The role of bisphenol A and its analogues as endocrine disruptors influencing the thyroid gland: a short review

Justyna Milczarek-Banach
Department of Internal Medicine and Endocrinology, Medical University of Warsaw

Piotr Miśkiewicz
Department of Internal Medicine and Endocrinology, Medical University of Warsaw

Bisphenols (BPs) are common plastic additives widely used in industry, hence, human exposure to BPs is inevitable. The best known BP is bisphenol A (BPA), the production of which and its analogues has been increasing worldwide. This chemical is classified as an endocrine-disrupting chemical, infering with hormonal homeostasis. Indeed, BPA is associated with the development of oestrogen-dependent neoplasms, infertility, metabolic disorders and neurobehavioral disturbances. However, there is a lack of evidence regarding the impact of BPA and its analogues on the thyroid, with most studies mainly performed on animals or in vitro. This review aims to summarise the knowledge regarding the relationship between BPA and its analogues on the thyroid gland.

Introduction

Bisphenols (BPs) are common plastic additives widely used in industry. They are products in the manufacture of polycarbonate plastics, such as water bottles, toys, food boxes, teethers, baby pacifiers, thermal paper, inner linings of beverage and food containers, dental sealants, epoxy resins [1-6]. People are exposed to BPs mainly due to contaminated food, especially in high temperatures or acidic conditions [6,7]. Nonetheless, the other possibilities of exposure to BPs include transdermal or inhalation routes [8].

The most common BP is bisphenol A (BPA; 4,4′-isopropylidenediphenol), which is composed of two benzene rings and two 4,4′-OH substituents (Figure 1). Since its industrial application, many studies have revealed the harmful effects of this chemical on human health, especially on hormonal homeostasis. Subsequently, BPA has been classified as an endocrine-disrupting chemical (EDC) [5,9-11]. BPs act as xenoestrogens, impacting the development of oestrogen-dependent neoplasms (e.g., breast or endometrial cancers) [12-14], as well as being associated with infertility [15] and polycystic ovary syndrome [16]. Moreover, BPA may contribute to the development of metabolic disorders (e.g., insulin resistance, diabetes, obesity) [17] and neurobehavioral disturbances [18]. Furthermore, the specific molecular structure that mimics thyroid hormones allows BPA to influence thyroid hormone homeostasis [19-21] but most of these studies were conducted in vitro [19,22,23] or on animals [24,25].
Since the use of BPA in products for children has been prohibited, the large-scale production of BPA analogues has escalated. Ideally, substitutes intended to replace a specific chemical should be less toxic than the original substance. Unfortunately, many chemical replacements introduced into the industry have never been studied and are often more harmful than the original chemical.

BPA analogues are compounds with a chemical structure similar to BPA, which means they include at least two phenyl rings, but their substituents differ depending on the type of the analogue (i.e., methyl, bromine or chlorine substituents in 3,3’ or 3,5-positions of the phenyl rings). BPA analogues include bisphenol F (BPF), bisphenol B (BPB), bisphenol Z (BPZ), bisphenol C (BPC), bisphenol P (BPP), bisphenol M (BPM), bisphenol AP (BPAP), bisphenol AF (BPAF), bisphenol AD (BPAD), tetrabromobisphenol A (TBBPA), tetrachlorobisphenol A (TCBPA), tetramethylbisphenol A (TMBPA), and dimethylbisphenol A (DMBPA) [19,22,23,26].

After oral consumption, BPA undergoes first-pass metabolism in the intestine and liver, then it is metabolised by UDP-glucuronosyltransferase in the liver. After glucuronidation, BPA is eliminated via renal clearance within 24 hours [27]. Nonetheless, there is a concern about the other routes of human exposure to BPA, mainly via inhalation or transdermally, which bypass the first pass in the gastrointestinal tract, hence there is a longer exposure to unconjugated BPA. It is well documented in the literature that BPA is ubiquitous and has been measured in a variety of human body fluids [28] including placenta, maternal milk and amniotic fluid [29,30]. The detection rates of BPs differ according to the detection method used (LC-MS, GC-MS, HPLC, HPLS-MS/MS) and the form of BPs (conjugated, unconjugated or total). Importantly, there is a lack of information regarding the metabolism of BPA analogues in humans.

BPs can interact with the thyroid gland via a variety of routes, therefore, the potential crosstalk needs to be considered at multiple levels. BPA is the first environmental chemical known to bind to the thyroid receptor (TR) and affect thyroid hormone homeostasis in vitro [25]. Lee et al. [22], as well as Moriyama et al. [21], suggested that BPA can influence thyroid hormones at the transcriptional level. Moreover, Schmutzler et al. [31] reported that BPA interferes with thyroid function by inhibiting recombinant thyroid peroxidase (TPO) activity. Furthermore, an in vitro study of Kudo et al. [32] found the antagonistic ability of BPA derivatives to triiodothyronine (T3) in binding to transthyretin (TTR), which is the transport protein for thyroid hormones.

Influence of BPs on thyroid function
The results regarding the influence of BPs on thyroid function are conflicting and depend on the study design (in vivo or in vitro) and the examined group (human, animals, cell lines). According to in vitro studies of rat pituitary (GH3) cells, BPs (BPA, BPAF, BPAP, BPB, BPC, BPF, BPM, BPP, BPZ) have an agonistic effect on thyroid hormones, which is dose- and time-dependent [23]. Co-exposure of GH3 cells to 17β-oestradiol enhanced this effect. Similarly, in another study [22] on rat pituitary (GH3) and thyroid follicular (FRTL-5) cells, the authors suggested that the results were different according to cell type, with BPA and its analogues (BPAF, BPAP, BPB, BPF, BPM, BPP, BPS, BPZ, BPC) significantly downregulating tshβ, tra, trβ, dio1 or dio2 genes in GH3 cells, whereas in FRTL-5 cells, the genes responsible for hormone synthesis were upregulated. Furthermore, in the first in vitro study on the influence of BPA on thyroid [21], BPA antagonised T3 action at the transcriptional level in a dose-dependent manner. Kitamura et al. [19] reported that in the rat pituitary cell line GH3, selected BPs exhibited thyroid hormonal activity (TBBPA, TCBPA, TMBPA), while others (BPA, BPF, BPS, BPAF, BPAD, BPB, DMBPA) did not show such effect. The authors suggested that the chemical structure (the type of substituents of the phenyl rings of BPs) is crucial for the thyroid hormonal activity, particularly, hydroxyl groups in 4,4'-positions and methyl, bromine or chlorine in 3, 3’, 5 and 5’-positions of the phenyl rings.

The results of the animal studies are inconsistent. Perinatal exposure to BPA in pups [33] or adult polecats [34] did not show any statistically significant influence on thyroid hormones, whereas there was a positive relationship between concentrations of BPA and thyroxine (T4) levels in rats [25]. Also, Lee et al. [26] demonstrated that selected BPs disrupted thyroid hormone levels by increasing T3 and T4 in embryo-larval zebrafish, suggesting that the potency of BPA analogues could be even stronger than that of BPA. It is of note that BPA derivatives could be more harmful than BPA as they act in much lower concentrations than BPA itself.

Regarding human studies, the data considering the relationship between BPs and thyrotropin (TSH) and T4 are conflicting. According to correlations between TSH and BPs in humans, there is an inverse relationship in both sexes [35] and only in women [36], suggesting that exposure to BPs may lead to the development of hyperthyroidism. Also, Meeker et al. [37] measured BPA concentrations in the urine of 1346 adults and 329 adolescents (aged 1–19 years) from the National Health and Nutrition Examination Survey (NHANES) in the period 2007–2008, observing a suggestive inverse association (but without statistical significance) between urinary BPA and TSH. In contrast, Andrianou et al. [28] suggested a positive correlation between BPA with its derivatives and TSH, which could lead to the development of hypothyroidism. Furthermore, there was a positive association between urinary BPA and serum TSH in lean individuals [38]. Taking into the consideration that BPs influence thyroid hormones in humans, the authors of several studies in pregnant women reported that BPA levels were positively [35] or inversely [20] correlated with maternal T4 levels, with two other studies found no association [36,39].

**BPs influence on the formation of thyroid nodules**

Nodular goitre and thyroid cancer are related to endogenous oestrogen activity [40-42], hence, as a xenoestrogen, BPA could impact the formation of thyroid nodules. Zhou et al. [43] showed that higher BPA concentrations in urine are potentially linked to the genesis of nodular goitre and papillary thyroid carcinoma (PTC), with women with nodular goitre and PTC having higher concentrations of BPA than men. Moreover, females from the PTC group presented lower urinary BPA levels than those of the nodular goitre group. Furthermore, Marotta et al. [44] described a dose-independent correlation between BPAF and the risk of development of differentiated thyroid cancer in subjects with thyroid nodules. Li et al. [45] also showed a significant association between BPA and a higher risk of thyroid nodules in Chinese women, but only in subjects with positive TgAb and TPOAb, whereas Wang et al. [46] observed a negative correlation between urinary BPA and the risk of forming multinodular goitre, but not of solitary thyroid nodules in schoolchildren. In another study, Andrianou et al. [28] reported no association between BPs and higher risk of thyroid nodules in adult females.
BPs influence on autoimmune thyroid disease

Several studies have assessed the relationship between BPA and the development of autoimmune diseases, including autoimmune thyroid disease [47-49]. BPA can affect the immune system directly and indirectly [50]. Özaydın et al. [48] proved the influence of BPA on the alteration of immune parameters, such as cytokine profile and the distribution of CD8+ and CD4+ T lymphocytes in rats which can result in the development of immunodeficiencies and autoimmune diseases. Also, two case reports described the possible relationships between BPA exposure and immune system-related diseases [51,52]. Chailurkit et al. [47] also documented the independent, statistically significant association between BPA and thyroid peroxidase antibodies (TPOAb).

Conclusions

In conclusion, the results of the studies concerning the impact of BPs on the thyroid are conflicting and are dependent on the study design and the detection methods used. It seems that BPA derivatives could be even more harmful to humans than BPA as they could act in much lower concentrations than BPA itself. As the exposure to these endocrine disruptors is inevitable, there is a strong need for large randomised human trials to establish the potentially detrimental effects of BPA and its analogues before their industrial application.

References

5. Hehn Rebecca Simonne. NHANES Data Support Link between Handling of Thermal Paper Receipts and Increased Urinary Bisphenol A Excretion. Environmental Science & Technology. 2015; 50(1) DOI
10. Zoeller R. Thomas, Brown T. R., Doan L. L., Gore A. C., Skakkebaek N. E., Soto A. M.


15. Mantzouki Christina, Bliatka Despoina, Iliadou Paschalia K., Margeli Alexandra, Papassotiriou Ioannis, Mastorakos George, Kousta Eleni, Goulis Dimitrios G.. Serum Bisphenol A concentrations in men with idiopathic infertility. Food and Chemical Toxicology. 2019; 125 DOI

16. Konieczna Aleksandra, Rachoń Dominik, Owczarek Katarzyna, Kubicz Pawel, Kowalewska Agnieszka, Kudlak Blazej, Wasik Andrzejj, Namieśnik Jacek. Serum bisphenol A concentrations correlate with serum testosterone levels in women with polycystic ovary syndrome. Reproductive Toxicology. 2018; 82 DOI


22. Lee Sangwoo, Kim Cheolmin, Youn Hyewon, Choi Kyungho. Thyroid hormone disrupting potentials of bisphenol A and its analogues - in vitro comparison study employing rat pituitary (GH3) and thyroid follicular (FRTL-5) cells. Toxicology in Vitro. 2017; 40 DOI


25. Zoeller R. Thomas, Bansal Ruby, Parris Colleen. Bisphenol-A, an Environmental Contaminant that Acts as a Thyroid Hormone Receptor Antagonist in Vitro, Increases Serum Thyroxine, and Alters RC3/Neurogranin Expression in the Developing Rat


31. Schmutzler Cornelia, Bacinski Anja, Gotthardt Inka, Huhe Katrin, Ambrugger Petra, Klammer Holger, Schlecht Christiane, Hoang-Vu Cuong, Grüters Annette, Wuttke Wolfgang, Jarry Hubertus, Körhrle Josef. The Ultraviolet Filter Benzophenone 2 Interferes with the Thyroid Hormone Axis in Rats and Is a Potent in Vitro Inhibitor of Human Recombinant Thyroid Peroxidase. *Endocrinology*. 2007; 148(6)[DOI]


38. Klinge. Estradiol-induced proliferation of papillary and follicular thyroid cancer cells is mediated by estrogen receptors α and β. *International Journal of Oncology*. 2010; 36(5)[DOI]

39. Liu Jia, Chen Guang, Meng Xian-Ying, Liu Zhong-Hui, Dong Su. Serum levels of sex
hormones and expression of their receptors in thyroid tissue in female patients with various types of thyroid neoplasms. *Pathology - Research and Practice.* 2014; 210(12) DOI


44. Marotta Vincenzo, Russo Giacomo, Gambardella Claudio, Grasso Marica, La Sala Domenico, Chiofalo Maria Grazia, D'Anna Raffaella, Puzziello Alessandro, Docimo Giovanni, Masone Stefania, Barbato Francesco, Colao Annamaria, Faggiano Antoniglio, Grumetto Lucia. Human exposure to bisphenol AF and diethylhexylphthalate increases susceptibility to develop differentiated thyroid cancer in patients with thyroid nodules. *Chemosphere.* 2019; 218 DOI


47. Chailurkit La-or, Aekplakorn Wichai, Ongphiphadhanakul Boonsong. The Association of Serum Bisphenol A with Thyroid Autoimmunity. *International Journal of Environmental Research and Public Health.* 2016; 13(11) DOI

48. Özaydın Tuğba, Öznurlu Yasemin, Sur Emrah, Çelik Ilhami, Uluışık Deniz. The effects of bisphenol A on some plasma cytokine levels and distribution of CD8+ and CD4+ T lymphocytes in spleen, ileal Peyer’s patch and bronchus associated lymphoid tissue in rats. *Acta Histochemica.* 2018; 120(8) DOI


51. Jensen Charlotte D, Andersen Klaus E. Two cases of occupational allergic contact dermatitis from a cycloaliphatic epoxy resin in a neat oil: Case Report. *Environmental Health.* 2003; 2(1) DOI

52. Hannu Timo, Frilander Heikki, Kauppi Paula, Kuuliala Outi, Alanko Kristiina. IgE-Mediated Occupational Asthma from Epoxy Resin. *International Archives of Allergy and Immunology.* 2009; 148(1) DOI