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Bisphenol A and other related bisphenols as pervasive environmental toxicants affecting the human health mainly through endocrine disruption

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ABSTRACT

Synthetic substances - bisphenols (BPs), especially bisphenol A (BPA), and also BPs F and S, are recognized disruptors of hormonal functions both in males and females and also disruptors of glucose metabolism. These compounds are used in the production of various plastic materials, and as such, they enter the human environment. BPA was always considered to be responsible for malignant transformations of hormone-sensitive cells. However, recent data show BPA and other BPs being involved in an increased incidence of some hormone-non-sensitive tumors through the etiopathogenesis of involving various factors of genetic, epigenetic, inflammatory, immune, metabolic, hormonal and oxidative stress nature. On the other hand, short-time exposures to BPA seem not to be responsible for any hormonal dysfunction or carcinogenicity in dental patients. Attempts to replace BPs, especially BPA, with another BP are so far not successful because various BPs share the same structural features necessary for endocrine dysfunction. At this moment, the only feasible way to mitigate toxic effects of various BPs used in the production of plastic materials seems to be a replacement of the whole group by new substances that would not have structural features necessary for the endocrine disruption in mammals.

Keywords: Bisphenols, bisphenol A, obesity, diabetes, endocrine disruption, cancer, dental composite, dental sealants.

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INTRODUCTION

Bisphenols (BPs) are synthetic chemicals applied mainly in the chemical industry in the production of plastics and resins and even in the production of items such as various food containers, various types of coating or thermal paper and other products containing polycarbonates [1]. Moreover, it can also be used in flame retardants. Bisphenol A (BPA) is the most 'famous' substance of this group due to its ability to disrupt endocrine homeostasis. Some compounds of this group were used to replace BPA or to serve as alternatives to BPA but the success of these replacements needs to be verified.

This review aims at clarifying what disruptive properties are related to BPA and other BPs and what is the potential risk of malignancies caused by BPs, BPA, BPS, and BPF particularly.

Chemical structure of bisphenols

Bisphenols are substances obtained from the reaction of 2 phenol molecules (or less often of 2 other molecules, such as o-cresol, 2-isopropylphenol, 2-phenylphenol or even BPA) with acetone (bisphenol A, BPA, Fig. 1A), acetophenone (bisphenol AP, Fig. 1B), hexafluoroacetone (bisphenol AF, BPAF, Fig. 1C), butanone (bisphenol B, Fig. 1D), benzophenone (bisphenol BP, Fig. 1E), ethanol (bisphenol E, Fig. 1F), formaldehyde (bisphenol F, Fig. 1G), sulfuric acid or sulfur trioxide (bisphenol S, Fig. 1H) and some other (see PubChem for formulas and other information) [2]. These substances contain at least 2 aromatic rings and 2 phenolic –OH groups and are similar in the structure to nonsteroidal estrogen - stilbestrol. Its derivative diethylstilbestrol (DES, Fig. 1J) was in the past used for its estrogen-like properties as hormone therapy in women. It is also applied in the therapy of prostate and breast cancers [3].

BPA is the most studied bisphenol concerning human health. The information regarding health effects on humans is significantly smaller in the case of other BPs but is still very important.

Main chemical properties of BPA

Chemically, BPA is 2,2-Bis(4-hydroxyphenyl)propane or, according to IUPAC nomenclature, 4-[2-(4-hydroxyphenyl)propane-2-yl]phenol. Its molecular formula is $C_{15}H_{16}O_2$ or $(CH_3)_2C(C_6H_4OH)_2$. BPA has a molecular weight of 228.3 g/mol. BPA has a boiling point of 250-252 ^oC and a melting point of 150-157 ^oC. It is denser compared to water (1200/m^3) but it is very poorly soluble in it as indicated by the octanol-water partition coefficient value of log P = 3.32 [4]. BPA possesses a light phenolic odor [5]. The level of its dissociation is reflected by the pK_a value of 9.6 [6].

Consequences of environmental exposure of humans to BPA

There is a vast amount of scientific literature reporting on the presence of BPs and specifically of BPA in the environment and in the human body. The fate of BPA in the environment is followed as it affects humans from birth and then during all of their life. The study from Taiwan reported on the fact that 3% of children at the age of 1 month had daily BPA intake exceeding 4 μg/kg of body weight per day – the limit suggested by the European Food Safety Authority [7]. This is important as BPA negatively affects birth size [8]. It seems that increased oxidative stress due to increased BPA concentrations may also be associated with obesity as BPA exposure during pregnancy affects body weight in children by stimulating differentiation of adipocytes [9,10]. BPA toxicity at the

early stages of the fetus development may be demonstrated in the form of toxicoepigenetic modifications possibly affecting female fetuses more than male ones (sex specificity). The changes linked to pregnancy exposure to BPA possibly results in diseases appearing later in life [11]. Additionally, it was shown that BPA exposure during pregnancy may increase the possibility of gestational diabetes in overweight or obese mothers [12]. BPA in the environment affects lipid metabolism. Data from 4733 participants in the Canadian Health Measures Survey conducted during the period between 2007 and 2011 evaluated association of BPA concentrations in urine with body mass index and elevated waist circumference. A positive association was shown between BPA in urine and body mass index-defined obesity [13]. It was also shown that exposure of the fetus to BPA is negatively reflected in the concentrations of leptin and is positively associated with concentrations of the high-molecular-weight adiponectin [14]. BPA seems to be influencing the risk of developing obesity later in the life of the exposed person and should be regarded as an environmental obesogen responsible for pathophysiological processes related to obesity (increased adipogenesis, lipid, and glucose dysregulation, and adipose tissue inflammation) [15]. This is especially true for the early stages of a person's development.

BPA as an endocrine disruptor

Various aspects of endocrine disruption by BPA were studied from the beginning of the 21st century (2004) where data were published regarding the difference of BPA concentrations in premenopausal women and those with endometrial hyperplasia [16]. The authors have shown associations between BPA serum concentrations and complex hyperplasia of the endometrium and cancer in this area. Simple benign hyperplasia was not associated with BPA exposure. In 2006, BPA was studied from the angle of its estrogen-mimicking properties [17]. It was shown that perinatal exposure to BPA in concentration that a present in the environment leads to morphological and functional changes of genial tracts and mammary glands of males and females that may decrease fertility and increase the incidence of breast and prostate cancers. In vitro experiments shown that BPA may interact with human estrogen and androgen receptors, and also with aromatase converting testosterone to estrogen and with various genes [18, 19] This area of research is very alive today as the need for an assessment of the potential damages caused by the presence of BPs (including BPA) in the environment and for the understanding of the mechanism(s) of these damages and consequences for humans is highly significant.

A) Male endocrine functions

As the investigations of the BPA effects continue, more and more data on the aspects of its negative effects on the human body are accumulated. BPA is recognized to be a pervasive environmental toxicant affecting reproductive systems. Exposure to BPA leads to changed hormonal levels in males resulting in the worsening sperm quality [20]. Recently, the data were published from the study assessing the relationships between BPA concentration in urine, quality of sperm and hormonal levels (follicle-stimulating hormone, luteinizing hormone, testosterone, inhibin B and estradiol) in 215 healthy Spain university students (age span 18-23 years). The median urine concentration of BPA in the studied subjects was 2.8 ng/ml. A significant positive association of urinary BPA level and serum luteinizing hormone concentration was discovered together with significant inverse association with sperm concentration and total sperm count only. It was concluded that BPA in the body decreases sperm counts in young men [20]. However, some published data are conflicting or they link BPA exposure and endocrine functions to other environmental factors that are not clear [21]. Data on BPA concentration in adipose tissue (144 patients) showed that a median accumulation of BPA was 0.54 ng/g of tissue [22].

B) Female endocrine functions

The effects of female endocrine function also seem highly important since a fetus is vulnerable to external factors due to rapid cell division, development of various systems of the human body and also due not fully functioning detoxification mechanisms. BPA was tested on its ability to affect ovaries during the prenatal period. The published review summarizes the information and raises concerns regarding BPA effects on ovaries and their functions [23]. An important fact was already established that replacing BPA with its analogs (BPS or BPAF) does not decrease the risk of endocrine interference and disruption. On the other hand, this replacement may lead to an even higher level of endocrine disruption [24]. Endocrine disruption is reflected by changed concentrations of human chorionic gonadotropin (hCG), a hormone playing a key role during pregnancy. BPA influences the production of hCG and this hormone may subsequently be suitable for becoming a clinical biomarker of fetal damage by any endocrine disruptor, BPA included [25]. The data were reported that the BPA exposure affecting methylation of some specific genes may be female-specific [26]. This indicates that epigenetic changes happening early in life (even prenatally) may be reflected by the increased risk of some diseases during life, especially in females. However, these associations need to be further elucidated. It is clear at the moment that BPA adversely affects neuronal development because it acts not only as an endocrine disruptor but also as a non-gender-specific neurodevelopmental disruptor [27].

C) Glucose-control system

BPA acts not only as an endocrine disruptor but also as a metabolic disruptor. It was shown that exposure to BPA is mirrored by increased concentrations of inflammatory markers (interleukin 6 – IL-6; tumor necrosis factor-alpha – TNF-α), senescence markers and some receptor markers. BPA concentrations are positively correlated with decreased glycemic control and insulin resistance, and negatively correlated to telomere length [28]. Estrogen-related receptor gamma (ERRγ) was recently found to serve as a BPA receptor and its levels are also increased in patients with diabetes mellitus [28-30].

BPA and cancer

Exposure to BPA was always considered to be leading to malignant transformations of hormone-sensitive cells. As this issue is still very important, various epidemiological, clinical and experimental studies are being conducted. Recently it was shown that female mice fetuses exposed to this substance or during their early life had 17 altered proteins in thyroids. Some of these proteins (ANXA6 and VCP) can be utilized as biomarkers indicating the potential risk of thyroid cancer (in women) that depends on BPA-early life exposure [31]. Additionally, prenatal BPA

exposure affects obesity later in life as shown by modified methylation in gonadal tissue [32]. The intensity of Fggy mRNA expression correlated with increased body weight and weight of fat in gonads of males but this is not reflected in females. Consequently, prenatal BPA exposure modifies some epigenetic regulation of Fggy in mice [32] BPA is obviously associated with cell signaling taking place in cancer development and inflammatory or immune response-related cell signaling and also in other pathways implicated in cancer development. Diverse molecular and epigenetics processes modified by BPA exposure consequently lead to the development of hormone-dependent tumors of several organs (breast, ovary, prostate). This area was well covered by some recent reviews [33]. Application of modern analytical instrumental methods made it possible to study the potential increase in cancer risk through BPA exposure through BPA metabolic intermediate and DNA adduct formation [34]. It was documented that BPA-DNA interaction is based on the reaction /adduct formation of BPA 3,4-quinone (BPAQ) and of 2'-deoxyguanosine resulting in the formation of 3-hydroxy-BPA-N7-guanine. Consequently, the ability of bisphenols to form quinone metabolites may reflect on their carcinogenic potential. Another factor contributing to the carcinogenicity of bisphenols is their ability to cause oxidative DNA damage, even at a concentration as low as 1 ng/ml [35]. Additionally, at the cellular level, BPA interacts with GTPases that control cellular processes by their activation/deactivation. The alteration of various activities may lead to malignancy [36]

The various BPA-induced processes related to its carcinogenicity (cytotoxicity, reactive oxygen species formation, DNA fragmentation, caspase-3 activity, genes expression, and others) were studied in cell lines of various organ origin, such as human bronchial epithelial cells or human ovarian adenocarcinoma [37, 38]. It was shown that BPA doses that are environmentally relevant can affect the gene expression profile and that these doses increase epithelial to mesenchymal transition through the Wnt signaling pathway (transducing molecular signals initiated by binding of a Wnt protein on the surface of the target cell resulting in a change in cell state) [38].

An interesting observation was made when breast and breast cancer cells were exposed to hormonally stimulated mixtures of different xenoestrogens (BPA, p-methylparaben and perfluorooctanoic acid). Because these substances are present in the human environment, humans are subjected to the toxicity of all of these compounds at once [39]. There were both additive and synergistic effects observed. The combination of compounds mentioned above that were used at comparably low concentrations had distinct complex effects on the functioning of normal breast cells. These effects are different from the effects of single components of the mixture. Synergistic effects in the presence of BPA were mainly related to estrogen receptors. The important finding is that nonmalignant breast cells possess increased sensitivity towards the action of the compounds tested compared to breast cancer cell lines, and this was confirmed in experiments using material from the normal breast tissue (14 women) [39]. BPA is a strong estrogen disruptor because of its binding to non-classical membrane estrogen receptors (estrogen-related and G protein-coupled receptors - GPER). BPA-exposure direct link to the incidence of breast cancer was shown as this substance can change various molecular pathways in cells (i.e. GPER pathway, estrogen-related receptor gamma (ERRγ) pathway, HOXB9 or homeobox-containing gene pathway, bone morphogenetic proteins 2 and 4 (BMP2 and BMP4), immunoregulatory cytokine disturbance in the mammary gland, EGFR-STAT3 pathway, FOXA1 in ER-breast cancer cells, enhancer of zeste homolog 2 (EZH2), and epigenetic changes [40] Consequently, removing BPA from a human environment should result in a decreased risk of breast cancer. [40] Additionally, it is important to notice that BPA decreases the cytotoxicity tamoxifen (*in vitro*), an estrogen receptor antagonist through suppression of apoptotic processes, disturbance of cell cycle and upregulation of estrogen receptor α. Consequently, the presence of BPA in the environment may cause resistance to therapy by tamoxifen in breast cancer patients [40]

Interesting work was published showing the interaction of BPA and its alternative bisphenol S (BPS) with the thyroid and its functions [41]. The authors evaluated the potential interactions of both BPA and BPS with thyroidal transcription factors Pax 8 and TTF1. Some differences in BPA and BPS interactions with proteins were discovered that may explain variations of biological activities of these compounds in the thyroidal tissue [41]. Examination of the effect of the urinary BPA concentration on the occurrence of thyroid nodules in Chinese women patients (705 patients with thyroid nodules compared to 711 controls). [42] It was concluded that increased BPA levels in the urine are associated with an increased incidence of thyroid nodules but only in women that are positive for thyroid autoantibodies. This relationship was almost linear. This led to the conclusion that any increase in BPA in an environment and consequently in the urine increases the risk of thyroid nodules. Recently it was demonstrated that BPA is implicated in the incidence of not only hormone-sensitive malignancies but also in the incidence of hormone-non-sensitive tumors through the etiopathogenesis of involving various factors of genetic, epigenetic, inflammatory, immune, metabolic, hormonal and oxidative stress nature. BPA was shown to deregulate various signaling pathways as shown in cases of oral cancer and the most prevailing subtypes of head and neck tumors [43].

BPA in dentistry

The dental practice is an area of health-care that where patients may be exposed to increased BPA concentration as it is a part of various fillings, sealants, etc, but it was reported that the risk of BPA release is quite low as determined by using instrumental analytical methods [44]. However, it was shown that BPA concentrations in the saliva of patients undergoing dental restoration using a BPA-containing polymer increased for approximately one week. Such changes were not observed in the urine of these patients [45]. Until now, it is not clear how the potential increase in BPA concentrations in body fluids of dental patients may affect their wellbeing as relevant toxicological data are not available [46]. On the other hand, the reported concentration observed in patients are under the daily reference doses or they are evaluated as “did not reach toxic levels for the pulp”, or as “very low” [47], Additionally, when the suggested-by-European-Food-Safety-Authority limit of 50 µg/kg/day (Tolerable Daily Intake of BPA) was considered, the BPA concentrations in saliva after dental restorations with composite materials were safe and not hazardous [48]. Additionally, the investigation that used data from the Norwegian Mother

and Child Cohort Study regarding 90,886 pregnancies out of which 33,727 women reported dental interventions and 10,972 got white fillings placement during the pregnancy period shown that there was no increased risk of adverse birth outcomes in mothers who obtained white fillings during their pregnancy [49]. Consequently, it seems that the short-time exposure to BPA and BPA-containing dental material is not risky for the patient but that the attention should be paid to chronic exposures to BPA in the environment.

Properties of some BPA alternatives: An example of BPF and BPS

Because of the biological, especially hormone-disrupting properties of BPA, and consequently, because of the determined risk of this substance, several derivatives and analogs of BPA were prepared and tested. Two representatives of bisphenols, namely BPF (Fig.1G) and BPS (Fig. H) will be discussed further.

BPF is 4,4'-methylenediphenol or 4-[(4-hydroxyphenyl)methyl]phenol according to IUPAC nomenclature. Its molecular formula is $C_{13}H_{12}O_2$ or $CH_2(C_6H_4OH)_2$. Its molecular weight is smaller than in the case of BPA due to the absence of methyl groups and is 200.2 g/mol. As BPF sublimes, it does not have has a boiling point value, its melting point is 162.5 ^oC. Compared to BPA, it is a bit less lipophilic as its log P-value is 2.91 but it has a bigger dissociation constant pKa of the value 7.55 [50]. BPF is soluble in ethanol, ether, chloroform and alkaline solutions due to its phenolic hydroxyls [50]. BPF possesses estrogenic properties [51]. It is eliminated from the body as glucuronide and sulfate, and also in the form of several hydroxylated products of metabolism. Its prevailing metabolites are 2- and 3-hydroxylated BPF products of the metabolism and also some dimeric compounds. It is similar to other BPs in this regard [52].

BPS is another broadly used BP. BPS is chemically 4,4'-sulfonyldiphenol or, according to IUPAC, 4-(4-hydroxyphenyl)sulfonylphenol. BPS has molecular formula $C_{12}H_{10}O_4S$ and molecular weight 250.3 g/mol. Its melting point is 240.5 ^oC and decomposes under further heating. BPS is insoluble in water but soluble in ethanol. Its log P-value is 1.65 and dissociation constant value of pKa = 8.2 [52].

Recent scientific reports bring new data on the potential risk of both of these compound BPF and BPS. It was reported that not only BPA but also its derivatives are present in the environment, food, and also in the human body. Important findings are that toxicities of BPs are similar to those of BPA and that these toxicities are in some cases even higher than in the case of BPA. Both BPF and BPS together with BPA were detected even in the human breast milk samples [53]. Also, the presence of seven BPs was confirmed in various personal care products, i.e. in hand sanitizers with the maximum concentration of 87 ng of BPs/g of a product [54]. BPA and BPF being in general of the highest concentrations. The presence of BPs in personal care products is a significant finding as the skin is the main point of entry of all BPs to the body from these products [54]. Because of the body of information available on BPA, there are attempts to be replaced with other BPs, i.e. BPS and BPF. There is less information on endocrine-disrupting properties of these BPs and also less information on their other potentially-harmful effects on the human body. Additionally, the scientific literature today shows that both BPS and BPF have the same/similar hormonal (endocrine) disrupting properties as BPA [54].

The study on the presence of BPs in food samples taken in the USA showed their presence in 75% of the samples analyzed. The highest concentration of BPF was discovered in a sample of mustard – 1130 ng of BPF per g of mustard [55]. In general, canned food was found to contain a higher concentration of BPs. Worryingly, the highest intake of BPs was calculated to be in the group of toddlers (243 ng/kg of body weight per day). These values decrease gradually with age and were 'only' around 59 ng/kg of body weight per day in adults [56]. When BPS was followed, it was proved is present in the human environment in the dust, water, sediments, plants, food, etc., and even in the human body. [56] Its toxicity is similar to BPA but toxicity profile is not fully identical as it may cause decreased hormonal disruption and decreased eproductive toxicity [56]. However, further investigations are required for full understanding and elucidation of its actions in humans. This is especially important as BPS is starting to contaminate the human environment [57]. The study performed on water samples from the Yangtze river and human serum sample from donors living in its proximity showed that BPS concentrations were 0.18 - 14.9 ng/l. Human serum samples contained a maximum of 169 ng/ml of BPS, however, the median value was 0.65 ng/ml of BPS. Data provided by a pharmacokinetic study performed on 7 healthy and young volunteers getting one oral dose of deuterated BPS (8.75µg/bw of d_4-BPS) indicated rapid absorption of BPS less than 1 hour (0.7±0.3 h) [57]. BPS was excreted in the urine. Men excreted BPS faster compared to women as they excreted 92±17% of BPS during 48 hours and women excreted only 70±36% of BPS [57]. An excellent review summarizes various data from BPS investigations published between 2010 and 2017 [58]. These data indicate that BPS is present in the environment at concentrations lower than BPA. This reflects so far more extensive use of BPA compared to BPS. All the data taken together show that BPS negatively affects reproductive, endocrine and also nervous systems. Food is the most significant in human BPS exposure [58]. However, non-dietary types of BPS exposure are also important for the BPS health risk assessment [58].BPS and BPF were introduced into the production of various materials as substitutes of BPA as this compound was investigated quite extensively because of its endocrine-disrupting properties. Unfortunately, both of these substances have a similar-to-BPA effect on the human body and the "BPA-free" labeling of various products is the kind of misleading for the population using such products as the effects of BPS and BPF are, basically, of the same significance as the effects of BPA (estrogenic, antiestrogenic, androgenic, and antiandrogenic) as tested both *in vitro* and also *in vivo* [59]. The fact the various BPs possess similar endocrine-disrupting activity is not surprising as the requirements for this type of activity are fulfilled in these compounds [60]. e structure-estrogen-disrupting activity relationship was analyzed and it was determined the various BPs fulfill the criteria of their structure resembling endogenous 17β-estradiol during their interactions with estrogen receptors. Namely, two hydroxyl groups can mimic the proton-bonding ability of 17β-estradiol hydroxyl groups in positions 3 and 17β and the appropriate distance between these two hydroxyls (or more precisely, between their oxygen atoms). The steric parameters of BPs molecules mimic hydrophobic centers created by the substituents at positions 7R- and 11β. BPs possess hydrophobicity appropriate-for-this-interaction, and also, they contain aromatic ring(s) with their rigidity

favoring estrogen-receptor binding. Simplification of these requirements specifically for BPs' to bind their structure to estrogen receptors requires the presence of a phenolic ring connected to another benzene ring directly or through one, two or maximum three other atoms [60].

In summary, the endocrine-disrupting and other toxic side effects of BPA are relatively well established. It is also shown that short exposure to BPA should not be risky, i.e. in dentistry. However, long exposures to BPA are damaging to individuals and the whole population. Attempts to replace BPA with other BPs in products that are coming to close contact with people and potentially stay in our environment were undertaken to replace a substance with relatively well-researched toxicities by similar substances. It seems at this moment that this strategy does not work well for two reasons: 1) as these newer substances are being researched more in detail, the presence of similar-to-BPA toxicities of the 'newer' BPs are discovered rendering this replacement problematic; 2) study of the structural requirements for a molecule to serve as an endocrine-disruptor shown that, in principle, all BPs fulfill structural requirements necessary for endocrine disruption. Consequently, according to our opinion, there are 3 main directions for development in the area of bisphenols use and utilization. These are 1) Finding ways that prevent the liberation of BPs into an environment through the use some other co-additives in the production of various plastic materials; 2) findings ways of better elimination of liberated-into-the-environment BPs from the human environment, i.e. water or soils; and 3) finding replacements for BPs currently used. These potential new replacements should not have structural features necessary for the endocrine disruption in mammals.

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Conflicts of Interest

The authors declare no conflict of interest. We also declare that the funding source had no involvement in study design, in collection, analysis and interpretation of data, in writing of the report; and in the decision to submit the article for publication.

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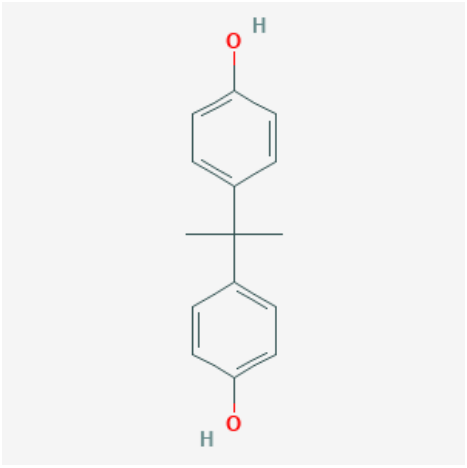
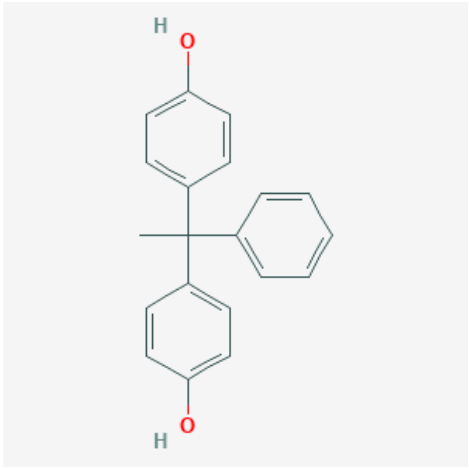
Fig. 1. Chemical formulas of selected bisphenols and related-to-them diethylstilbestrol. A) BPA; B) BP AP; C) BPAF; D) BPB; E) BPBP; F) BPE; G) BPF; H) BPS; J) diethylstilbestrol.



A



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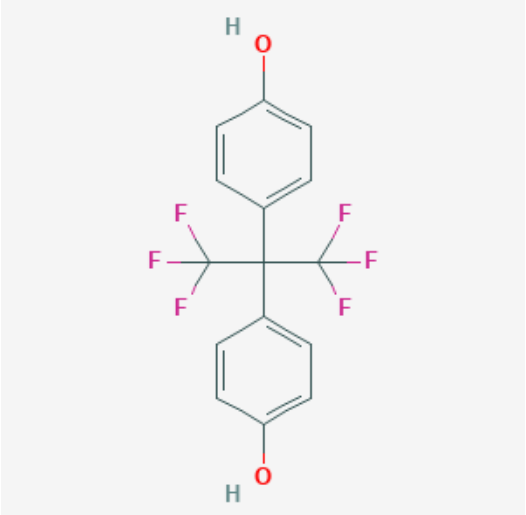

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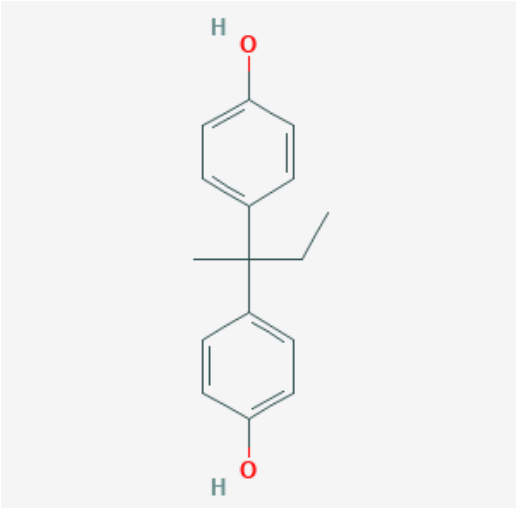

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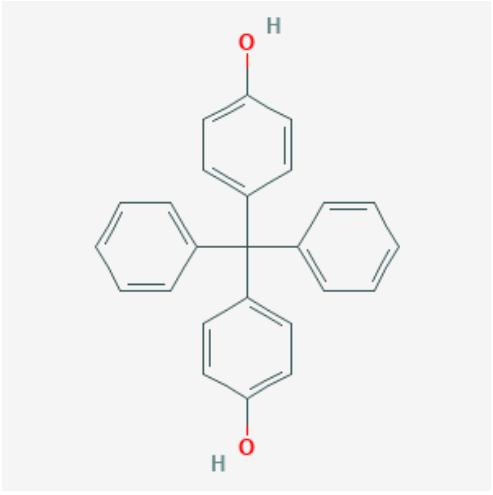

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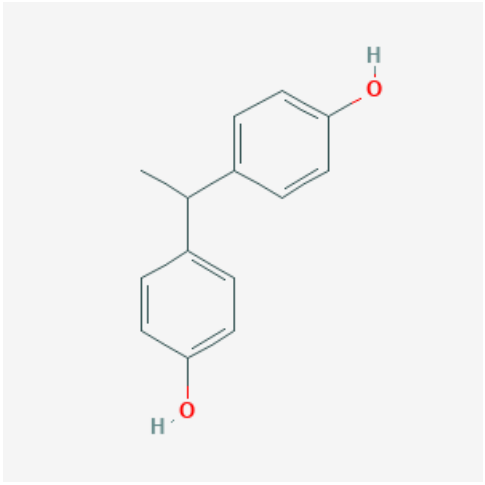

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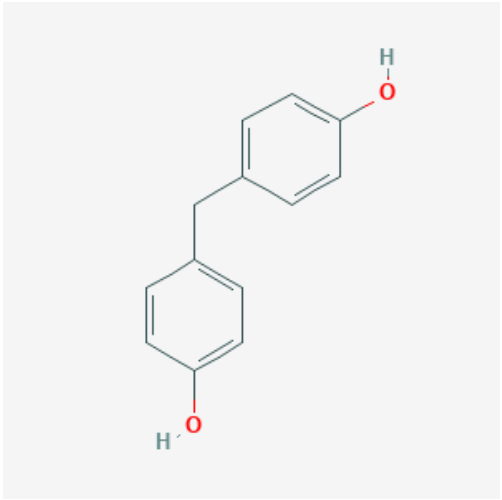

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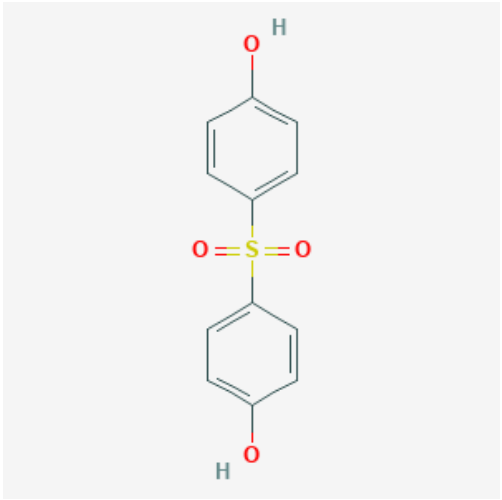

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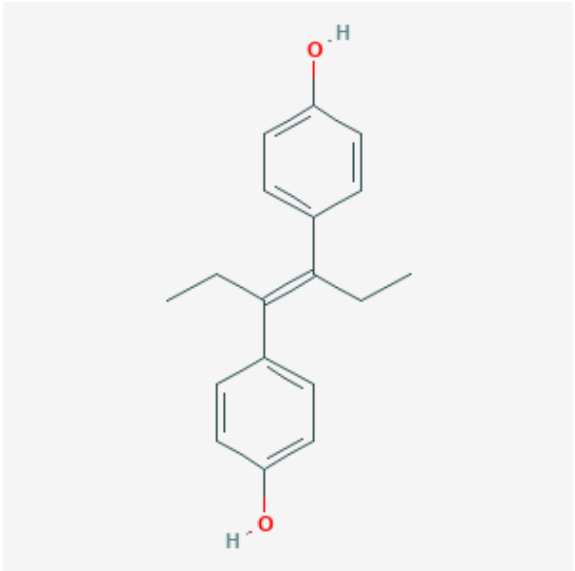

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