type 1
DIO2	deiodinase type 2
DIO3	deiodinase type 3
DMD	diethylnitrosamine(DEN)-N-methyl-N-nitrosourea (MNU)-N,N-bis(2-hydroxypropyl)nitrous amide (DHPN)
EDCs	endocrine-disrupting chemicals
ERK	extracellular signal-regulated kinases
GH	growth hormone
HDAC6	histone deacetylase 6
HPT	hypothalamus-pituitary-thyroid
MCT8	monocarboxylate transporter 8
MEHP	phthalic acid mono-2-ethylhexy
NIS	sodium–iodide symporter
NKX2.1	NK2 homeobox 1 or thyroid transcription factor 1
OCPs	organochloride pesticides
Pax8	paired box 8
PBDEs	polybrominated diphenyl ethers
PCBs	polychlorinated biphenyls
PFASs	per- and polyfluoroalkyl substances
PFDoDA	perfluorododecanoic acid
PFHxS	perfluorohexanesulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PFUnDA	perfluoroundecanoic acid
PND	post-natal day
PTEN	phosphatase and tensin homolog
rT3	reverse T3
T2	diiodothyronine
T3	triiodothyronine
T4	thyroxine
TBBPA	tetrabromobisphenol A
TBBPS	tetrabromobisphenol S (TBBPS)
TBG	thyroxine-binding globulin
TG	thyroglobulin
TH	thyroid hormones
THRB	thyroid hormone receptor beta
TPO	thyroid peroxidase
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone or thyrotropin
TSHR	thyrotropin receptor
TTR	transthyretin

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