

# A Comparative Study of Effects of 28-Day Exposure of Bisphenol A and Bisphenol S on Body Weight Changes, Organ Histology, and Relative Organ Weight

## Abstract

**Context:** Bisphenol A (BPA), a known endocrine disrupting chemical, is of widespread use in manufacturing of plastic products. Documenting ill health effects of BPA has led the plastic industrialists to replace BPA by its alleged safer alternative, bisphenol S (BPS). BPS belongs to the same chemical family and shares endocrine disrupting properties with BPA. **Aims:** We compared the effects of 28-day exposure of BPA and BPS on body weight changes, organ histology, and relative organ weight in rats. In addition, we detected BPA and BPS in the rat's blood serum. **Settings and Design:** Adult male albino rats were administered BPA (50 mg/kg/day) or BPS (50 mg/kg/day) or equivolume vehicle in different groups by oral gavage for 28 days. **Subjects and Methods:** The weight of each rat was noted at the commencement of the study and weekly afterward. On 29<sup>th</sup> day, the animals were sampled for whole blood and then sacrificed. The dissected out wet viscera were weighed and subjected to the standard protocol for histological examination. Serum samples were prepared and analyzed for the detection of BPA and BPS by high-pressure liquid chromatography. **Statistical Analysis Used:** Paired and unpaired Student's *t*-test, one-way ANOVA test, and Bonferroni test for multiple comparisons were used, as required for statistical analysis, and  $P < 0.05$  was considered statistically significant. **Results:** Both BPA and BPS produced similar detrimental changes in body weight, histology of stomach, small intestine, lung, and kidney, and relative organ weight of lung and kidney. BPA and BPS detected in the serum of rats were nearly 45 times of the control. **Conclusions:** Present data suggest caution about the application of BPS as a substitute of BPA.

**Keywords:** Albino rats, bisphenol A, bisphenol S, plastic chemicals, serum bisphenol

## Introduction

Chemical bisphenol A (BPA) is widely used in the production of plastic goods.<sup>[1]</sup> It leaches from plastic<sup>[2]</sup> and pollutes the environment.<sup>[3]</sup> BPA enters the biological systems mainly along with food and beverages and has been detected in various human body fluids.<sup>[4]</sup> Deleterious impact of BPA on health is well documented.<sup>[5]</sup> This has led the plastic industrialists to replace BPA by another allegedly safer substitute, bisphenol S (BPS), in some of the consumer products.<sup>[6,7]</sup> BPS belongs to the same chemical family and shares the endocrine disrupting properties with BPA.<sup>[8]</sup> This raises suspicion regarding its application as harmless alternative to BPA. Moreover, ongoing research reports BPS to have a deleterious impact on health.<sup>[8]</sup>

Since both the bisphenols are chemically similar, their impact on body systems may be speculated to be similar. Application of BPS in manufacturing of plastic goods is relatively new. In view of fast replacement of BPA by BPS, comparative studies of both these bisphenols regarding their impact on biological systems are relevant and deserve exploration.

Since BPS is being used as substitute of BPA in many plastic items, this study was planned to ascertain the impact, if any, of oral exposure of BPS in rats and compare it, with that of BPA.

Therefore, this study was conducted with the objective to assess the comparative effects of BPA and BPS on changes in body weight, organ histology, relative organ weight, and serum free bisphenol concentration after exposing the adult male albino rats to equal doses of BPA and BPS for 28 days.

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## Subjects and Methods

Present animal experimental study was taken up after obtaining ethical clearance from the ethical clearance committee of the institute. All the ethical considerations for animal studies were followed. Apparently healthy adult male albino rats of Charles Foster strain (weighing 175–225 g) were obtained from animal house of the institute. The rats were harbored in the departmental animal room with conditions of controlled temperature ( $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$ ) and light (12:12 h light dark). The animals were provided with standard laboratory food and water *ad libitum*.

The drugs (BPA and BPS) were obtained from Sigma Aldrich, USA. Ether and dimethyl sulfoxide (DMSO) were obtained from Merck, Mumbai.

The study was performed on total 24 rats. After 7 days of acclimatization in departmental animal room, animals were divided into four groups (I–IV), each consisting of randomly selected six animals.

At the start of the study, the weight of each rat was noted. Animals were administered 0.5 ml of tap water in Group I, 20% DMSO (vehicle) in Group II, BPA (50 mg/kg body weight/day) in Group III, and BPS (50 mg/kg body weight/day) in Group IV by oral gavage for 28 days. Group I served as time-matched control and Group II served as vehicle control.

The changes if any in body weight of rats in different groups were observed by weighing the rats after 7, 14, 21, and 28 days of treatment.

On day 29, the overnight-fasted rats were anesthetized using ether, and whole blood sample (1 ml) was withdrawn from retro-orbital blood plexus using capillary tubes.<sup>[9,10]</sup> This whole blood was centrifuged at 4000 rpm for 10 min, and serum obtained was separated and stored at  $-20^{\circ}\text{C}$  for the determination of serum levels of bisphenols by high-pressure liquid chromatography (HPLC).

The rats were sacrificed by cervical dislocation and abdomen was cut open to separate the viscera. The wet weight of liver, pancreas, heart, both lungs, and both kidneys was taken with the help of a fine balance. Corpus parts of stomach and a small segment from small intestine were also dissected out and cleaned. Thereafter, all viscera were fixed in formalin (10%) and were subjected to standard protocol for histological examination after staining with hematoxylin and eosin.

The initial body weight (IBW) of the rats was considered as 100%. Body weight at various time points of observation (after 7, 14, 21, and 28 days of treatment) was calculated as percentage of IBW. Weight observed after 28 days of treatment was considered as final body weight (FBW). The relative wet organ weight, described as % of FBW, was obtained by the formula: wet organ weight (g)/FBW (g)  $\times 100$ .

For measurement of bisphenol concentration in the rat's serum, sample preparation was done as follows. A 0.5 ml serum was diluted with BPA-free water to make final volume to 5 ml. The samples were purified by removing fat with 3 ml 30% ethanol and 3 ml petroleum ether, followed by washing with BPA-free water. Finally, BPA was eluted. The solvent was evaporated. The residue was dissolved in 1 ml of acetonitrile–water (50:50) solution. A stock solution of BPA and BPS was prepared (1 mg/ml) in mobile phase of acetonitrile: Water (50:50), and different concentrations (0.1 ~ 500  $\mu\text{g/ml}$ ) were made as required.

The HPLC system (Shimadzu, USA) consisted of a chromatographic pump (LC-20AD), manual Rheodyne injector, and ultraviolet-visible detector (SPD-20A); all operated at room temperature ( $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$ ). Data collection, calibration, and integration were done using LC Solutions Data Analysis System. Reversed Phase C18 column (250 mm  $\times$  4.6 mm, particle size 5  $\mu\text{m}$ ) was used for the detection of BPA and BPS. The mobile phase consisted of acetonitrile: water (50:50), pH  $4 \pm 1$ , at a flow rate of 1 ml/min. A Millipore filter system equipped with a 0.22- $\mu\text{m}$  filter was used to filter the mobile phase prior using for the experiment. Further, degassing was performed for 30 min immediately after filtration. BPA and BPS peaks were detected at a wavelength of 280 nm throughout the experiments.

Serum samples obtained from tap water-administered and vehicle-administered rats were assessed for both BPA and BPS. BPA- and BPS-treated rats were assessed for only BPA and BPS, respectively.

In each group, body weight after 7, 14, 21, and 28 days of treatment (expressed as percentage of IBW) was compared to IBW by paired *t*-test. Groups were mutually compared for body weight at respective time points of observation by one-way ANOVA followed by Bonferroni test (*post hoc* test) for multiple comparisons.

Similarly, groups were compared for relative organ weight by one-way ANOVA and Bonferroni test for multiple comparisons. Serum concentrations of free bisphenols were compared within a group and between groups by unpaired Student's *t*-test. The software used for statistical analysis was SPSS (version 20, IBM®), and  $P < 0.05$  was considered statistically significant.

## Results

Table 1 shows mean  $\pm$  standard error of the mean (SEM,  $n = 6$ ) of absolute values of IBW and FBW (g) of rats in different groups. Table 2 shows mean  $\pm$  SEM of body weight of rats (expressed as percentage of IBW) after 7, 14, 21, and 28 days of treatment in different groups.

In Group I (only tap water-treated rats; time-matched control), the body weight of rats increased by 18% at the end of the treatment period. In Group II (vehicle-treated

rats; vehicle control), the increase in body weight was similar (18%) to Group I after 28-day treatment. In Group III (BPA-treated rats), there was a decrease in body weight by 12%–13% of IBW, at the end of treatment, while in Group IV (BPS-treated rats), the FBW was similar to IBW.

When groups were mutually compared, Group II (vehicle control) was insignificantly different from Group I (time-matched control) at all the time points of observations. After 2-week treatment, BPA-treated group was found to have significantly less body weight as compared to vehicle control group, while body weight in BPS-treated group was similar to vehicle control. After 3-week treatment, the body weight in both Group III and Group IV was significantly less as compared to vehicle control. Mutually, both the BPA- and BPS-treated groups were not significantly different from each other at all time points of observation ( $P < 0.05$ , one-way ANOVA and Bonferroni test for multiple comparisons).

Organ histology in the vehicle control group was similar to time-matched control rats, while both the BPA- and BPS-treated groups showed histological alterations, as compared to controls, as below.

The goblet cells in the mucosa layer of the small intestine were reduced in number. Further, there were inflammatory cells as eosinophil and plasma cells in the mucosa along with hyperchromatic nucleus, nucleus atypia, and focal mitosis. No microscopically visible changes were observed in the muscle layer of small intestine [Figure 1].

**Table 1: Mean±standard error of mean (n=6) of absolute values of initial body weight and final body weight in different groups**

Group	IBW	FBW
I	188.33±8.03	222.50±6.55
II	194.17±8.51	229.17±11.50
III	212.50±8.54	186.67±6.79
IV	195.00±9.57	185.83±15.67

Rats were administered only tap water (Group I), vehicle (Group II), BPA (Group III), and BPS (Group IV). IBW: Initial body weight; FBW: Final body weight; BPS: Bisphenol S; BPA: Bisphenol A

**Table 2: Mean±standard error of mean (n=6) values of body weight of rats expressed as percentage of initial body weight, after 7, 14, 21, and 28 days of treatment in different groups**

Group	IBW	Weight after 7 days of treatment	Weight after 14 days of treatment	Weight after 21 days of treatment	Weight after 28 days of treatment
I	100.00±0.00	103.38±5.16	114.00±2.94*	119.30±1.92*	118.61±3.13*
II	100.00±0.00	103.25±2.06	110.53±3.39	115.79±3.80*	118.32±4.89*
III	100.00±0.00	93.33±2.68	84.16±2.83*.@	83.27±2.19*.@	87.77±1.26*.@
IV	100.00±0.00	93.78±2.53	93.98±1.94	93.96±4.18@	94.62±3.76@

\*Indicates significant difference from IBW in the same group (Student's paired *t*-test); @Indicates significant difference from vehicle control on corresponding day (one-way ANOVA and Bonferroni test for multiple comparisons). Rats were administered only tap water (Group I), vehicle (Group II), BPA (Group III), and BPS (Group IV). IBW: Initial body weight; BPS: Bisphenol S; BPA: Bisphenol A

Inflammatory cells as eosinophils and plasma cells were found in gastric mucosa. No microscopically visible changes were observed in gastric muscle layer [Figure 2].

Local dense inflammatory cell infiltrates and coalescent alveoli were observed. Further, fragmented and irregular nuclei were found. Increased cellularity and degenerative changes were observed in interstitial space along with widening of interstitial spaces [Figure 3].

Kidneys in the BPS-treated rats showed dilatation and degenerative changes in some tubules. BPA-treated rats showed severe inflammatory cell infiltrates in the pelviuretric junction as compared to control [Figure 4].

In Group II (vehicle control), the relative weight of the lungs was similar to Group I (time matched control). In both Group III and Group IV (BPA- and BPS-treated rats, respectively), the relative weight of the lungs was significantly more than vehicle control group. Both Group III and Group IV were mutually, statistically not different. Similarly, treatment by vehicle did not affect the relative kidney weight as compared to tap water treatment, but both the BPA- and BPS-treated rats showed statistically significant increase in relative kidney weight as compared to vehicle control, and mutually, both the bisphenol-treated groups were statistically not different in respect to relative kidney weight ( $P < 0.05$ , one-way ANOVA followed by Bonferroni test for multiple comparisons) [Figures 5 and 6].

There was no significant difference in the relative weight of heart, liver, and pancreas, among all the groups.

Figure 7 shows representative HPLC obtained from a serum sample of tap water-treated (a), vehicle (b), BPA-treated (c), and BPS-treated (d) groups. Figure 7e and f shows standard BPA and standard BPS chromatogram.

Both BPA and BPS were detected in the serum of rats in Group I (time-matched control). The serum levels of BPA and BPS in these rats were of similar magnitude and statistically, insignificantly different [ $P > 0.05$ , unpaired *t*-test; Table 3]. Similarly, in Group II (vehicle control),



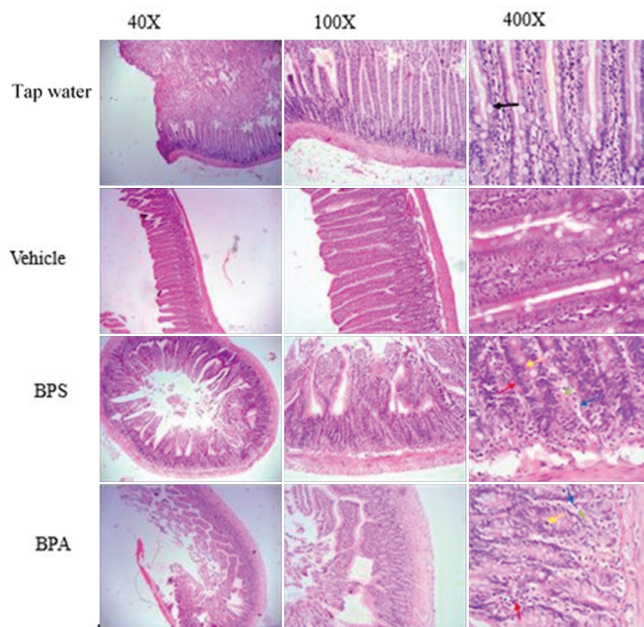


Figure 1: H and E-stained ( $\times 40$ ,  $\times 100$ ,  $\times 400$ ) photomicrographs of rat small intestine (normal, vehicle, BPS-treated, and BPA-treated rats). In the first row (normal), black arrow indicates normal goblet cells ( $\times 400$ ). In the third row (BPS) and fourth row (BPA), red arrow indicates area of hyperchromatic nucleus ( $\times 400$ ), yellow arrow indicates area of mitosis ( $\times 400$ ), green arrow shows eosinophil ( $\times 400$ ), and blue arrow shows plasma cell ( $\times 400$ ). BPS: Bisphenol S; BPA: Bisphenol A

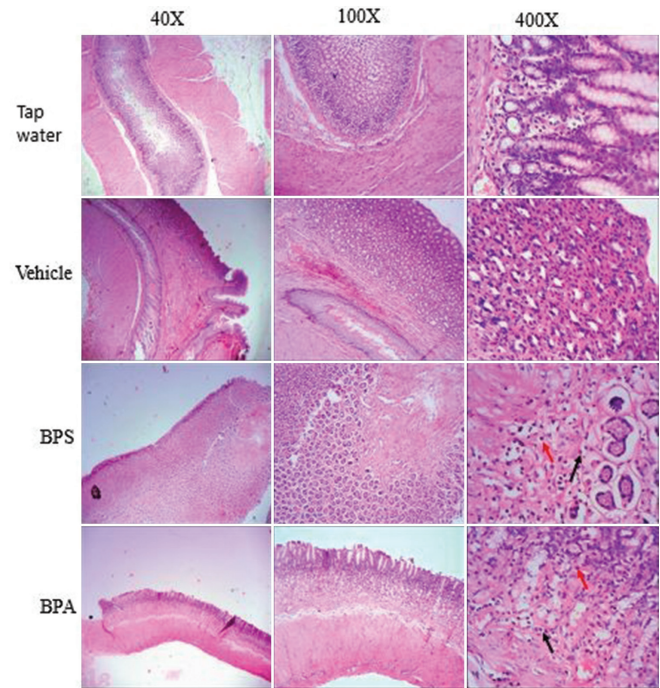


Figure 2: H and E-stained ( $\times 40$ ,  $\times 100$ ,  $\times 400$ ) photomicrographs of rat stomach (normal, vehicle, BPS-treated, and BPA-treated rats). In third row (BPS) and fourth row (BPA), black arrow indicates eosinophil and red arrow indicates plasma cell ( $\times 400$ ). BPS: Bisphenol S; BPA: Bisphenol A

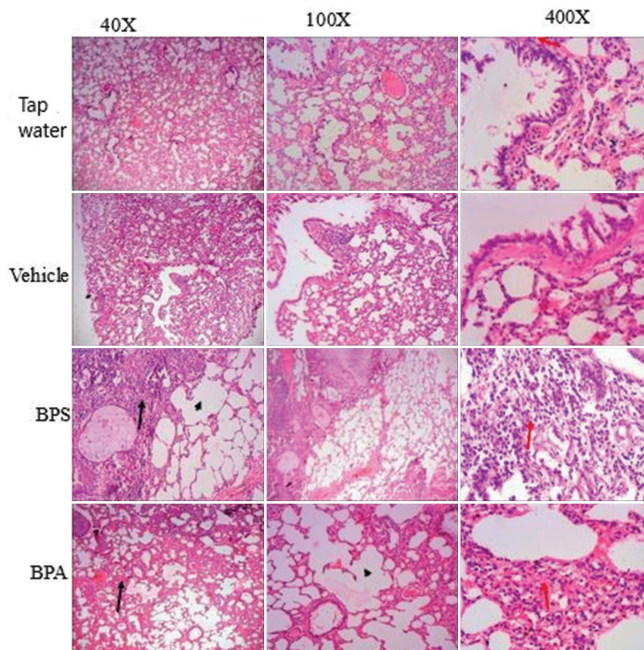


Figure 3: H and E-stained ( $\times 40$ ,  $\times 100$ ,  $\times 400$ ) photomicrographs of rat lungs (normal, vehicle, BPS-treated, and BPA treated rats). In third row (BPS) and fourth row (BPA), black arrow ( $\times 40$ ) indicates inflammatory cell infiltrates in interstitial space. Arrow head ( $\times 100$ ) shows coalescent alveoli, and red arrow ( $\times 400$ ) indicates increased cellularity and degenerative changes. BPS: Bisphenol S; BPA: Bisphenol A

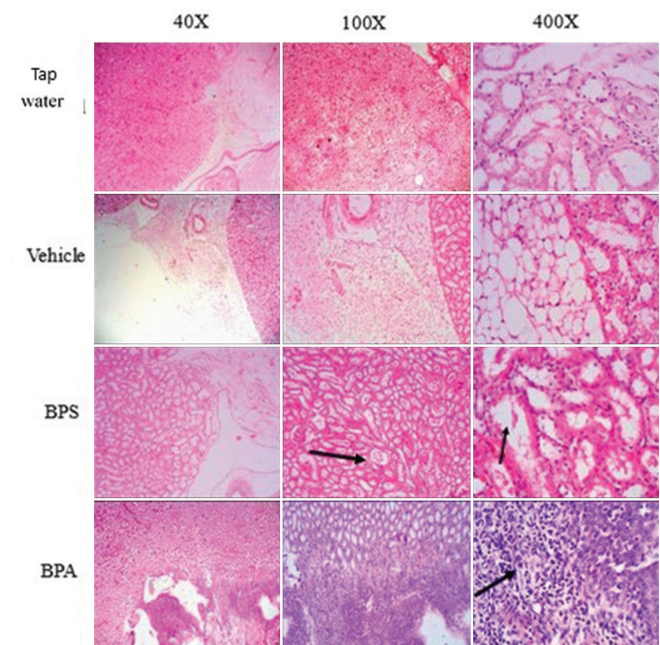


Figure 4: H and E-stained ( $\times 40$ ,  $\times 100$ ,  $\times 400$ ) photomicrographs of rat kidneys (normal, vehicle, BPS-treated, and BPA-treated rats). Black arrows in the third row (BPS;  $\times 100$ ,  $\times 400$ ) shows dilatation of tubules along with degeneration and black arrow in BPA ( $\times 400$ ) treated samples indicate inflammation in pelviuretral junction. BPS: Bisphenol S; BPA: Bisphenol A

both BPA and BPS were detected in the serum, but statistically difference ( $P > 0.05$ , unpaired  $t$ -test) in their levels was not significant. Vehicle control group was similar

to time-matched control group when these two groups were mutually compared for their respective BPA and BPS serum concentrations [ $P > 0.05$ , unpaired  $t$ -test; Table 3].

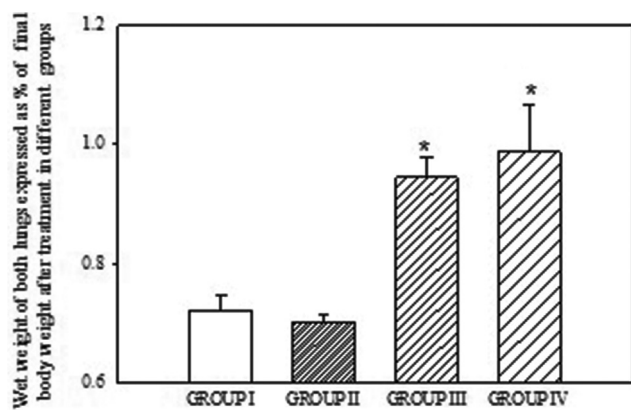


Figure 5: Wet weight of both lungs, expressed as percentage of final body weight in different groups. \*shows significant difference from vehicle control group ( $P < 0.05$ , one-way ANOVA and Bonferroni test for multiple comparisons). Rats were administered only tap water (Group I), vehicle (Group II), BPA (Group III), and BPS (Group IV). BPS: Bisphenol S; BPA: Bisphenol A

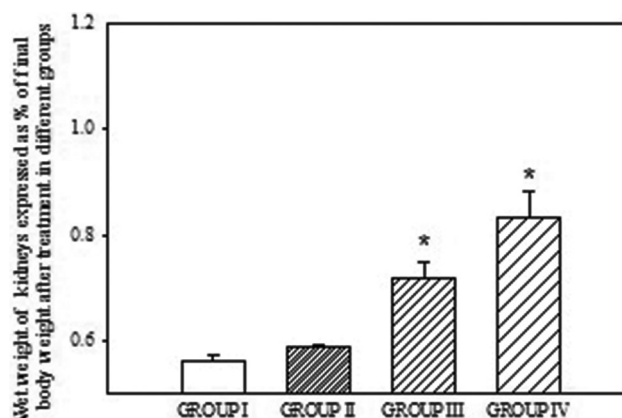


Figure 6: Wet weight of both kidneys, expressed as percentage of final body weight in different groups. \*shows significant difference from vehicle control group ( $P < 0.05$ , one-way ANOVA and Bonferroni test for multiple comparisons). Rats were administered only tap water (Group I), vehicle (Group II), BPA (Group III), and BPS (Group IV). BPS: Bisphenol S; BPA: Bisphenol A

**Table 3: Mean±standard error of mean (n=6) values of serum concentrations (ug/ml) of free bisphenol A and bisphenol S in different groups**

Groups	Serum concentrations (ug/ml) of free BPA	Serum concentrations (ug/ml) of free BPS
Group I	0.20±0.04	0.25±0.04
Group II	0.16±0.05	0.19±0.08
Group III	7.42±0.73*	-
Group IV	-	8.19±1.18*

\*Indicates significant difference from Group II; Student's unpaired *t*-test. Rats were administered only tap water (Group I), vehicle (Group II), BPA (Group III), and BPS (Group IV). BPS: Bisphenol S; BPA: Bisphenol A

BPA serum concentrations were significantly ( $P < 0.05$ , unpaired *t*-test) high in BPA-treated group (Group III) as compared to that in vehicle control group. Similarly, BPS serum concentrations in BPS-treated rats were significantly increased as compared to that in vehicle control ( $P < 0.05$ , unpaired *t*-test). Mutually, Group III (BPA-treated rats) and Group IV (BPS-treated rats) were compared for their BPA and BPS serum concentrations, respectively, and the difference was statistically insignificant [ $P < 0.5$ , unpaired *t*-test; Table 3].

### Discussion

Present study observed the comparative effects of BPA and BPS on changes in body weight, organ histology, and relative organ weight after exposing adult male albino rats to 50 mg/kg body weight/day of both chemicals in different groups for 28 days.

The body weight of the experimental animals naturally increases with progressing age<sup>[10]</sup> as observed in tap water-administered rats in the present study, which showed 18% increase in the body weight over a period of 4 weeks. Weight changes in vehicle control group were similar to

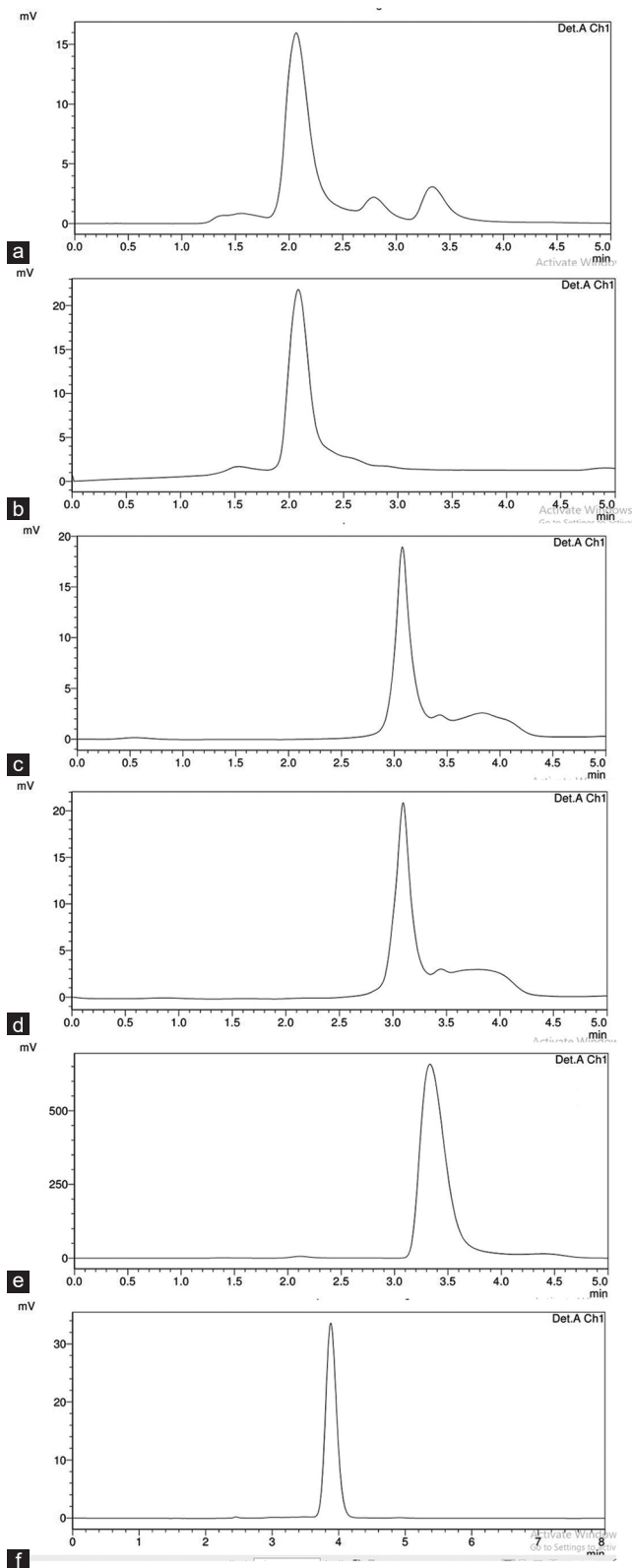
time-matched tap water-administered rats, indicating no impact of vehicle on body weight changes. BPS treatment prevented the natural weight gain in rats as evidenced by no increase in body weight over the entire treatment period of 4 weeks. In BPA-treated rats, the body weight rather decreased by 13%, indicating its more pronounced effect on body weight changes. Significantly less weight in both the BPA- and BPS-treated groups as compared to control suggests the similar toxic effects of both bisphenols.

Body weight loss in rats treated orally with BPA was reported earlier as well.<sup>[10-12]</sup> In earlier reports, the body weight loss in BPA treated rats has been attributed to different changes induced by BPA as, oxidative stress to liver,<sup>[12]</sup> anorexia,<sup>[11]</sup> inhibition of enzyme P 450 (which is involved in the synthesis of testosterone),<sup>[13]</sup> decrease in serum testosterone levels along with deteriorated number and activity of the Leydig and Sertoli cells,<sup>[10]</sup> and decrease in relative weight of male reproductive organs.<sup>[14]</sup> Noteworthy is that all the animals included in our study were adult males. Decreased testosterone levels cause decrease in muscle and bone mass.<sup>[15]</sup>

There is a paucity of data to claim that BPS has similar impact on body weight changes. Although BPS has not been studied as much as BPA, its hormonal potency has been reported to be in the same order of magnitude and of similar action as BPA *in vitro* and *in vivo*.<sup>[16]</sup> It induced testicular oxidative damage along with altered morphology of the testis and reduced intratesticular as well as testosterone concentration.<sup>[17]</sup> Therefore, it may be speculated that, in our study, impairment of healthy weight gain in BPS-treated adult male rats may be caused through mechanisms similar to those of BPA.

In some *in vitro* studies, BPA and BPS have shown obesogenic potential by their action on adipocytes.<sup>[18]</sup> Further, some human studies have reported association of urinary BPA<sup>[19]</sup> and





**Figure 7: Representative HPLC chromatogram obtained from a serum sample of tap water (a), vehicle (b), BPA-treated (c), and BPS-treated (d) groups. (e and f) show standard BPA and standard BPS chromatogram. BPS: Bisphenol S; BPA: Bisphenol A**

BPS<sup>[20]</sup> concentrations with obesity. These were cross-sectional studies limited in their capacity to determine if exposure to

bisphenols may cause weight gain or obese participants have greater exposure to, or excretion of, bisphenols.

Histologically, abnormalities in small intestine, stomach, lungs, and kidneys in both the BPA- and BPS-treated rats are suggestive of inflammatory pathology in all of these organs, in addition to dysplastic changes in small intestine and degenerative changes in lungs. These changes were similar in both the bisphenol-treated groups, indicating their comparable impact on body organs. The vehicle control group showed normal organ architecture in all the organs, similar to time-matched control rats.

In small intestinal and gastric mucosa, decreased goblet cells along with the appearance of inflammatory cells indicate enteritis and gastritis, respectively. In addition, decrease in goblet cells along with mitosis and hyperchromasia of nucleus in small intestinal mucosa suggest possibility of dysplastic changes. Although carcinomatous potential of BPA and BPS, in other organs, has already been reported,<sup>[21,22]</sup> detrimental impact of BPA as well as BPS on the gut tissue has not been investigated so far, to the best of our knowledge.

Inflammatory changes observed in the lungs were also reported earlier. The increase in relative organ weight of the lungs may be attributed to inflammatory edema. The coalescent alveoli indicate emphysematous changes and fragmented nuclei indicate nuclear degeneration. Earlier also, BPA was reported to induce inflammatory changes in rat lungs along with evidence of oxidative stress and improvement with concomitant administration of antioxidants.<sup>[23]</sup> Exposure to BPA could be a risk factor accountable for the development of inflammatory lung diseases such as asthma, emphysema, and bronchitis.

In the current study, inflammatory cell infiltration in the pelviuretric junction in BPA-fed rats is suggestive of BPA-induced pyelitis. BPA-induced increase in relative renal weight along with histological abnormalities has been reported earlier and has been attributed to BPA-induced oxidative stress.<sup>[24]</sup>

BPS-induced toxicity and histological alterations in male reproductive organs have been studied widely, but there is a paucity of previously reported data regarding histological alterations induced by BPS in nonreproductive viscera such as lung, kidney, small intestine, and stomach, as reported in our study.

Once the bisphenols enter the body, conjugation with glucuronic acid is the predominant metabolic pathway. Glucuronidation stimulates their excretion from the body and is an important mechanism for bisphenol detoxification.<sup>[25]</sup> Despite rapid conjugation of bisphenols, biologically active aglycones have still been detected in numerous bio-monitoring studies and in various biological matrices, such as serum, urine, and breast milk.<sup>[26]</sup>

Serum concentrations of free bisphenols in tap water- and vehicle-treated rats indicate the environmental contamination and therefore inevitable exposure. Comparable magnitude of serum levels of BPA and BPS within a group is intriguing and suggests similar environmental contamination with both BPA and BPS. Application of BPS is increasing as manufacturers are replacing BPA with BPS. The exposures may be declining or BPA or on the rise for BPS.<sup>[27]</sup>

Thus, the overall effects on organ histology and body weight changes were similar for BPS- and BPA-treated rats. This may be resulted from similar concentration of BPA and BPS in the serum and possibly similar toxicity.

## Conclusion

28-day exposure of BPA and BPS produced detrimental effect on body weight changes, organ histology, and relative organ weight. The changes observed were comparable in both the bisphenol-treated rats, which suggest their similar detrimental impact on health. This work clearly suggests that BPS, an alleged safer substitute to BPA, possesses risk of health hazard similar to BPA.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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