

# Concern about the Safety of Bisphenol A Substitutes

Min Kyong Moon<sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine, Seoul National University College of Medicine, Seoul,

<sup>2</sup>Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea

Bisphenol A (BPA) is a base material for the production of polycarbonate plastic and epoxy resin, and it is one of the most produced chemicals [1]. BPA is a well-known endocrine disruptor and has a weak estrogenic effect. The adverse effects of BPA are largely related to its estrogenic activity [2,3], and they can disturb reproductive function. In addition, recent epidemiologic evidence has also shown that BPA is implicated in cardiovascular disease, type 2 diabetes mellitus, and obesity: high serum or urine BPA levels have been positively associated with diabetes mellitus [4,5], cardiovascular disease [4], obesity, and insulin resistance [6]. Therefore, BPA has been regulated in many countries. BPA was banned in baby bottles in Canada in 2008, in France in 2010, and in the European Union in 2011 [7]. Such regulations have led to the development of substitutes such as bisphenol S (BPS) and bisphenol F (BPF).

These BPA substitutes-based products are consumed under the label of “BPA-free.” This term gives the impression that the products are safe, but the safety of the substitutes is not fully verified [8,9]. Because of structural similarities with BPA (Fig. 1), these alternatives also show endocrine disruption effects like BPA, and many studies on adverse health effects of these alternatives are being reported.

In this issue of the *Diabetes and Metabolism Journal*, Liu et al. [10] evaluated the associations of BPA, BPF, and BPS with obesity in children and adolescents using data from the U.S. National Health and Nutrition Examination Survey 2013 to 2014. They found that exposure to BPF was positively associated with higher risk of obesity in children and adolescents, especially in boys. In terms of BPS, they did not observe signifi-

cant associations with either general obesity or abdominal obesity. In their previous article, BPF or BPS was not significantly associated with obesity in U.S. adults [11]. BPS and BPF may have less harmful impact on health than BPA. However, as noted by the authors, since BPS or BPF has not replaced BPA for a long time, no significant results could be obtained due to their relative low exposure.

In a systematic review regarding comparison of the hormonal activity of BPA substitutes, the hormonal activities of BPS and BPF were in the same order of magnitude and of similar action as BPA (estrogenic, anti-estrogenic, androgenic, and anti-androgenic) *in vitro* and *in vivo* [9]. BPS and BPF showed altered organ weights, reproductive end points, and enzyme expression. In a recent study, the agonistic and/or antagonistic activities of BPA and its eight analogues (BPAF, BPAP, BPP, BPE, BPF, BPP, BPS, and BPZ) against human nuclear receptors (estrogen receptors [ERs], androgen receptor, glucocorticoid receptor, pregnane X receptor, and constitutive androstane receptor) were characterized via *in vitro* transactivation assays (Fig. 2) [12]. All the test compounds, except for BPP, showed both ER $\alpha$ - and ER $\beta$ -agonistic activities, with BPAF being the most potent. BPF and BPS were found to show weaker estrogenic activities than BPA. Their results suggested that BPA analogues demonstrate multiple effects via human nuclear receptors in a similar manner to BPA, and several analogues might have more potent endocrine-disrupting activity than BPA.

In Korea, BPS are used for thermal receipt papers and BPF as a water pipe coating agent instead of BPA [13]. In the study

Corresponding author: Min Kyong Moon  <https://orcid.org/0000-0002-5460-2846>  
Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine,  
20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea  
E-mail: mkmoon@snu.ac.kr

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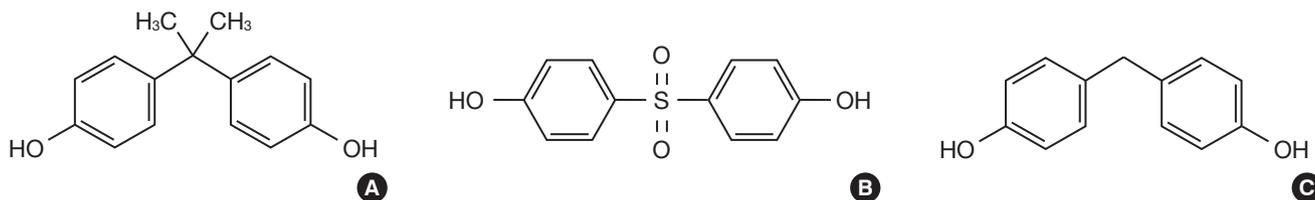


Fig. 1. Chemical structures of (A) bisphenol A, (B) bisphenol S, and (C) bisphenol F.

	ER $\alpha$	ER $\beta$	AR	GR	PXR	CAR
BPA	Red	Red	Blue	Blue	Yellow	Blue
BPAF	Brown	Brown	Blue	Blue	Yellow	Blue
BPAP	Brown	Red	Blue	Blue	Yellow	Blue
BPB	Red	Brown	Blue	Blue	Yellow	Blue
BPE	Red	Red	Blue			
BPF	Brown	Red	Blue			
BPP	Brown	Blue		Blue	Yellow	Blue
BPS	Brown	Brown				
BPZ	Red	Brown	Blue	Blue	Yellow	Blue

<u>Agonistic activity</u>		<u>Antagonistic activity</u>	
REC20		RIC20	
Brown	10 <sup>-9</sup> M ~ 10 <sup>-8</sup> M	Dark Blue	10 <sup>-9</sup> M ~ 10 <sup>-8</sup> M
Red	10 <sup>-8</sup> M ~ 10 <sup>-7</sup> M	Medium Blue	10 <sup>-8</sup> M ~ 10 <sup>-7</sup> M
Orange	10 <sup>-7</sup> M ~ 10 <sup>-6</sup> M	Light Blue	10 <sup>-7</sup> M ~ 10 <sup>-6</sup> M
Yellow	10 <sup>-6</sup> M ~ 10 <sup>-5</sup> M	Very Light Blue	10 <sup>-6</sup> M ~ 10 <sup>-5</sup> M

Fig. 2. Profiling of bisphenol A (BPA) and eight its analogues on transcriptional activity via human nuclear receptors. Adapted from Kojima et al. [12], with permission from Elsevier. ER $\alpha$ , human estrogen receptors  $\alpha$ ; ER $\beta$ , human estrogen receptors  $\beta$ ; AR, androgen receptor; GR, glucocorticoid receptor; PXR, pregnane X receptor; CAR, constitutive androstane receptor; REC20, the concentrations of the compound equal to 20% of the maximal response of the positive control intensity; RIC20, the concentrations of the test compounds showing 20% inhibition of the activities induced by the endogenous hormones or vehicle control.

measuring the concentrations of BPA, BPS, and BPF in the rivers of Japan, Korea, China, and India, BPF was the major bisphenol in rivers and the levels exceeded those of BPA. In the Han River in Korea, median concentrations of BPA, BPS, and BPF were 144, 41, and 555 ng/L, respectively. These were much higher compared with Nakdong River or Yeongsan River, where no BPF was detected [14]. This could be associated with the use of BPF-coated water pipes in Seoul [13]. In 2012, Liao et al. [14] analyzed BPS concentrations in 315 urine samples collected from the general populations in the United States and

seven Asian countries including Korea. The urinary BPS concentration in Korea was very low (0.030 ng/mL) compared with Japan (1.18 ng/mL), United States (0.299 ng/mL) or China (0.226 ng/mL). However, the results are likely to change as BPS is replacing BPA for thermal receipt papers.

Because BPA substitutes such as BPS and BPF have similar structures to BPA, they appear to have similar metabolism, potencies, and action to BPA. In addition, they may pose similar potential health hazards as BPA. Continued biomonitoring of these bisphenols in populations and thorough investigations on their health effects in humans are needed. Manufacturers should continue to seek alternative safe materials rather than merely replacing BPA with bisphenol analogs.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES

- Vandenberg LN, Maffini MV, Wadia PR, Sonnenschein C, Rubin BS, Soto AM. Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. *Endocrinology* 2007;148:116-27.
- Hiroi H, Tsutsumi O, Momoeda M, Takai Y, Osuga Y, Taketani Y. Differential interactions of bisphenol A and 17 $\beta$ -estradiol with estrogen receptor alpha (ER $\alpha$ ) and ER $\beta$ . *Endocr J* 1999;46:773-8.
- Kurosawa T, Hiroi H, Tsutsumi O, Ishikawa T, Osuga Y, Fujiwara T, Inoue S, Muramatsu M, Momoeda M, Taketani Y. The activity of bisphenol A depends on both the estrogen receptor subtype and the cell type. *Endocr J* 2002;49:465-71.
- Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, Melzer D. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormali-

- ties in adults. *JAMA* 2008;300:1303-10.
5. Shankar A, Teppala S. Relationship between urinary bisphenol A levels and diabetes mellitus. *J Clin Endocrinol Metab* 2011; 96:3822-6.
  6. Wang T, Li M, Chen B, Xu M, Xu Y, Huang Y, Lu J, Chen Y, Wang W, Li X, Liu Y, Bi Y, Lai S, Ning G. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J Clin Endocrinol Metab* 2012;97:E223-7.
  7. Cano-Nicolau J, Vaillant C, Pellegrini E, Charlier TD, Kah O, Coumailleau P. Estrogenic effects of several BPA analogs in the developing zebrafish brain. *Front Neurosci* 2016;10:112.
  8. Eladak S, Grisin T, Moison D, Guerquin MJ, N'Tumba-Byn T, Pozzi-Gaudin S, Benachi A, Livera G, Rouiller-Fabre V, Habert R. A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound. *Fertil Steril* 2015;103:11-21.
  9. Rochester JR, Bolden AL. Bisphenol S and F: a systematic review and comparison of the hormonal activity of bisphenol A substitutes. *Environ Health Perspect* 2015;123:643-50.
  10. Liu B, Lehmler HJ, Sun Y, Xu G, Sun Q, Snetselaar LG, Wallace RB, Bao W. Association of bisphenol A and its substitutes, bisphenol F and bisphenol S, with obesity in United States children and adolescents. *Diabetes Metab J* 2019;43:59-75.
  11. Liu B, Lehmler HJ, Sun Y, Xu G, Liu Y, Zong G, Sun Q, Hu FB, Wallace RB, Bao W. Bisphenol A substitutes and obesity in US adults: analysis of a population-based, cross-sectional study. *Lancet Planet Health* 2017;1:e114-22.
  12. Kojima H, Takeuchi S, Sanoh S, Okuda K, Kitamura S, Uramaru N, Sugihara K, Yoshinari K. Profiling of bisphenol A and eight its analogues on transcriptional activity via human nuclear receptors. *Toxicology* 2019;413:48-55.
  13. Song CY, Kim W, Gye MC. Current state of use and the risks of bisphenols: a minireview. *Korean J Environ Biol* 2017;35:581-94.
  14. Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, Moon HB, Nakata H, Kannan K. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. *Environ Sci Technol* 2012;46:6860-6.