REVIEW ARTICLE

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Mechanistic actions of Bisphenol A and its analogues as thyroid-disrupting chemicals

Mechanizmy działania bisfenolu A i jego analogów jako związków zaburzających funkcję tarczycy

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Abstract

Introduction and Objective. Bisphenol A (BPA) is among the most extensively studied endocrine-disrupting chemicals. Because its chemical structure resembles that of endogenous hormones, BPA and its analogues are capable of interacting with intracellular pathways, including those governed by thyroid hormones. The this aim of the review is to outline the molecular mechanisms through which bisphenols exert their effects, and to evaluate how these interactions may influence thyroid function.

Brief description of the state of knowledge. BPA and its structural analogues are widely present in the environment, which has stimulated ongoing interest in their potential effects on thyroid physiology. Epidemiological studies suggest that higher concentrations of urinary or serum BPA may be linked to changes in T4, T3 and TSH levels, although findings remain inconsistent across populations. Experimental evidence from cellular and animal models provides additional support, showing that BPA can impair thyroid hormone synthesis, alter glandular architecture, and influence the expression of genes essential for hormone production. BPA has also been shown to interfere with thyroid hormone receptor activity, thereby modifying downstream signalling. Comparable effects have been observed for several BPA substitutes, including BPS and BPF.

Summary. Available evidence indicates that BPA and its analogues can interfere with thyroid hormone signalling through multiple molecular mechanisms. Experimental studies demonstrate effects on receptor activity, non-genomic signalling and local hormone metabolism, while animal models support thyroid related effects *in vivo*. Human data remain heterogeneous and suggest modest associations, underscoring the need for well designed longitudinal studies to clarify clinical relevance.

Key words

Thyroid, Bisphenol A, Endocrine-disrupting chemicals

Streszczenie

Wprowadzenie i cel pracy. Bisfenol A (BPA) należy do najlepiej poznanych związków zaburzających funkcjonowanie układu hormonalnego, tzw. dysruptorów endokrynnych. Ze względu na podobieństwo strukturalne do hormonów endogennych BPA i jego analogi mogą oddziaływać ze szlakami wewnątrzkomórkowymi, w tym z tymi zależnymi od hormonów tarczycy. Celem niniejszego przeglądu jest przedstawienie mechanizmów działania bisfenoli oraz ocena, w jaki sposób mogą one wpływać na funkcję tarczycy.

Opis stanu wiedzy. BPA i jego analogi są szeroko rozpowszechnione w środowisku, co od lat skłania do badania ich potencjalnego wpływu na fizjologię tarczycy. Badania epidemiologiczne wskazują, że wyższe stężenia BPA w moczu lub surowicy mogą wiązać się ze zmianami stężeń T4, T3 i TSH, choć wyniki badań przeprowadzonych w różnych populacjach są niejednoznaczne. Dane z badań komórkowych i modeli zwierzęcych dodatkowo potwierdzają te obserwacje, wskazując, że BPA może zaburzać syntezę hormonów tarczycy oraz modyfikować ekspresję genów regulowanych przez hormony T3. Wykazano również, że BPA może zakłócać działanie receptorów hormonów tarczycy, modyfikując dalsze etapy sygnalizacji. Podobne efekty odnotowano dla kilku zamienników BPA, w tym BPS i BPF.

Podsumowanie. Dostępne dane sugerują, że BPA oraz jego analogi mogą wpływać na sygnalizację hormonów tarczycy

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na kilku poziomach. Badania pokazują zaburzenia aktywności receptorów, sygnalizacji niegenomowej i lokalnego metabolizmu hormonów, a te przeprowadzone na modelach zwierzęcych potwierdzają występowanie takich efektów *in vivo*. Dane pochodzące z badań u ludzi są niespójne i sugerują zależności o niewielkim nasileniu, bez jednoznacznych implikacji klinicznych.

Słowa kluczowe
bisfenol A, dysruptory endokrynne, tarczyca

INTRODUCTION

Bisphenols (BPs) are synthetic chemicals widely used in the production of polycarbonate plastics and epoxy resins, resulting in their presence in food containers, thermal paper, medical materials, and numerous everyday consumer products. Structurally, they are formed by the condensation of two phenolic rings connected by different bridging groups, which determine their physicochemical properties and biological activity. The most common representatives include bisphenol A (BPA), bisphenol S (BPS) and bisphenol F (BPF), where the letter designation reflects the bridging group (acetone in BPA, sulfone group in BPS and formaldehyde-derived structure in BPF). In addition to these widely studied compounds, other derivatives, such as bisphenol AF (BPAF) and tetrabromobisphenol A (TBBPA), are also used in industrial applications [1].

Bisphenol A (BPA), the most extensively studied compound in this group, has been detected in blood, urine, breast milk and foetal fluids, indicating continuous and almost universal human exposure [2]. As regulatory restrictions on BPA have expanded, structurally similar analogues, such as BPS and BPF, have increasingly been used as replacements, although their safety profiles remain uncertain [3].

Thyroid hormones play a central role in growth, metabolic regulation and brain development, and even small disturbances in their balance can have meaningful health consequences, particularly during pregnancy and early life [4]. At the same time, the incidence of thyroid disorders, including autoimmune thyroid disease and thyroid cancer, has increased in many countries in recent decades, prompting interest in the potential role of environmental factors [5]. An increasing number of studies suggest that several endocrine-disrupting chemicals, including polybrominated diphenyl ethers, PCBs, pesticides, and phthalates, may alter thyroid function in animals, with more variable findings in human populations [6]. Recent studies suggest that changes in thyroid morbidity may also reflect everyday environmental exposures. People come into contact with many synthetic chemicals on a routine basis, and some of these compounds can influence endocrine pathways even at low doses. Cohort data also indicate that early-life exposure to bisphenols may be linked to later differences in thyroid hormone levels [7]. These observations have strengthened the view that environmental factors deserve closer attention when considering current trends in thyroid health.

Bisphenols belong to a broader group of endocrine-disrupting chemicals (EDCs) that can interfere with various steps of hormone action, including synthesis, transport, metabolism and cellular response [6]. Evidence shows that many EDCs exert biologically relevant effects even at low exposure levels, and simultaneous exposure to multiple chemicals acting on the same pathways may further enhance these effects [8]. Experimental studies support this concern: rodent models demonstrate alterations in circulating thyroid hormone concentrations following BPA exposure, while *in vitro* data indicate direct effects on thyroid cells, suggesting several pathways through which bisphenols may disturb thyroid physiology [9–12].

Findings from human studies are heterogeneous. In paediatric cohorts, higher BPA levels have been associated with hyperthyroid patterns, while in young adult women, certain bisphenol analogues correlate with reduced thyroid volume but not with hormone levels [13, 14]. Such variability likely reflects population differences, methodological factors and the short half-life of bisphenols.

Given the widespread exposure to BPA and the recognised sensitivity of the thyroid axis, a clearer understanding of potential impacts is needed. This review synthesises experimental evidence from rodent and *in vitro* models to describe the mechanisms through which BPA may affect thyroid hormone homeostasis, and to evaluate the consistency of current data.

MATERIALS AND METHOD

A narrative review of the available literature was conducted using the PubMed and Google Scholar databases. The search strategy included combinations of the terms: 'bisphenol A', 'bisphenols', 'BPA analogues', 'EDC' (endocrine-disrupting chemicals), 'thyroid', 'thyroid hormones', 'thyroid hormone receptor', 'deiodinases', 'transthyretin', 'thyroid hormone signalling' and 'endocrine disruption'.

Original research articles, experimental studies, and review papers published in English were considered for inclusion. Particular emphasis was placed on mechanistic *in vitro* studies, animal models, and human observational studies relevant to thyroid hormone synthesis, metabolism, transport and signalling. Reference lists of selected articles were also screened to identify additional relevant publications.

As the review was narrative, it did not follow a formal systematic review protocol.

***In vitro* studies on bisphenol-induced thyroid dysfunction.** Thyroid hormone (TH) action depends on a tightly regulated system controlling hormone synthesis, secretion, transport in the circulation, cellular uptake and intracellular activation. Even subtle alterations within this pathway can lead to impaired thyroid hormone signalling.

The thyroid gland produces predominantly thyroxine (T4) and, to a lesser extent, triiodothyronine (T3), which is the biologically active form [15]. A large proportion of intracellular T3 is generated locally from T4 through the activity of deiodinases (DIO1 and DIO2), whereas DIO3 inactivates thyroid hormones by converting T4 into reverse T3 (rT3) and T3 into T2. This enzyme system fine-tunes T3 availability at the tissue level, allowing local regulation of thyroid signalling independently of circulating hormone concentrations [16]. T3 exerts its classical genomic effects by binding to nuclear thyroid hormone receptors (TRs), modulating the

transcription of target genes involved in metabolism, growth and differentiation. Three major TR isoforms are recognised: TRα1, TRβ1 and TRβ2, which show tissue-specific distribution, with TRα1 abundantly expressed in the heart and bone, TRβ1 prevalent in the liver and kidneys, and TRβ2 enriched in the hypothalamus and pituitary, where it contributes to regulation of the hypothalamic-pituitary-thyroid axis [15]. In addition to these genomic pathways, T3 can elicit rapid non-genomic responses through membrane-associated receptors, such as integrin αvβ3, or cytoplasmic/mitochondrial TR isoforms. These effects activate intracellular kinases, regulate ion fluxes and modulate cellular physiology within seconds to minutes, independently of transcriptional changes [17].

In vitro studies have demonstrated that BPA and its analogues can interfere with thyroid hormone signalling at several molecular levels. The cellular response varies according to dose and the presence of T3. Lower concentrations primarily influence receptor-dependent transcription, whereas higher concentrations activate stress pathways or induce cytotoxicity [5]. These mechanisms are discussed in the sections below.

Disruption of TR-dependent transcription and hormone binding interactions. Bisphenols can interfere with thyroid hormone signalling by attaching to the hormone receptor in place of T3. Structurally, BPA contains two phenolic rings resembling those of T3 and T4, which enable interactions with components of the thyroid hormone signalling system. Bisphenol S (BPS) and bisphenol AF (BPAF) share this same phenolic ring architecture, allowing them to mimic thyroid hormones in a similar way and potentially disrupt the same molecular targets (Fig. 1). This resemblance forms a mechanistic basis for their potential to disturb receptor function or related regulatory pathways. Their two phenolic rings resemble key structural features of thyroid hormones, which allows them to enter the receptor's binding pocket and reduce the chance that T3 will activate its normal transcriptional response [20, 21].

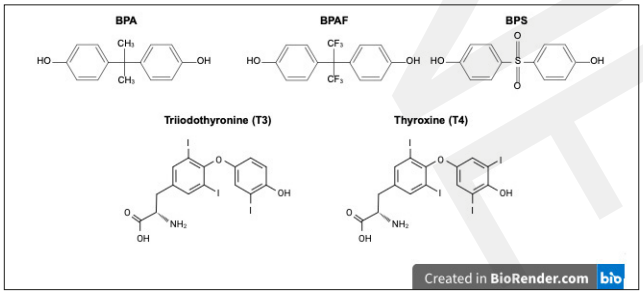

Figure 1. Structural comparison of bisphenol A (BPA) and its analogues bisphenol AF (BPAF) and bisphenol S (BPS) with the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Bisphenols share key structural features with T3 and T4, including phenolic rings and a similar spatial arrangement, which enables them to interact with components of thyroid hormone signalling pathways.
Source: based on references [1, 13, 20]

BPA interferes with thyroid hormone signalling at both the membrane and nuclear level as shown in the figure (Fig. 2). At the cell surface, it disrupts the rapid, non-genomic actions normally triggered when T3 or T4 bind to the integrin αvβ3 receptor. This reduces ERK/MAPK activation and alters ion fluxes, such as calcium entry, making the cell less responsive to the initial signals that prepare it for a full hormonal response [18]

Inside the nucleus, BPA further weakens thyroid hormone action by binding to the TR–RXR complex. Instead of allowing T3 to activate transcription, BPA stabilises a receptor state that keeps co-repressors attached. As a result, even with normal T3 levels, the expression of T3-dependent genes is reduced. Together, these effects explain how BPA can dampen both the rapid and the genomic responses to thyroid hormones. [19]. Figure 2 summarises how BPA disrupts those pathways.

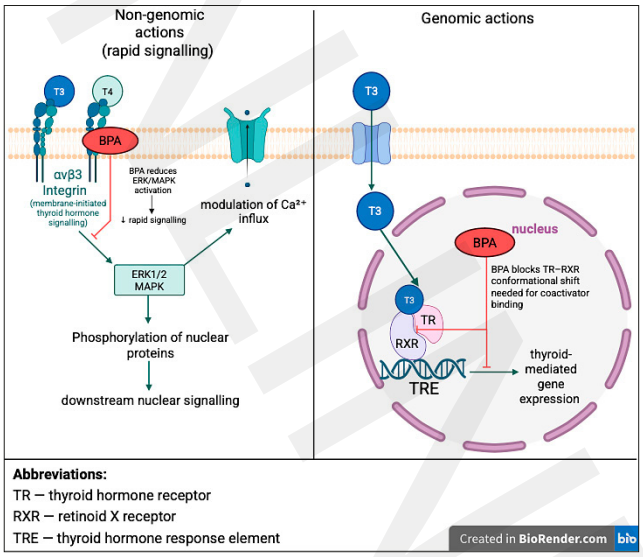

Figure 2. Thyroid hormones act through two complementary mechanisms: rapid non-genomic signalling at the cell surface and classical genomic regulation within the nucleus. At the membrane, T3 and T4 engage the integrin αvβ3 receptor to stimulate ERK/MAPK activity and modulate calcium flux. BPA interferes with this early signalling, blunting kinase activation. In the nucleus, BPA associates with the TR–RXR complex and promotes a configuration that retains co-repressors, thereby preventing full transcriptional activation by T3. Together, these actions show how BPA can disrupt both branches of the thyroid hormone signalling network.
Source: based on references [17–19, 28]

Cell proliferation. Several studies indicate that bisphenols can modulate thyroid cell proliferation through a combination of oxidative and kinase-mediated mechanisms. In normal human thyroid follicular cells, BPA demonstrates a hormetic pattern: low concentrations enhance proliferation, whereas higher concentrations suppress growth. Environmentally relevant doses (0.1–0.5 μM) have been shown to increase proliferation and DNA synthesis in both non-malignant thyroid cells and papillary thyroid carcinoma lines, with effects confirmed across CCK-8, EdU and colony-formation assays [21, 22]. Oxidative signalling appears central to this response. BPA increases intracellular ROS and activates growth-related kinases that facilitate cell-cycle progression [20, 23]. Analogues such as BPS and BPF evoke similar proliferative changes, suggesting that substitution of BPA does not eliminate growth-modulating potential [23, 24]. Although these findings do not directly indicate tumourigenesis, they align with epidemiological reports linking higher bisphenol exposure to altered thyroid morphology and increased nodule frequency.

Cytotoxicity. At higher concentrations, bisphenols shift from promoting proliferative signals to inducing clear cytotoxic injury. BPA triggers a pronounced rise in reactive oxygen species, disrupts mitochondrial membrane potential and lowers ATP production, ultimately activating the intrinsic

apoptotic pathway [25]. Because thyroid hormone production relies heavily on mitochondrial energy, these disturbances are especially impactful in thyrocytes. When ATP levels fall, essential processes such as iodide uptake, hormone synthesis and local T3 generation can all be compromised. These mitochondrial disturbances are accompanied by increased Bax expression, permeabilisation of the mitochondrial membrane and caspase-dependent execution of cell death, confirming that apoptosis is a major mode of toxicity at elevated doses [26, 27].

Cytotoxicity also affects the differentiated function of thyroid cells. BPA, BPS and BPF consistently reduce the expression of key thyroid-specific genes, including NIS, TPO and thyroglobulin, indicating that functional impairment emerges before overt structural injury becomes detectable [28, 29]. With ongoing exposure, oxidative damage progresses to lipid peroxidation and loss of membrane integrity [11]. Together, these findings show that bisphenols compromise both thyrocyte viability and specialised function when present at cytotoxic levels.

Effects of bisphenols on deiodinases (DIO1, DIO2, DIO3). Local activation and inactivation of thyroid hormones depend on the coordinated work of the deiodinase enzymes, a system that is usually quite precise but also surprisingly vulnerable to disruption. Several independent studies suggest that bisphenols can interfere with this machinery at different points. In thyroid and liver cell models, BPA clearly reduces DIO1 activity, which means less conversion of T4 into active T3 and, as a result, less hormone available inside the cell [30]. In zebrafish, BPA at concentrations between 0.1–1 μM increased the expression of *dio1* and *ugt1ab*, the gene coding for UDP-glucuronosyltransferase. BPS and BPF behave in much the same way [31]. Some models also show an increase in DIO3 expression at higher bisphenol concentrations, which tilts metabolism even further toward hormone inactivation [32]. This points to a tissue-level disturbance that can occur even when circulating hormone levels remain normal. These mechanisms are summarised in Figure 3, which depicts the bisphenol induced inhibition of DIO1 and DIO2 alongside enhanced DIO3 mediated hormone inactivation.

Effects of bisphenols on thyroid hormone transport: interactions with transthyretin (TTR). Bisphenols can also disturb thyroid hormone signalling by interfering with how these hormones are carried through the bloodstream. Transthyretin (TTR) is one of the major carrier proteins for T4 in both plasma and cerebrospinal fluid, and several experimental studies indicate that BPA has a measurable affinity for its binding pocket. In competitive binding assays, BPA is able to displace T4 from TTR [33]. Although TTR has a relatively high affinity for T4, it is worth noting that albumin carries the largest share of circulating T4 in humans, which is important when interpreting displacement assays and their potential physiological impact. The overall effect on total circulating T4 tends to be modest, yet even small shifts in the free hormone fraction may influence tissue uptake or modify the feedback response of the thyroid axis.

These interactions are not restricted to BPA. BPS, BPF and a number of halogenated bisphenols show similar or even stronger affinity for TTR, which raises the concern that replacement of BPA with closely related analogues may not reduce transport-related interference at all [6]. Because

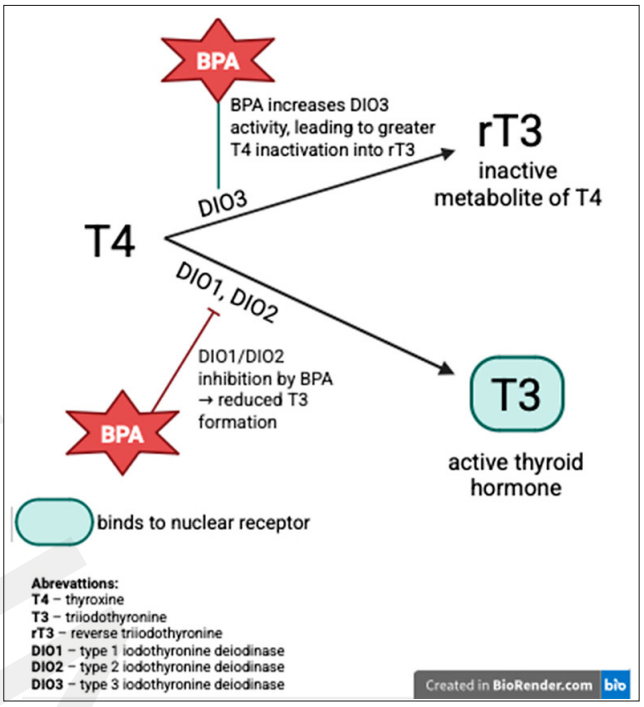

Figure 3. Effects of bisphenol A (BPA) on peripheral thyroid hormone conversion. BPA interferes with the enzymatic pathways that convert T4 into its active and inactive metabolites. By increasing DIO3 activity, BPA enhances the inactivation of T4 to reverse T3 (rT3), a biologically inactive product. At the same time, BPA inhibits DIO1 and DIO2, reducing the peripheral conversion of T4 to the active hormone T3. These combined effects shift thyroid hormone metabolism toward reduced T3 availability and increased formation of inactive rT3. BPA can additionally bind to thyroid hormone receptors, further modifying the cellular response to T3.
Source: based on literature [30–32]

TTR plays a central role in delivering thyroid hormones to the developing foetus, this mechanism may be particularly relevant in pregnancy. Altogether, the evidence suggests that bisphenols can influence thyroid physiology not only through receptor-mediated pathways or intracellular signalling, but also by altering hormone transport, which adds another layer to their potential harmful impact on thyroid function.

Animal studies. Experimental work research in animal models gives a broader view of how bisphenols may interfere with thyroid regulation in a living organism, where multiple pathways interact at once. Several rodent studies report that BPA exposure can change circulating thyroid hormone levels, although the direction of these changes is not identical across experiments. In some models, serum T4 and T3 fall while TSH rises, a pattern that suggests impaired hormone synthesis or reduced peripheral activation [6, 31].

Animal studies provide additional evidence that the thyroid gland itself may be a direct target of bisphenol exposure. In a rat model, BPA administration produced measurable changes in circulating thyroid hormones and altered the expression of genes involved in thyroid hormone metabolism, together with morphological disturbances that included irregular follicular structure and changes in colloid appearance [34]. Similar patterns have been described across multiple *in vivo* experiments summarised in an independent review, where repeated BPA exposure consistently led to enlarged follicles, disrupted epithelial organisation and other microstructural abnormalities of the thyroid gland [6]. The convergence of biochemical and histological findings across these studies supports the idea that BPA is able to interfere

with thyroid function not only through peripheral metabolic pathways but also by acting directly on thyroid tissue.

Many experimental studies in animals rely on BPA doses that exceed typical human exposure, which limits the ability to directly extrapolate these results to real-world conditions [35]. Despite this limitation, several independent models have shown recurring patterns of hormonal and structural alterations in the thyroid, indicating that bisphenols can affect the gland at multiple regulatory levels [36]. How these findings translate to humans remains uncertain, as species differ in thyroid hormone turnover, iodine handling, and the metabolism and clearance of bisphenols [37]. These physiological differences make it likely that dose–response relationships observed in rodents do not fully mirror those occurring in human populations.

Human data. Human exposure to bisphenols is widespread. Biomonitoring studies consistently detect BPA in urine, blood and fetal compartments across diverse populations, reflecting ongoing low level exposure from sources such as food packaging, thermal paper and medical devices [38]. Importantly, this exposure pattern has not declined following regulatory restrictions on BPA. Instead, BPA substitutes such as BPS and BPF are now detected as frequently as BPA itself, indicating that regulatory changes have altered the profile rather than the overall burden of bisphenol exposure [29, 31, 39].

Epidemiological studies examining thyroid function have reported inconsistent findings. In both the general population and mother-child cohorts, associations between BPA exposure and serum T4 concentrations have been reported as positive, negative, or absent [40–42]. Fewer studies have assessed serum T3, and these have likewise produced inconsistent findings [10, 13].

In contrast, alterations in TSH appear more consistently linked to BPA exposure. Several studies report changes in serum TSH levels, suggesting a potential disturbance of thyroid regulation. In a large cross-sectional study from Shanghai, China, which included 3,394 participants, higher urinary BPA concentrations were associated with increased free triiodothyronine FT3 and reduced TSH levels [43]. Similarly, data from the CHAMACOS cohort showed that prenatal BPA exposure was associated with lower T4 concentrations in pregnant women, and decreased TSH levels in male neonates [44].

Beyond functional measures, structural outcomes have also been reported, particularly in children. A study conducted in China found that higher urinary BPA levels were associated with smaller thyroid volume and more frequent structural alterations in school aged children, independent of iodine status. Notably, these changes were not accompanied by clear alterations in thyroid hormone levels, suggesting an effect on thyroid morphology rather than overt hormonal dysfunction [39].

At present, available evidence does not support a direct role of BPA in initiating thyroid cancer. However, experimental studies indicate that BPA may influence tumour growth and invasive behaviour, indicating a possible contribution to disease progression rather than disease initiation [20]. Hman studies also indicate associations between BPA exposure and a wider spectrum of health outcomes, including estrogen-dependent neoplasms [45,46], reproductive disturbances [47], and cardiometabolic disorders, such as cardiovascular disease, type 2 diabetes and obesity [48, 49]. Although causal links remain difficult to establish, the consistent involvement of endocrine regulated pathways across these conditions suggests that the biological impact of chronic bisphenol exposure is not confined to a single hormonal axis. In this broader endocrine context, the reported thyroid disrupting effects of BPA, including interference with thyroid hormone signalling, metabolism and regulatory feedback, observed in both experimental models and human studies, merit careful consideration.

Differences between studies likely reflect heterogeneity in exposure levels and timing, as well as modifying factors such as iodine intake, age, ethnicity, diet, socio-economic conditions and methodological variability in thyroid hormone assessment.

Limitations of the study. Although the studies reviewed provide detailed insights into how bisphenol A and its analogues may interfere with thyroid hormone signalling, several limitations should be acknowledged. Much of the mechanistic evidence is derived from *in vitro* models, which allow precise assessment of receptor interactions, deiodinase activity and cellular stress responses, but do not fully capture the complexity of thyroid regulation *in vivo.* Findings from human studies remain inconsistent, with variability in study design, sample size, exposure assessment, and control of confounding factors making it difficult to determine the clinical relevance of the observed associations.

The analysis was narrative rather than systematic, and study selection was limited to articles published in English and accessible through major scientific databases. As a result, some relevant data may not have been included, and publication bias cannot be excluded. Furthermore, because BPA substitutes such as BPS and BPF are relatively new, the available literature on their thyroid effects is still limited, which restricts the ability to draw firm conclusions about their safety.

Despite these limitations, this review integrates current mechanistic and epidemiological findings and highlights several pathways through which bisphenols may influence thyroid physiology. Continued research using complementary experimental and population-based approaches is needed to clarify the relevance of these mechanisms for human health.

CONCLUSIONS

Experimental studies indicate that bisphenol A and several of its commonly used analogues can interfere with thyroid hormone signalling through multiple molecular pathways. Reported effects include modulation of thyroid hormone receptor activity, disruption of non-genomic signalling, alterations in local hormone activation and inactivation by deiodinases, and changes in the expression of genes essential for thyrocyte function. Together, these findings provide a mechanistic basis for potential interactions between bisphenols and thyroid hormone action.

Animal studies support the occurrence of thyroid-related effects *in vivo,* including changes in circulating thyroid hormone concentrations and structural alterations of the thyroid gland. However, differences in exposure levels, experimental design and species-specific thyroid physiology limit the extent to which these results can be extrapolated to human populations.

Evidence from human studies remains inconsistent. Associations between bisphenol exposure and thyroid hormone levels or thyroid morphology are generally modest and variable, and their clinical relevance is uncertain. Current data do not support a direct role for bisphenols in the initiation of thyroid cancer, although experimental findings suggest that they may influence cellular processes relevant to tumour growth and progression.

Available data also indicate that replacement of BPA with structurally similar analogues, such as BPS and BPF, does not eliminate thyroid-related biological activity, as these compounds appear to interact with overlapping components of thyroid hormone signalling.

Overall, existing evidence suggests that bisphenols can modify thyroid hormone signalling without clear proof of overt thyroid disease in humans. Further progress will depend on longitudinal human studies with repeated exposure assessment, improved characterisation of individual bisphenol compounds, and closer integration of mechanistic and population-based research.

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