Chapter

Toxic Effects of Bisphenols: A Special Focus on Bisphenol A and Its Regulations

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Abstract

Bisphenol A (BPA), which is an abundant chemical in the environment, is suggested to cause different toxic effects, including endocrine disruption, reprotoxicity, developmental toxicity, and neurotoxicity. Due to these effects, regulatory authorities have restricted the use of BPA in different consumer products, particularly in products used by children. These restrictions have led to researchers and plastic industry to find new and safer alternatives. Today, bisphenol F (BPF) and bisphenol S (BPS) are highly used although their toxic effects are less known. In the past years, several studies showed that these derivatives might also act as endocrine disruptors and cause toxic effects. BPA is a substance that is carefully monitored by regulatory agencies, and toxicological data are evaluated regularly. The alternatives, such as BPF and BPS, should also be monitored, and the regulations concerning their use in consumer products must be implemented soon. The increase in the number of studies on BPA and different bisphenols is very important in terms of obtaining new toxicological data and guiding regulatory institutions. This chapter will mainly focus on BPA, its toxicity, BPA alternatives, and regulations implemented by different American and European authorities.

Keywords: bisphenol derivatives, endocrine disruptor, bisphenol A, bisphenol F, bisphenol S, regulations

1. Introduction

Bisphenols are a large family of chemicals used to produce polycarbonate and epoxy resins. Bisphenols contain two phenolic rings linked by a bridge formed by carbon and other chemical structures. There are many different derivatives of bisphenols, and the capital letter after bisphenol is used to express the reactant atom/component within the molecule. For example, the reactant group is acetone in bisphenol A (BPA), formaldehyde in bisphenol F (BPF, 4,4′-dihydroxydiphenylmethane) and sulfur trioxide in bisphenol S (BPS, 4,4′-sulfonylbisphenol) [1, 2].

The most commonly used derivative of bisphenols is BPA. BPA is a compound that consists of two phenol rings linked by a methyl bridge containing two functional methyl groups. Bisphenol A (BPA) was first synthesized in 1905 by the condensation of phenol and acetone in the presence of acidic catalyst. BPA is generally used to harden plastics since the 1940s. In the early 1930s, the use of BPA as an artificial estrogen was considered. However, diethylstilbesterol (DES), a more potent estrogenic compound, was preferred to BPA in pharmaceutical use [3, 4].

BPA is being used in plastics for many years in combination with other chemicals. BPA-containing plastics are on the market since 1957. In 2003, 856,000 tons of BPA was produced. It was recorded that 72% was used in the production of polycarbonate plastics and 21% was used in the production of epoxy resin. In 2009, global production of BPA exceeded 2.2 million tons. In 2011, it was reported that ~5 million tons were produced [5]. It is estimated that its production will increase to 10.6 million tons by 2022 [6].

It is shown that BPA can leach from polycarbonate plastics, epoxy resins, and other products in contact with foods and beverages, resulting in continuous exposure of the general population. Especially food coating materials or food containers containing BPA lead to a high risk of human exposure. In addition, actions such as mechanical abrasion, rubbing, or exposure to high temperatures also cause an increased risk of BPA release from these materials [7].

2. Biotransformation of bisphenol A

After oral exposure to BPA, this compound is rapidly absorbed from the gastrointestinal tract and undergoes first-pass effect in liver and intestines [8]. On the other hand, it is reported that BPA does not undergo the first-pass effect and is excreted more slowly after inhalation or dermal exposure [9]. Following oral absorption, BPA is rapidly metabolized in the human liver mainly by cytochrome P450 enzymes (CYP2C18 and to a lesser extent by CYP2C19 and CYP2C9) [10]. BPA is converted to inactive glucuronide conjugates by phase II reactions in the liver and kidney. In the presence of high levels of BPA, the glucuronidation pathway becomes saturated and the sulfatation pathway becomes active. BPA glucuronide formation is mediated by uridine diphosphate glucuronosyltransferases (UGT). UGT enzyme activity is lower in newborns compared with adults. Therefore, since the main detoxification pathway for BPA in humans and many other species is mainly by glucuronidation, it can be suggested that early-life exposure to BPA may have more serious consequences than exposure in adulthood. BPA is mainly excreted by urine. The elimination half-life of BPA is approximately 2–6 h, and almost the entire compound is excreted in the urine in approximately 42 h. In a study conducted with a small number of volunteers, it was shown that 9.5% of BPA was excreted unchanged in the urine, 69.5% as BPA glucuronide conjugate, and 21% as BPA sulfate conjugate [11, 12].

3. Studies on the toxic effects of BPA

In vitro, *in vivo,* and human studies have shown that BPA can have a wide variety of adverse effects on human health. Among these effects, reproductive and development problems due to estrogenic and anti-androgenic effects of BPA (i.e., alterations in estrogen and/or testosterone levels, changes in semen quality, low birth weight), metabolic diseases (such as diabetes and obesity), thyroid hormone disorders, organ damage (possibly due to oxidative stress, epigenetic alterations, and direct toxic effect), cancer (breast, prostate, etc.), and neurotoxicity (behavioral disorders, changes in brain chemistry, neurological diseases/disorders) are highly studied, and BPA exposure is linked to different disorders by many scientists [13–15].

3.1 Reproductive toxicity

Bisphenols may affect both female and male reproductive health although their effects are suggested to be more pronounced in males. Recent human studies show

that BPA exposure in adulthood is associated with decreased ovarian response, lower fertilization success and embryo quality, and polycystic ovary syndrome (PCOS). Moreover, BPA may cause male sexual dysfunction, decreased sperm quality, and changes in sex hormone concentrations. Both *in vitro* and *in vivo* studies indicate that environmental exposure to high doses of BPA may have adverse effects on reproductive health [13, 16, 17].

The harmful effect of BPA on male reproductive health can occur during embryonic and/or pubertal and/or adulthood. BPA may affect the hypothalamic-pituitary-testicular axis by modulating hormone synthesis, altering the expression and function of related receptors and disrupting testicular functions. Bisphenols, including BPA, are associated with reproductive disorders and infertility in males. In addition, BPA causes oxidative stress in testis and epididymis by inhibiting antioxidant enzymes and stimulating lipid peroxidation. BPA has been reported to have both estrogenic and anti-androgenic effects through interaction with estrogen (ER) and androgen receptors (AR) [18, 19].

3.2 Metabolic disorders

In the last 40 years, humans are abundantly exposed to wide variety of endocrine disrupting chemicals (EDCs) including bisphenols. Therefore, the first question that comes to mind is whether these diseases are associated with EDCs.

Many epidemiological studies associate EDCs, especially BPA, with obesity in humans. Most studies are cross-sectional analyses of the US National Health and Nutrition Examination Survey (NHANES) data in adults and children. The results of these research show that the higher the urinary BPA concentration, the higher the odds of obesity and larger waist circumference. Another study using a cohort in China reported an association between urinary BPA concentrations and overweight, obesity, insulin resistance, and diabetes mellitus. To our knowledge, only one prospective study has examined the association between prenatal and early-life exposure to BPA and children's body mass in 9-year-old girls. That work concluded that girls with the highest exposure to BPA *in utero* had lower weight for the same height than girls with the lowest exposure, a result that contradicts the previous studies. Due to such inconsistencies, further studies are required on larger sample sizes [20, 21].

Although pancreatic cells and adipocytes are not estrogen target tissues, they contain functional estrogen receptors (ERs). The insulin-increasing effect of BPA is similar to the effect of estrogen and occurs *via* ERα. Chronic hyperinsulinemia and subsequent insulin resistance have been observed in chronic administration of BPA [22].

3.3 Thyroid disruption

According to the results of the mechanistic studies, it has been stated that BPA can impair thyroid functions through many pathways. BPA has both agonistic and antagonistic effects on thyroid function as it can bind to thyroid receptors. It is suggested that BPA acts as a T_3 antagonist by binding to thyroid receptors with weak bonds and can inhibit transcriptional activity mediated by these receptors [23].

In a study conducted to examine the possible relationship between BPA exposure during pregnancy and thyroid hormone levels in the newborns and the mothers, urine samples were obtained from 476 women in the first and second trimesters of their pregnancies and their free and total T_4 and thyroid stimulating hormone (TSH) levels were measured. In addition, TSH levels were determined in newborns. Researchers stated that exposure to BPA during pregnancy might cause a decrease in

total T_4 levels in pregnant women and significant decreases in TSH levels especially in male newborns [24].

3.4 Neurodevelopmental and neuroendocrine effects

In the recent years, studies showed that the exposure to EDCs was related to cognitive deficiencies, slow neurodevelopment, increases in the incidence of aggression and depression, hyperactivity, and attention deficit problems [25–27].

It is reported that EDCs can have a wide range of effects on brain development, and many different mechanisms are proposed. Some of these effects are suggested to be through the neuroendocrine system. The neuroendocrine system is a complex system consisting of neurons, glands, non-endocrine tissues, humoral signals, hormones, and neurochemicals that function to regulate physiological and behavioral processes. There is a growing evidence that antropogenic chemicals, such as EDCs, may act on the neuroendocrine system, and they may affect peripheral organ systems and physiological processes. Functions of neuroendocrine system are largely related to the functions of neurotransmitters. Evidence suggests that brain neurotransmitter systems (including dopaminergic, adrenergic, serotonergic, and cholinergic systems) play an important role in the activation and/or inhibition of neuroendocrine system. This relationship necessitates the examination of neurotransmitters for the evaluation of neuroendocrine system. The regulation of both dopamine and serotonin production by estrogen-dependent mechanisms makes these systems vulnerable to the adverse effects of EDCs. Previous studies have reported that BPA and phthalate exposure might lead to imbalance in the levels of these neurotransmitters in various regions of the brain [15, 28, 29].

3.5 Atopic diseases

Estrogen receptors are found in many immune regulatory cells. Not only endogenous estrogens, but also environmental estrogens (xenoestrogens) play a role in allergic reactions. Worsening of asthma symptoms is reported among women (30–40%) at certain times of the menstrual cycle. Estrogens can increase antigen-presenting cell function and immunoglobulin E (IgE) synthesis by B cells, both in turn can trigger allergic diseases. It also promotes degranulation of mast cells/basophils. Studies show that BPA exposure increases the risk and incidence of allergic diseases [30, 31].

4. Bisphenol derivatives as alternatives to bisphenol A

Due to its adverse effects on human health, regulations have limited the use of BPA in various products (bottle bottles, toys, food containers, thermal papers). This has led to the search for alternative substances to BPA. BPF and BPS are structurally similar to BPA and they are widely used in industrial products as alternatives [4, 6]. It is known that BPS has a very common use. According to the European Chemicals Agency (ECHA), 1000–10,000 million tons of BPS are produced or imported annually in Europe [32]. BPF is still a low-use chemical, at least in Europe when compared with BPA and BPS [4, 6].

The sources of exposure to BPA and its derivatives BPS and BPF are very similar worldwide. Humans are exposed to bisphenol derivatives orally through food, dermally with personal care products and thermal papers, and by inhalation of environmental dusts. BPA, BPF, and BPS have been detected in many environmental samples, including soil, sediments, water, and sewage sludge [4, 6]. In addition,

BPS and BPF have been detected in the content of many products, such as personal care products in daily use (e.g. body washes, hair care products, makeup, lotions, toothpaste) [33], paper products (e.g. currency, food cards, flyers, tickets, mailing envelopes, plane boarding), and foods (e.g. dairy products, meat and meat products, vegetables, canned foods, cereals) [4, 6]. BPS is also used in cleaning products, electrical product coatings, and various industrial applications as a component of phenolic resin, as well as in thermal papers, including products marketed as "BPA-free paper." BPF is present in systems requiring increased thickness and durability such as water pipes, dental sealants, tank and pipe coatings, industrial floors, road and bridge deck coatings, structural adhesives, and mortars (i.e., high solids/high build systems). Moreover, it is also used in food packaging. BPF is also a component of epoxy resins [4, 6].

Recently, BPS and BPF have attracted the attention of many researchers due to their increasing use. Numerous studies on BPF and BPS have contributed to the determination of their toxic effect profiles and have guided various regulations. Various *in vitro* and *in vivo* studies have shown that these substances may also show estrogenic activity similar to BPA and may have endocrine disrupting effects due to its effects on ERs, ARs, and thyroid hormone receptors. Studies have also shown that they might cause reproductive toxicity, cytotoxicity, genotoxicity, and mutagenicity [34–37].

5. Regulations on bisphenol A and its derivatives

5.1 Food and drug administration

Food and Drug Administration (FDA) banned the use of BPA in baby bottles and sippy cups in June 2012. Afterward, the FDA banned the use of BPA in food packages used in baby nutrition products in June 2013 [38]. FDA has set the oral "no observed adverse effect level (NOAEL)" value for BPA at 5 mg/kg bw/day [39].

5.2 European food safety authority

The European Food Safety Authority (EFSA) comprehensively reassessed BPA exposure and toxicity in January 2015 and reduced the tolerable daily intake (TDI) for BPA from 50 to 4 μg/kg body weight/day. EFSA stated that different evaluations will be made and that this is a temporary value. EFSA experts calculated the "benchmark dose" for BPA (in which BPA causes a small adverse effect in the kidneys of mice) as 8960 μg/kg bw/day. Considering the difference between species, this value has been calculated as 609 μg/kg bw/day for humans [40].

In 2020, two projects carried out by Belgium and ECHA on the toxic effects of BPS were completed. According to the results of these two studies, the oral NOAEL value was determined as 20 mg/kg/day in rats. It has been concluded that this value is not at a level to change the "specific migration level" (SML) (i.e., the amount of substance allowed to leak into the food), which is 0.05 mg/kg, and therefore, there is no risk of BPS in contact with food [41]. EFSA's scientists recommend that more toxicological data are needed for the safe use of BPS in food contact materials. They suggest that these data can clarify its possible use as an alternative to BPA [42].

The NOAEL value of BPS for developmental toxicity and developmental immunotoxicity was determined as 20 mg/kg bw/day [42]. While the NOAEL value for general systemic toxicity was 60 mg/kg body weight, a high value of 180 mg/kg bw/day was determined for developmental neurotoxicity, fertility, and reproductive disorders [42]. However, new data on the biotransformation of BPS support that

BPS is rapidly metabolized and eliminated from rats [42]. Therefore, EFSA recommends that more toxicological data should be collected in order to put new regulations on action for BPS [42].

5.3 European Commission

Bisphenol A is classified as a substance, which "may harm fertility (Repr. 1B)"; "cause respiratory tract irritation (STOT SE 3)"; lead to "to serious eye damage (eye damage 1)" and cause "skin allergies (skin sen. 1)" in the EU in 2008 [43]. On March 29, 2010, the Danish Government banned the use of BPA-containing food contact containers for children between 0 and 3 years of age. In July 2010, the Commission of the French Government and on July 9, 2010 all EU member States decided to implement the safeguards laid down in Article 18 of Regulation (EC) No 1935/2004 and to temporarily prohibit the importing, exporting, marketing, and manufacturing of baby bottles containing BPA. Therefore, it was stated that all BPA-containing baby bottles on the EU market should be replaced by mid-2011. With the Commission's updated opinion in 2011, the decision to ban the use of BPA in the production of polycarbonate baby bottles continues [44].

In EU, permissible migration limit values for chemicals used in chewable toys, which are used by children under the age of 3, are set within the scope of the "Toy Safety Directives." According to this directive, it states that the BPA content that can be found in toys should be lower than 0.04 mg/L [45].

By the regulations accepted in 2011, the specific migration limit (SML) was determined as 0.6 mg of BPA per kg of food. The opinion adopted in the EU on December 11, 2014 also defined sources of non-dietary exposure (airborne exposure, ingestion of dust, and ingestion through the skin because of contact with thermal paper and cosmetics). The panel concluded that exposure estimates to BPA through dietary and non-dietary sources were below the TDI and lower than levels that might lead to health effects for the highest-exposure groups, including infants, children, and adolescents [44].

In the EU, restrictions and regulations for food-contact plastics are also beginning to be applied to the use of BPA in the inner coatings and varnishes of non-plastic food containers. In particular, precautions should be taken for the coating materials used in baby and child products so that BPA does not migrate to this product. The SML level should not exceed 0.05 mg BPA per kg food. Therefore, producers should submit to the competent authorities appropriate supporting documents confirming the declaration of conformity. Varnished or coated materials and items that were legally released before September 6, 2018 are allowed to remain on the market until stocks last. The regulation is valid for productions after this date [46].

The classification of substances of very high concern (SHVC) by Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) is based solely on the properties of the substance itself, without considering the potential risks associated with the use and exposure of the substance [47]. BPA is included in the REACH SVHC Candidate List. In April 2019, the German authorities presented the proposal to classify BPA as both acute and chronic hazard Category 1 for the aquatic environment [48]. At the initiative of the French authorities, the use of BPA in thermal paper has been evaluated. In their assessments, the ECHA Committees stated that the BPA used in thermal paper does not pose a risk to consumers, but has potential risks to the health of workers who process receipts [49]. As of January 2, 2020, a concentration limit of 0.02% (w/w) has been set for the use of BPA in thermal papers [49]. For BPS, in accordance with Regulation (EU) No. 10/2011, the SML value for use as a monomer in food contact plastic materials (FCM) is 0.05 mg per kg food currently [49].

5.4 BPA regulations predicted for the future

BPA is a substance that is carefully monitored by regulatory agencies, and toxicological data are evaluated regularly. In addition, alternatives to BPA, which are planned to be replaced in the industry due to its toxic effects, are also closely monitored regulatory authorities [50]. In this context, ECHA and EU Member States have started to evaluate data on a large group of bisphenols, such as BPA, BPS, BPF, and their derivatives, from the beginning of 2020. In addition, France and Sweden suggested that the use of these substances in the textile, leather, and fur industries should be restricted because they may cause dermal toxicity [49]. More than 1000 substances, including BPA and its derivatives, are covered by Skin Sens under Regulation 1272/2008 on Labeling and Packaging of Chemicals (CLP), and they were classified as Skin irrit 2 (causes skin irritation) and/or Skin corr. 1/1A/1B/1C (causes severe skin burns and eye damage) [51]. For this reason, it is suggested that the use of BPA and its derivatives will most likely face restrictions. The increase in the number of studies on BPA and different bisphenols is very important in terms of obtaining toxicological data and guiding regulatory institutions.

6. Conclusion

Although complete of ban of BPA in different consumer products seems to be impossible in the near future, new and safer alternatives of this substance should be synthesized. Although BPF and BPS were suggested to be safer, data from different *in vitro*, *in vivo,* and human studies show that they may also cause toxic effects. Therefore, regulations for the use of different bisphenol derivatives should be implemented, and new data on their different toxic effects should be evaluated. Although life is inevitable without plastics, their uses particularly in products used by susceptible populations, such as infants and children, should be restricted by regulatory authorities. In addition to the restrictions imposed by regulatory agencies, public awareness will make a great contribution to reducing the exposure of sensitive populations to common plasticizers such as bisphenols.

Conflict of interest

The authors declare no conflict of interest.

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