

Bisphenol S: A potential toxicant in daily use (Review)

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Abstract. Plastics are being increasingly used in the preparation of products for daily use and have been reported to produce various harmful effects. Therefore, these effects are a matter for concern. These effects have been often attributed to the presence of Bisphenol A (BPA), which has been a key important component in the manufacturing of plastic wares. In view of the increasing concerns, currently, the chemical is being replaced by its analogues, which are considered to be safer, leading to the production of new-generation BPA-free products. However, the analogues of BPA are also reported to exert toxic effects. BPA is being replaced by Bisphenol S (BPS) in plastic products and is considered to be safer due to its extremely decreased ability to leach out from plastic wares. However, various *in vitro* and *in vivo* studies have demonstrated that BPS exerts toxic effects on physiological processes; however, due to the limited number of available studies on the toxicity of BPS, a number of undesired effects of this compound remain unexplored. In the present short review, the toxic effects of BPS are described.

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1. Introduction

Bisphenols are group of organic compounds used for the manufacturing of plastic wares. Over a number of years, Bisphenol A (BPA) was a key constituent in the manufacturing of plastic products. The global production of BPA has

exhibited progressive increase due to the increasing demand of plastic wares (1). BPA is also used as a coating for food and beverage cans, and thermal papers, which are commonly used by individuals (2-5).

Researchers worldwide have raised their concern over the use of BPA in plastic wares, food cans, thermal papers, etc., since BPA has been reported to exert significant health-related and environmental toxic effects (6-11). BPA is an endocrine disruptor and BPA exposure has been associated with diseases, such as cancer, diabetes, obesity, reproductive disorders, neuronal disorders, immune disorders and cardiovascular (CV) system dysfunction (6-11). BPA has been reported to produce behavioural abnormalities and prenatal exposure to the chemical has been shown to be associated with respiratory disorders in childhood. Detectable levels of BPA have been found in the urine of >90% of individuals examined in US sample populations (12). It has been reported to leach from infant feeding bottles made of plastic and produce tissue damage in rats due to oxidative stress (13). Furthermore, it has been reported that the feeding of infants through these bottles produces alterations in biochemical parameters (14). Recently, BPA has been reported to exert a hyperglycemic effect, and changes in albumin and total protein levels in mice (15).

Amidst these concerns, bans/regulations have been imposed on the use of BPA by governments in several countries (16,17). Hence, manufacturers are gradually replacing BPA with BPA analogues, such as Bisphenol G (BPG), Bisphenol S (BPS) and Bisphenol F (BPF) due to the toxic effects of BPA. BPS is a commonly used analogue in industrial applications, replacing BPA. BPS has two phenol functional groups on either side of the sulphonyl group, which renders it heat-stable and sunlight-resistant. Chemically, it is being used as a reagent in polymer reactions. Due to its heat-resistant property, it is less likely to leach out, as compared to BPA and is hence considered safe for use (18).

However, in the study by Danzl *et al* (19), it was found that there was no BPS degradation in sea water, which suggests that the compound is expected to stay in the environment for a longer duration. This is relatively alarming as the burden of the chemical is expected to increase with time. In another study by Ike *et al* (20), the biodegradability of various bisphenols was examined, and it was found that their order of biodegradability under aerobic conditions was BPF,HBP>>BPA>BPP>BPE>BPB>TDP>>BPS, whereas the order of anaerobic biodegradability was BPF>HBP>BPS,BPA,TDP>BPE>BPB.

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Although BPS is currently considered to be the least toxic chemical in the family of bisphenols (BPA, BPG, BPS and BPF), emerging evidence has indicated that even BPS is not a safe substitute; by contrast, BPS exerts biological disruptive effects which are similar to or even more prominent than those of BPA (21-23). BPS has been found in canned foods (3,16). Recently, it was found that BPS in picomolar concentrations could disrupt the normal functioning of cells (24). Furthermore, as demonstrated in previous studies, when lower animals, such as zebrafish larvae were chronically exposed to BPS, it induced developmental deformities in several organs, including the heart (25,26). Recently, in a study on 315 urine samples collected from the USA and seven Asian countries from females and males aged 2-84 years, BPS was detected in 81% of the samples, with an overall mean urinary concentration of 0.65 ng/ml (2.6 nM) (27).

Previous studies have shown (28-30) that BPS also exerts toxic effects on multiple organs; however, the available data are limited. Hence, in the present review, the toxic effects of BPS on various organs are described. The search for articles was conducted using PubMed, Google Scholar and Web of Science. Articles from the year 2005 onwards were selected for inclusion in the present review. The criteria used to select relevant articles were exposure to BPS, and its effects on the reproductive system, cardiovascular system, neural growth and behaviour, obesity, liver and gut motility.

2. Exposure to BPS

Humans are exposed to both BPA and BPS mainly through the dietary route by ingesting canned foods and beverages. Likewise, the inhalation and cutaneous absorption of BPS through bank notes and thermal receipts have also been reported (3,31,32). BPS has been detected in numerous products used daily, such as shampoo, toothpaste, lotions, etc (33). BPS has been found in paired maternal and cord serum, suggesting that human foetuses may be exposed to BPS through the placenta (34).

In order to understand the toxicokinetics of BPS through the oral route in humans, the piglet model, which is considered a standard, was used by Gayrard *et al* (35). It has been reported that oral BPS is completely absorbed from the intestine in pigs. The ingested BPS is mainly metabolised in the liver and only 41% of this absorbed BPS is glucuronidated, which indicates that the remaining proportion remains within the body, in contrast to BPA, which has a 0.50% systemic bioavailability. This increases the availability of the chemical for the tissues, and hence remains a matter of concern (35). This may affect several organ systems in turn and can affect the overall health of an individual in the long-term.

Furthermore, it has been found that the intravenous administration of 5 mg BPS/kg body weight to rats lead to a plasma clearance of 0.92 l/kg/h. The plasma clearance in humans was estimated to be 0.92 l/min (0.79 l/kg/h), which was lower than the BPA clearance, suggesting an increased bioavailability in the tissues (36).

It has been reported that following the subcutaneous administration of BPS to pregnant sheep, the concentration of BPS which may be delivered to the maternal circulation is higher as compared to that of other bisphenols and has a very

short half-life; however, BPS has a long half-life with a low concentration in the foetus (37).

3. Adverse effects of BPS on various systems and processes

Adverse effects of BPS on reproduction. BPA has been reported to produce numerous reproductive abnormalities in the form of decreased fertility in male rats due to defective sperm quality and quantity (38), a decreased number of offspring per breeding pair, an altered oestrous cycle, and decreased offspring survival and its development (39-41). Similarly, BPS has also been reported to produce reproductive defects. In the study by Roelofs *et al* (42), it was demonstrated that the exposure of murine Leydig cells to BPS altered testicular steroidogenesis. Furthermore, the same study revealed that BPS also increased the levels of progestogens, formed in the initial stages of the steroidogenic pathway (42). Recently, it was found that the exposure of foetal rats to BPS increased the plasma level of testosterone in male offspring as compared to BPA exposure (43). Sperm motility was also reduced and the histological examination of the testes revealed a thick membrane with increased gap between seminiferous tubules and inflammatory changes in the testes (43).

BPS has been found to affect the female reproductive system even in very low doses of 0.001, 0.1, 10 and 100 ng/g/body weight/day (44). It has been reported that BPS reduces ovarian weight and the volume of ovaries, along with a reduction in the number of antrum follicles and their volume. This is accompanied by a reduction in plasma 17β -oestradiol levels in animals (44). A previous study also reported that BPS affected oestradiol production in bovine granulosa cells (45). It was found that 100 μ M BPS stimulated oestradiol production from granulosa cells under basal conditions, although it did not affect oestradiol production when stimulated with follicle stimulating hormone, which had a protective effect (45).

Adverse effects of BPS on the cardiovascular system. The cardiotoxic effects of BPA have already been documented in numerous studies and it is well proven that BPA decreases the atrial contractility, produces arrhythmias, and is associated with cardiovascular disorders in humans, and suppresses ventricular functions (46,47). It has been found that the urinary levels of BPA are higher in patients with coronary artery disease (48). Furthermore, Asano *et al* (49) demonstrated that BPA led to the vasodilatation of coronary arteries by opening Maxi-K channels. The exposure of cardiac myocytes to BPA has also been shown to promote arrhythmogenic changes in rats (50). In addition, the oral administration of BPA to juvenile rats has been found to increase the expression of genes controlling angiogenesis (Vegf and Vegfr) (51). Furthermore, in 2012, O'Reilly *et al* (52), demonstrated that BPA blocked the NaV 1.5 channel expressed in myocytes and affected the action potential. BPA has also been reported to inhibit calcium influx through voltage gated channels in cardiomyocytes (53).

Similarly, BPS has also been reported to exert cardiotoxic effects in some studies. Recently, it was found that BPS affects the blood function and leads to cardiovascular defects in rats (28). The results of that study demonstrated that the ingestion of BPS by rats at various doses (30, 60, 120 mg/kg body

weight/day) for 30 days significantly reduced the red blood cell and white blood cell count in whole blood, and decreased the haemoglobin concentration and clotting time possibly by inducing hypoxia and carbon dioxide toxicity in cells (28). Furthermore, the same study revealed that BPS increased the serum glucose level in a dose-dependent manner and increased the serum levels of total protein, serum cholesterol, triglyceride, glycerol, free triglyceride, low-density lipoprotein and very low-density lipoprotein in the blood of the rats. BPS also reduced the level of high-density lipoprotein. It was also observed that BPS significantly increased the serum levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in a dose-dependent manner. BPS was also found to increase the serum bilirubin and calcium levels, and the urea concentration in that study. The findings of that study suggested that BPS possesses toxicity and its use is associated with cardiovascular risks (28). In addition, it has been reported that in the case of exposure to BPA, serum glucose levels decrease along with hypoproteinemia and hypoalbuminemia; these effects are in contrast to those of BPS. However, BPA causes hypertriglyceridemia, hypercholesterolemia and an increase in urea and creatinine levels, mimicking the effects produced by BPS (54).

In another study, it was found that the heart rate was increased in female rat hearts upon acute exposure to 10^{-9} M BPS (29). It was also found that in the presence of β -adrenergic agonist, the frequency of ventricular arrhythmia was significantly increased. In female rats exposed to BPS, ventricular myocytes exhibited more arrhythmia due to the increased release of calcium from the sarcoplasmic reticulum. The effect of BPS on myocytes was mediated by oestrogen receptor β signalling and increased the phosphorylation of Ca^{2+} handling proteins, ryanodine receptors and phospholamban (29). Furthermore, that same study demonstrated that the pro-arrhythmic effect of BPS was confined to female rat myocytes and male rat hearts did not exhibit any affect following such an acute exposure to BPS (29).

Another previous study demonstrated that acute exposure to BPS suppressed left ventricular contractility (30). That study concluded that BPS increased serine 16 phosphorylation in females. The cardio-suppressive effects of BPS were relatively more prominent than those of BPA, and BPS was found to function through an oestrogen receptor-dependent pathway to produce the cardio-suppressive effects. Furthermore, BPS altered the protein phosphorylation profile (30). It was also reported that the effects of BPS were more evident on female rats than male rats (30). In the study by Dworatzek *et al* (55), it was proposed that differences in sex-dependent oestrogen receptor- β phosphorylation in cardiac tissue may be the reason for the more prominent effects of BPA on females. A recent study also reported the association of exposure to BPS with cardiovascular diseases and coronary heart diseases in the US population (56).

Adverse effects of BPS on neural development and behaviour. In a recent study by Xiao *et al* (57), it was found that nematodes [*Caenorhabditis elegans* (*C. elegans*)] were more responsive to BPS. BPS affected the locomotion behaviour of *C. elegans*. BPS was also reported to reduce the brood size of *C. elegans* in that study (57).

In the study by Gyimah *et al* (25), it was reported that the exposure of zebrafish to both BPA and BPS led to poor body growth and development. A hyperactive state was observed, with an increase in mania time, frequency of activity and the time of activity in the zebrafish. This was associated with an increase in the intensity of green fluorescence protein in embryos exposed to the chemicals, which marked an increase in mRNA expression of *elavl3*. That study revealed that a low dose of BPS may lead to behavioural abnormalities (25).

Furthermore, it has been reported that exposure to BPA and BPS leads to early hypothalamic neurogenesis in embryonic zebrafish (26). A 240% increase in neuron production was noted in the rostral hypothalamus, as well as a significant locomotor area bursting activity. This action of BPS was reported to be due to an androgen receptor-mediated mechanism (26).

Studies on the exposure of perinatal mice to BPS have revealed an altered maternal behaviour with a lack of care for offspring (58), similar to that reported for exposure to BPA and a delay in mating (59). Post-natal exposure to BPS has been shown to lead to an altered feeding behaviour in offspring (60). Furthermore, research on rats has revealed an increased anxiety in male offspring and decreased exploratory movements in female offspring (61).

Prenatal exposure to BPA in humans has been shown to lead to an altered psychomotor development in boys at 2 years of age (62). The study by Jiang *et al* (62) indicated that neurobehavioral changes were observed in boys, as several earlier studies (63–67) have reported for the reduced testosterone synthesis due to BPS. Hence, neurobehavioral development in girls is not markedly affected. The study by Jiang *et al* (62) claimed to be the first study in which prenatal exposure to BPS produced neurobehavioral changes in boys. These findings suggest that during the period of early neuronal development, the effects of exposure to BPS are more prominent.

Adverse effects of BPS on tissues, leading to obesity. A previous study reported that perinatal exposure to BPS led to an increase in body weight in male mouse offspring (68). It was reported that 100 ng/g body weight/day dose of BPS caused an increase in liver weight. Furthermore, that same study revealed increase in epididymal white adipose tissue (epiWAT), and in serum alanine aminotransferase, triglyceride and cholesterol levels (68). This was reported to be due to the toxic effects of BPS, which led to an increased genetic expression of inflammatory mediators in liver tissue and epiWAT, as observed through a histopathological examination in that study. Briefly, the liver tissues and epididymal white adipose tissues were initially cut into smaller sections after freezing with liquid nitrogen. RNA was isolated from both tissue types using TRIzol reagent. The RNA was then reverse transcribed into cDNA. The Fast Quant RT Kit was used for the process. This was followed by reverse transcription-quantitative PCR analysis and the observations for target genes were normalized to glyceraldehyde-3-phosphate dehydrogenase. That study also demonstrated that the metabolites associated with lipid and glucose metabolism were altered due to exposure to BPS (68).

Another study also reported that BPS exerted obesogenic effects in male mice offspring ingesting a high-fat diet (69). BPS altered the mRNA expression of genes involved in regulating adipose tissue levels in the body, such as hormone

sensitive lipase, peroxisome proliferator activated receptor γ (PPAR γ), insulin receptor, SOCS3 and adiponectin (69). This was also observed by an increase in fat mass in the animals, hyperinsulinemia and hyperleptinemia. Furthermore, the plasma triglyceride clearance was also found to be increased in that study (69).

Ahmed and Atlas (70) also reported that BPS induced adipogenesis and upregulated the lipoprotein lipase, adipocyte protein 2, PPAR γ , perilipin, adiponin and CCAAT/enhancer-binding protein α mRNA expression levels. BPS also inhibited rosiglitazone-activated PPAR γ (70). These effects were attributed to the direct activation of PPAR γ . Furthermore, in that study, the adipogenic property of BPS was compared with that of BPA, and the study revealed that BPS was more adipogenic as compared to BPA (70).

In addition, in the study by Héliers-Toussaint *et al* (23), it was demonstrated that BPS functions through the PPAR γ coactivator 1 α and oestrogen-related receptor (ERR) γ genes, and increases the lipid content in 3T3-L1 and hepatic cells. Furthermore, BPS was found to lead to an increased glucose uptake and synthesis of leptin. The toxicity of BPS was attributed to SREBP-1c, PPAR γ , alphaP2, ERR α and ERR γ modulation (23).

Another study demonstrated that BPS induced immunotoxicity in macrophages. Exposure to BPS was found to alter glycolysis, and glutathione and lipid metabolism in macrophages (71). BPS affected the secretion of cytokines and macrophage polarization. Pro-inflammatory changes were linked to the activation of TNF- α , IL-1 β and IL-6 along, with the modulation of pathways for glycolysis, glutathione, sphingomyelin-ceramide, glycerophospholipids and glycerolipids.

Adverse effects of BPS on the liver. Recently, it was found that BPS does not induce metabolic syndrome and hence may not lead to fatty liver disease (72). It is less toxic as compared to BPA, since it is not a PXR agonist and does not promote neutral lipid deposition. Moreover, it plays no role in the expression of CYP3A4, CYP2B6, ABCB1, FASN and PLIN. However, it has been reported to weakly affect GSTA4 protein expression and the Erk1/2 pathway (72).

In the study by Zhang *et al* (73), it was shown that exposure to 5,000 μ g/kg BPS for a period of 8 weeks was associated with liver injury with deranged biochemical parameters, such as an increase in the plasma levels of alanine aminotransferase, aspartate aminotransferase and total bilirubin. Cytoarchitectural damage to hepatic cells was also observed (73).

Adverse effects of BPS on gut motility. Recently, the effects of BPS and BPA on gut motility have been reported. In the study by Sharma and Mandal (74), it was revealed that the *in vitro* exposure of a small intestinal strip to both BPA and BPS reduced contractility, basal tone and contractile tension. Previously, Sarkar *et al* (75) reported that BPA decreased duodenal movements in rats, involving the α -adrenergic and nitric oxide-mediated soluble guanylyl cyclase signaling pathways. Furthermore, immunofluorescence analyses have revealed that BPA affects gastric wall neuronal cells, which are immunoreactive to vesicular acetylcholine transporter, substance P, vasoactive intestinal polypeptide,

galanin and cocaine- and amphetamine-regulated transcript peptide (76). It has also been reported that BPA reduces both the spontaneous and agonist-induced contractility of the gut of rats (77).

4. Conclusions and future perspectives

The present review summarizes the effects of toxicity of BPS on organs. Presently, BPS is one of the chemicals which is used as a replacement for BPA in products labelled as BPA-free. BPS is likely to accumulate in the body and environment, as a large proportion of it remains unconjugated in the body and it is also not completely biodegradable. Hence, this raises the question about the safety of its use in BPA-free products and raises some concerns regarding the safety of the use of plastics, thermal receipts, food and beverage cans.

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Availability of data and materials

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Authors' contributions

JP was involved in the conception of the study, in the literature search, the preparation of the final manuscript, as well as in the reviewing and editing of the manuscript and in correspondence. RA was involved in the literature search, in the preparation of the final manuscript, as well as in manuscript revision. LM was involved in the reviewing and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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