Review Article

Bisphenol-S Influence on Oxidative Stress and Endocrine Biomarkers of Reproductive System: A Systematic Review and Meta-Analysis

Abstract

Background: Bisphenol-S (BPS), as a new human public health concern, was introduced to the plastic industry by BPA-free labeled products following the restrictions of Bisphenol-A (BPA) as a safe alternative. However, recent research has revealed a controversial issue. In this regard, the present study aimed to review the relationship between BPS exposure and reproductive system dis/malfunction. **Methods:** PubMed and other databases were searched up to January 2021. The standard mean difference (SMD) with a 95% confidence interval (CI) was calculated for the main parameters using the random-effects model. Finally, 12 studies with 420 subjects were included in this research. Forest plot, meta-regression, and non-linear dose-response effect were calculated for each parameter by random-effects model. **Results:** Based on the results of *in vitro* assessment, a significant increase was found in the oxidative stress parameters, including superoxide dismutase (SMD: 0.63, 95% CI: 0.321, 0.939), thiobarbituric acid reactive substances (SMD: 0.760, 95% CI: 0.423, 1.096), and reactive oxygen species (SMD: 0.484, 95% CI: 0.132, 0.835). In addition, the hormonal assessment revealed a significant decrease in male testosterone concertation (SMD: -0.476, 95% CI: -0.881, -0.071). Moreover, *in vivo* examination revealed a significant decrease in hormonal parameters, such as female testosterone (SMD: -0.808, 95% CI: -1.149, -0.467), female estrogen (SMD: -2.608, 95% CI: -4.588, -0.628), female luteinizing hormone (SMD: -0.386, 95% CI: -0.682, -0.089), and female follicle-stimulating hormone (FSH) (SMD: -0.418, 95% CI: -0.716, -0.119). Besides, linear and non-linear correlations were detected in the main parameters. **Conclusion:** In conclusion, based on the current meta-analysis, BPS was suggested to be toxic for the reproductive system, similar to the other bisphenols. Moreover, a possible correlation was indicated between oxidative and hormonal status disruption induced by BPS in male and female reproductive systems dis/malfunction.

Keywords: *Bisphenol S, gland, meta-analysis, oxidative stress, reproductive system*

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Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_271_21

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Introduction

Endocrine-Disrupting Chemicals (EDCs), as a new human public health concern, have increased public anxiety due to their excessive global usage in various ways, such as pesticides and food packaging.[1] Among many EDCs released into the world, bisphenol-A (BPA) has been widely employed as an industrial component in the last decades. It was first produced in 1891[2] and has been a component of many key products, including plastic compounds as well as food and beverage containers.[3,4] Three main BPA entrance pathways have been suggested for human contamination, namely the dermal tissue system, gastrointestinal system, and respiratory tract.[5]

Multi-organelle toxicity was reported for BPA, even at low-dose exposure as it interacts with various biological receptors and induces oxidative stress which consequently, influences male and female reproductive systems.[6-9] Furthermore, tolerable daily intake of BPA was reduced from 50 µg/kg bw/day to 4 µg/kg bw/day by Food and Drug Administration (FDA) which increased public health concerns about BPA-based products.[10] Based on various scientific reports and FDA documents, BPA was classified as a toxic subject in the United States and European Union.[11]

Following BPA restrictions in 2012, BPA-free products were introduced to the European market and Bisphenol-S (BPS) replaced BPA in the plastic industry by labeling products "BPA-free."[12] The BPS

How to cite this article: Abouhamzeh B, Zare Z, Mohammadi M, Moosazadeh M, Nourian A. Bisphenol-S influence on oxidative stress and endocrine biomarkers of reproductive system: A systematic review and meta-analysis. Int J Prev Med 2023;14:37.

was first synthesized in 1869 and used as a common name for 4,4′- Sulfonyl diphenol (CAS NO. 80-09-1). Similar to BPA, BPS is a white colorless powder with a molecular weight of 250.27 g/mol, density of 1.3663 g/cm^3, and molten at 240–250°C with a chemical structure of (HOC6H4) 2SO2 which is reported in Figure 1.[13]

Regarding the level of toxicity of BPA and BPS, at first, from 2012 until 2017, it was considered that BPS has less toxic potential, compared to BPA.[14,15] However, recent research has revealed controversial issues about the toxic mechanisms of BPS, especially in pregnant women and infants.[16-18] The growing body of recent research has revealed that the induction of oxidative stress in the bisphenols family could be the main toxic mechanism in animals and humans.[19,20]

Based on *in vitro* and *in vivo* studies, BPA oxidative stress induction has been reported in the liver, brain, kidney, heart, and reproductive system.[21-25] However, many oxidative protective agents, such as trace elements (zinc, selenium) and nanomaterials were suggested in spermatogenesis and ovarian reservation[26-28] which had protective effects against BPA exposure since oxidation-reduction pathways play a key role in BPA and BPS toxicity.[29,30]

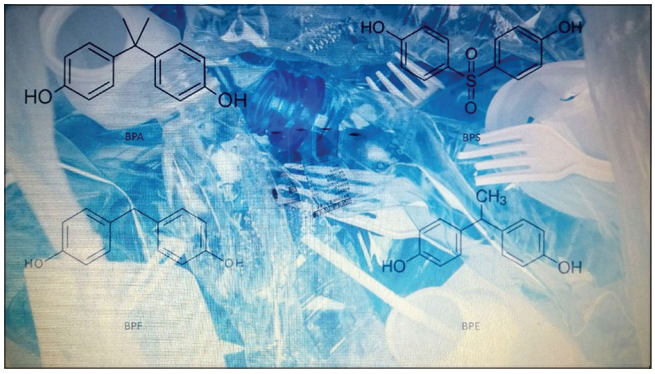

Figure 1: structure of common commercial bisphenols family

In light of the mentioned considerations, this study aimed to systematically review the published studies to investigate the correlation between exposure to BPS and the risk of reproductive malfunction induced by oxidation reduction and hormonal alteration [Figure 2].

Materials and Methods

Literature search and selection

The protocol of this study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis[31] [Figure 3] and the Cochrane Collaboration guideline.[32] The search was conducted in the following databases: PUBMED, Google Scholar, Web of Science, and Cochrane Library. It should also be mentioned that all the studies up to January 2021 were searched for the purposes of the study. The terms used in the literature search were: ("bisphenol A" OR "BPA" OR "bisphenol S" OR "BPS") AND ("oxidative stress" OR "reproductive system" OR "hormone" OR "male" OR "female" OR "ovary" OR "testis" OR "toxicity" OR "spermatogenesis" OR "accessory glad").

Eligibility criteria

Studies were excluded if they had one or more of the following criteria: (I) non-randomized experimental studies, (II) randomized experimental studies without accurate treatment duration, (III) studies without a control group, and (IV) studies with insufficient data. Discrepancies on inclusion and exclusion were resolved by a consensus meeting where additional reviewers were enrolled.

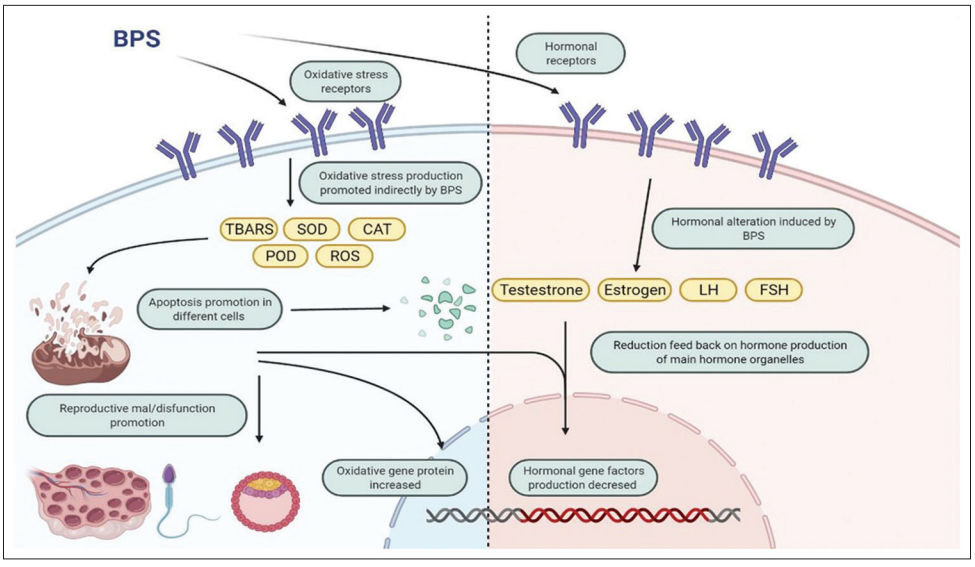

Figure 2: Schematic illustration of BPS influence on oxidative stress and hormonal alteration by boosting ROS generation and/or suppressing endocrine systems

Data extraction

The following data were extracted from the full text of the eligible studies using a pre-designed abstraction form: (I) name of the first author, (II) year of the publication, (III) location of the study, (IV) sample sizes of the intervention and control groups, (V) type of study, (VI) dose of the BPS used, and (VII) study duration.

Study quality assessment

The Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) was used for the systematic evaluation of the bias.[33] This tool aims to judge about 10 entries related to bias based on six main criteria, including selection, performance, detection, attrition, and reporting. Two researchers (A.N and Z.Z) independently assessed the method and quality of studies.

Meta-analysis of data

To evaluate the effect size for BPS, the mean difference (MD) and its standard deviation (SD) were calculated for both intervention and control groups. If the studies did not report the mean and SD values, the following formula was used to calculate the missing SDs for changes: SD change = square root ([SD baseline2 + SD final2] – [2 × R × SD baseline × SD final]).[34]

To estimate the overall effect size and separate effect sizes for studies, Cohen's D, which was used to calculate the standard mean difference (SMD), and the corresponding standard error (SE) with a 95% confidence interval (CI) were calculated. The standardized or statistical effect size, or Cohen's D, indicated the mean difference in a variable of interest between two groups in SD units.[35] Heterogeneity in the articles was evaluated by the Cochran Q and the I^2 statistics (I^2= (Q-df)/Q × 100%; I^2 <25%: no heterogeneity; I^2 = 25-50%: moderate heterogeneity; I^2 = 50-75%: large heterogeneity, I^2 >75%: extreme heterogeneity).[36] To evaluate the association among pooled effect size, BPS dose (μg/L), and duration of the intervention (hours and days), the potential non-linear effects of BPS dosage (μg/L), and duration of the intervention (in weeks) were examined by using fractional polynomial modeling and linear meta-regression analysis.

Sensitivity analysis was conducted by removing each study one by one and re-calculating the pooled evaluations. Egger's weighted regression tests, visual inspection of the funnel plots, and trim and fill method were performed for the detection of potential publication bias.[37] Statistical analysis was conducted using STATA, version 16 (Stata Corp, College Station, TX). It should be noted that a *P* value of less than 0.05 was considered statistically significant.

Results

Selection and identification of studies

Based on the database search, 1162 potentially acceptable articles were obtained by electronic and hand search, 527 of which were duplicates. Therefore, 635 studies were screened according to the inclusion criteria. Subsequently, after the exclusion of unrelated studies, 16 studies remained, 4 of which did not meet the proper information. Finally, 12 eligible studies [Figure 3] were included in the final analysis.

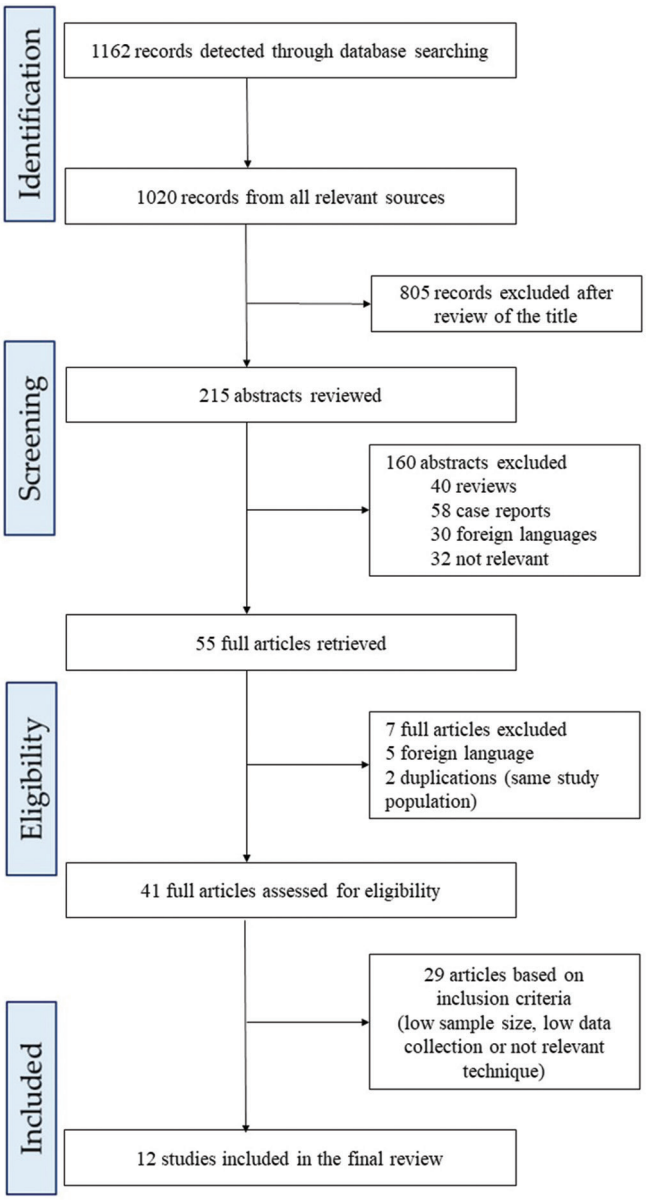

Figure 3: PRISMA flow diagram of studies included in the Review

Characteristics of studies

The main characteristics of the included studies in this meta-analysis are summarized in Table 1. Overall, 53 effect sizes were extracted from 12 eligible studies which included a total of 420 subjects that were equally divided into the BPS different group (n = 210) and the control group (n = 210). Based on the SYRCLE scores, the quality of four studies was classified as fair or weak,[38-41] while the rest were categorized as good.[42-52]

Table 1: Characteristics of the extracted studies

Study	Year	Country	Organelle/cell type	Number or sample size	Type of administration and Drug dosage	Treatment interval
Kose, Ozge, *et al*.	2019	France	RWPE-1 cells	20 000 cells/well	3834 µg/L	24 h
John, Naham, *et al*.	2019	Pakistan	The neonatal stage from postnatal day PND1 to PND 27.	36 mice	2 and 200 µg/L	26 days
Ullah, Asad, *et al*.	2019	Pakistan	In vitro Sperm incubation	108 cells/well (26 mice)	1, 10 and 100 µg/L	2 h
Shi, Mingxin, *et al*.	2018	Illinois	in vivo examination from gestational day 11 to birth.	5 mice	500, 20000 and 50000 µg/L	15 days
Ullah, Asad, *et al*.	2018	Pakistan	In vitro testis slice incubation	108 cells/well (7 mice)	1, 10 and 100 µg/L	2 h
			Sub Chronic treatment	13 mice	5000, 25000 and 50000 µg/L	28 days
Ullah, Hizb, *et al*.	2017	Pakistan	In vitro Sperm incubation	108 cells/well (7 mice)	0.5, 1, 10 and 100 µg/L	2 h
Ullah, Hizb, *et al*.	2016	Pakistan	In vitro testis slice incubation	5 mice	0.5,1,10 and100 µg/L	2 h
			In vivo administration	6 mice	1000,5000,25000 and 50000 µg/L	28 days
Nourian, Alireza, *et al*.	2020	Iran	*In vivo* ovarian tissue	10 mice	0,1,5,10,50 and 100 µg/L	21 day
Ijaz, *et al*.	2020	Pakistan	*In vivo* ovarian tissue	5 mice	50 µg/kg (50,500,5000,50000 µg/L)	28 days
Berni, M., *et al*.	2018	Italy	in vitro swine granolosa cell	104 cells/well	0.1 µM (3.55,35.5 and 355 µg/L)	48 h
Nevoral, Jan, *et al*.	2018	France	*In vivo* ovarian tissue	16 mice	0.001,.01,10 and 100 ng.g/bw/day	28 days
Nourian, Alireza, *et al*.	2017	Iran	*In vivo* ovarian tissue	10 mice	0,1,5,10,50 and 100 µg/L	21 days
Liu, Yanhua, *et al*.	2019	China	reproduction function of daphnia magna	25 mice	6.2 mg/L	24 h
Xiao, Xiang, *et al*.	2019	China	Caenorhabditis elegans	30 mice	0, 0.25, 0.5, 1, 1.5 and 2 mM	24 h
Qiu, Wenhui, *et al*.	2018	China	Zebra fish embryo	200 embryos per dish	0.1,1,10,100 and 1000 µg/L	120 h post fertilization
Park, Jun Chul, *et al*.	2018	South Korea	Marine rotifer Brachionus koreanus	6×10^4 cells/mL	0, 5, 10, 15, 20, 50 and 100 mg/l	24 h

The result of the quality assessment is tabulated in Table 2.

Meta-analysis of data

Effect of bisphenol-S in vitro administration on oxidative stress parameters of male reproductive system

Forest plots summarizing the efficacy of BPS on oxidative stress parameters of the reproductive system for *in vitro* assessment are summarized in Table 3. The pooled results of 4-8 eligible studies (4-8 treatment arms) for different oxidative stress parameters revealed different results for all parameters levels. Antioxidant parameters were calculated and the results indicated a significant increase, compared to the control group in superoxide dismutase (SOD) (SMD: 0.63, 95% CI: 0.321, 0.939), thiobarbituric acid reactive substances (TBARS) (SMD: 0.760, 95% CI: 0.423, 1.096), and total reactive oxygen species (ROS) (SMD: 0.484, 95% CI: 0.132, 0.835).

Moreover, a non-significant increase was detected in catalase (CAT) (SMD: 0.066, 95% CI: -1.206, 1.339) and peroxidase (POD) (SMD: 0.133, 95% CI: -0.27, 0.536). It should be mentioned that a large heterogeneity was only found in CAT (I^2 = 87.12%, P = 0.00). To detect the potential sources of heterogenicity, a subgroup analysis was run based on 50 µg/L upper and lower dosage subgroups; however, a non-significant alteration was detected in these subgroups.

Effect of bisphenol-S in vitro administration on testosterone status of male reproductive system

Forest plots summarizing the effectiveness of different BPS dosages on male testosterone concentration are tabulated in Table 3. The pooled results of 7 treatment arms for testosterone concertation revealed a significant decrease in male testosterone concertation, compared to the control group (SMD: -0.476, 95% CI: -0.881, -0.071).

Effect of bisphenol-S in vivo administration on oxidative stress parameters of reproductive system

Forest plots summarizing the efficacy of BPS on oxidative stress parameters of the reproductive system for *in vivo* assessment are illustrated in Figure 2. The pooled results of 2-8 eligible studies (4-12 treatment arms) for different oxidative stress parameters showed different results for all parameters levels. Antioxidant parameters were calculated, and the result indicated a significant increase, compared to the control group in female SOD (SMD: -0.808, 95% CI: -1.149, -0.467), male SOD (SMD: -1.432, 95%

Table 2: Quality assessment

Study	Random Sequence Generation (selection bias)	Baseline characteristics (selection bias)	Allocation concealment (selection bias)	Random housing) performance bias)	Blinding (performance bias)	Random outcome assessment (detection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other bias	General quality
Kose, Ozge, *et al*. 2019	H	H	L	H	L	H	U	H	U	H	Fair
John, Naham, *et al*. 2019	H	L	H	H	L	H	U	H	U	H	Fair
Ullah, Asad, *et al*. 2019	L	L	L	L	L	L	L	L	L	U	Good
Shi, Mingxin, *et al*. 2018	L	L	H	L	L	L	U	L	L	U	Good
Ullah, Asad, *et al*. 2018	L	U	H	L	L	L	L	L	L	U	Good
Ullah, Hizb, *et al*. 2017	L	L	L	L	L	L	L	L	L	U	Good
Ullah, Hizb, *et al*. 2016	L	L	H	L	L	L	L	L	L	L	Good
Nourian. Alireza, *et al*. 2020	L	L	L	L	L	L	L	L	H	L	Good
Ijaz, *et al*. 2020	L	L	L	L	H	L	U	L	H	L	Good
Berni, M., *et al*. 2018	L	L	H	L	H	L	L	L	U	L	Good
Nevoral, Jan, *et al*. 2018	L	L	U	L	L	L	U	L	L	L	Good
Nourian. Alireza, *et al*. 2017	L	L	H	L	L	L	L	L	H	U	Good
Liu, Yanhua, *et al*. 2019	L	L	H	L	L	L	L	L	H	U	Good
Xiao, Xiang, *et al*. 2019	H	U	L	L	L	H	U	L	L	U	Good
Qiu, Wenhui, *et al*. 2018	U	H	U	L	L	H	U	H	L	H	Weak
Park, Jun Chul, *et al*. 2018	U	H	U	H	L	H	U	H	L	H	Weak

L: low-risk of bias, H: high-risk of bias, U: unclear-risk of bias

Table 3: Summarized of the systematic review outcomes on oxidative stress and hormonal parameters

Outcome	Number of Primary Studies	Total sample size	SMD (95%CI)	Heterogenicity			Publication Bias (Egger)	
				I^2	Q	*P*	β	*P*
SOD								
In vitro	14	186	0.s63 [0.32, 0.94]	0.00%	18.89	0.13	4.77	0.0012
Female *In vivo*	10	160	-0.81 [-1.15, -0.47]	14.82%	11.68	0.23	-4.81	0.0022
Male *In vivo*	7	126	-1.43 [-2.08, -0.78]	62.94%	15.04	0.02	-4.84	0.0003
CAT								
In vitro	7	82	0.07 [-1.21, 1.34]	87.12%	34.89	0.00	8.95	0.0188
Female *In vivo*	10	160	-1.77 [-2.45, -1.09]	71.08%	30.74	0.00	-6.14	0.0003
Male *In vivo*	7	126	-3.83 [-6.00, -1.87]	94.71%	51.24	0.00	-5.31	0.00
TBARS								
In vitro	11	144	0.76 [0.42, 1.10]	8.20%	15.03	0.13	6.43	0.0002
Female *In vivo*	10	160	0.03 [0.85, 0.80]	84.47%	38.33	0.00	-6.51	0.000
Male *In vivo*	7	126	1.02 [0.45, 1.58]	57.29%	14.19	0.00	4.42	0.0777
ROS								
In vitro	14	186	0.40 [0.13, 0.04]	33.08%	30.89	0.00	6.44	0.000
Female *In vivo*	10	160	0.62 [0.16, 1.40]	82.78%	35.93	0.00	7.22	0.000
Male *In vivo*	7	114	1.04 [0.38, 1.69]	67.69%	18.31	0.01	0.68	0.514
POD								
In vitro	7	82	0.13 [-0.27, 0.54]	0.00%	3.50	0.74	4.28	0.39
Female *In vivo*	4	40	-1.16 [-2.06, -0.27]	49.28%	5.88	0.12	-11.22	0.0170
Male *In vivo*	7	126	-1.38 [-1.75, -1.00]	0.00%	6.13	0.41	-0.60	0.7858
Testosterone								
Male *In vitro*	7	82	-048 [-0.88, -0.07]	0.00%	0.61	1	0.02	0.00
Female *in vivo*	4	40	2.81 [0.22, 5.93]	89.80%	17.96	0.00	6.17	0.000
Intracellular testosterone								
Male *In vivo*	7	126	-2.08 [-3.08, -1.08]	80.83%	28.70	0.00	-7.15	0.11
Plasma testosterone								
Male *In vivo*	7	126	-2.36 [-3.31, 1.41]	76.34%	26.38	0.00	-6.35	0.2552
Estrogen								
Female *in vivo*	4	40	-2.51 [-4.59, -0.63]	82.60%	15.65	0.00	-6.81	0.0001
Male *in vivo*	3	30	1.19 [-0.12, 2.50]	67.35%	5.58	0.06	8.64	0.0187
LH								
Female *In vivo*	10	160	-0.39 [-0.68, -0.09]	0.00%	2.64	0.98	-1.57	0.4830
FSH								
Female *In vivo*	10	160	-0.42 [-0.72, -0.12]	0.00%	4.99	0.84	-2.20	0.2984

CI: -2.084, -0.780), female CAT (SMD: -1.771, 95% CI: -2.448, -1.094), male CAT (SMD: -3.833, 95% CI: -5.995, -1.670), male TBARS (SMD: 1.015, 95% CI: 0.448, 1.583), male total ROS (SMD: 1.035, 95% CI: 0.375, 1.695), female POD (SMD: -1.161, 95% CI: -2.056, - 0.266), and male POD (SMD: -1.376, 95% CI: -1.753, -0.998).

A non-significant alteration was detected in female TBARS (SMD: -0.025, 95% CI: -0.848, 0.797) and female total ROS (SMD: 0.619, 95% CI: -0.161, 1.399). To evaluate the dose-dependent effects of BPS, subgroup analysis was run based on 50 µg/L upper and lower dosage subgroups for both groups. Female TBARS subgroup analysis revealed a significant increase in the upper 50 µg/L subgroups; however, there was a high heterogenicity. Moreover, a non-significant increase with low heterogenicity was found in the lower 50 µg/L subgroups.

Female total ROS subgroup analysis revealed a significant increase in the upper 50 µg/L subgroups; however, a high heterogenicity was found in both subgroups. Moreover, a large heterogeneity was found in male CAT (I^2 = 87.12%, *P* = 0.00) and female TBARS (I^2 = 94.72%, *P* = 0.00). To detect the potential sources of heterogenicity, a subgroup analysis was run based on 50 µg/L upper and lower dosage subgroups; however, a non-significant alteration was detected in the subgroups.

Effect of bisphenol-S in vivo administration on hormonal parameters of reproductive system

Forest plots summarizing the efficacy of BPS on hormonal parameters of the reproductive system for *in vivo* assessment are represented in Table 3. The pooled results of 1-3 eligible studies (4-10 treatment arms) for different hormonal parameters revealed different findings for all parameters levels. Hormonal parameters were

calculated which indicated a significant decrease in female testosterone (SMD: -0.808, 95% CI: -1.149, -0.467), male intracellular testosterone (SMD: -2.075, 95% CI: -3.075, -1.075), male plasma testosterone (SMD: -2.360, 95% CI: -3.307, -1.414), female estrogen (SMD: -2.608, 95% CI: -4.588, -0.628), female luteinizing hormone (LH) (SMD: -0.386, 95% CI: -0.682, -0.089), and female follicle-stimulating hormone (FSH) (SMD: -0.418, 95% CI: -0.716, -0.119), compared to the control group.

A non-significant decrease was only detected in male estrogen (SMD: 1.186, 95% CI: -0.124, 2.496). A large heterogeneity was found in female testosterone (I^2 = 89.80%, P = 0.00), male intra testosterone (I^2 = 80.83%, P = 0.00), male plasma testosterone (I^2 = 76.34%, P = 0.00), and female estrogen (I^2 = 82.60%, P = 0.00). The subgroup analysis was performed based on 5000 μg/L upper and lower dosage subgroups for indication of the dose-dependent effect of BPS on hormonal parameters. A small heterogenicity was found only in lower than 5000 μg/L dosage of male plasma testosterone groups (I^2 = 40.31%, P = 0.180) without a significant alteration. However, a large heterogenicity and non-significant alteration were found in the upper than 5000 μg/L dosage group. Due to large heterogenicity in 50 μg/L upper and lower dosage subgroups, subgroup assessment could not be performed.

Sensitivity analysis

The sensitivity analysis demonstrated that the assessed overall effect sizes of the evaluated parameters did not substantially change after the removal of each article.

Publication bias

The publication bias was examined by Egger's-weighted regression test, visual inspection of the funnel plots, and trim and fill method [Table 3]. The outcomes of Egger's linear regression revealed no publication bias for male *in vivo* total ROS (P = 0.52), male *in vitro* POD (P = 0.39), male *in vivo* POD (P = 0.78), male *in vitro* testosterone (P = 0.99), male *in vivo* intracellular testosterone (P = 0.12), male *in vivo* plasma testosterone (P = 0.26), female *in vivo* LH (P = 0.48), and female *in vivo* FSH (P = 0.30).

Moreover, the visual inspection of the funnel plots and metatrim analysis revealed publication bias in some groups. Based on the Trim and Fill method, some potential studies (unpublished or missed due to language limitations) were predicted to be missing. Altogether, it seems that publication bias presents among the included studies.

Meta-regression analysis

A meta-regression analysis was employed to investigate the potential association between an alteration in oxidative stress indicators and the dose of BPS in various *in vitro* and *in vivo* situations in different genders. The meta-regression analysis indicated a linear relationship between dose and changes in the male *in vitro* SOD (P = 0.004), female *in vivo* TBARS (P = 0.000), male *in vitro* ROS (P = 0.006), and female *in vivo* ROS (P = 0.021). Furthermore, it was found that the hormonal status had a significant linear relationship with the dose of BPS exposure in the male *in vivo* testosterone (P = 0.05), male *in vivo* intracellular testosterone (P = 0.038), female *in vivo* LH (P = 0.037), and female *in vivo* FSH (P = 0.005).

Non-linear dose-response relationship of bisphenol-S dose with oxidative stress and hormonal parameters

Based on the dose of BPS administration, the dose-response analysis did not show any significant changes in the male *in vitro* SOD (r = -1.030, P-nonlinearity = 0.133), female *in vivo* SOD (r = -0.005, P-nonlinearity = 0.229), male *in vivo* SOD (r = 1.3935, P-nonlinearity = 0.706), male *in vitro* CAT (r = 0.746, P-nonlinearity = 0.604), female *in vivo* CAT (r = -1.524, P-nonlinearity = 0.104), male *in vivo* CAT (r = 0.0038, P-nonlinearity = 0.863), male *in vitro* TBARS (r = 0.384, P-nonlinearity = 0.192), male *in vivo* ROS (r = -0.06288, P-nonlinearity = 0.279), male *in vitro* POD (r = -0.675, P-nonlinearity = 0.341), male *in vivo* POD (r = -0.929, P-nonlinearity = 0.099), male *in vitro* testosterone (r = -1.335, P-nonlinearity = 0.154), male *in vivo* plasma testosterone (r = -0.1220, P-nonlinearity = 0.170), female *in vivo* estrogen (r = 0.000143, P-nonlinearity = 0.175), and female *in vivo* FSH (r = 0.01439, P-nonlinearity = 0.217).

However, significant alterations were detected in female *in vivo* TBARS (r = 0.1823, P-nonlinearity = 0.012), male *in vivo* TBARS (r = 08834, P-nonlinearity = 0.043), male *in vitro* ROS (r = -7.8662, P-nonlinearity = 0.042), female *in vivo* ROS (r = -0.3867, P-nonlinearity = 0.005), female *in vivo* POD (r = -0.00121, P-nonlinearity = 0.019), female *in vivo* testosterone (r = -0.0048, P-nonlinearity = 0.047), male *in vivo* intracellular testosterone (r = 0.273, P-nonlinearity = 0.052), and female *in vivo* LH (r = 0.0149, P-nonlinearity = 0.037).

Discussion

The results of this meta-analysis revealed evidence of an increased risk of oxidative stress with higher BPS dosage. Moreover, the findings indicated the deleterious effects of BPS on the endocrine system based on the measurement of the hormonal status of both genders as well as their *in vitro* and *in vivo* assessment.

To the best of our knowledge, this is the first meta-analysis study on the effects of different dosages of BPS on endocrine and oxidative stress parameters that has resulted in a potential linear and non-linear association between them. The most pronounced increase in risk was observed at a BPS >50 μg/kg; however, when the analysis was further restricted to studies among upper and lower than 50 μg/kg, a non-significant alteration was observed.

The present meta-analysis had some restrictions that might influence the interpretation of the outcomes. The main limitation was the low number of cohort studies reporting BPS effects on the reproductive systems of both genders. Moreover, a large heterogeneity was found in some analysis factors that might be due to the low number of studies which limited the ability to conduct subgroup and sensitivity analyses of these measures (female *in vivo* testosterone and male *in vivo* intra testosterone assessment).

Recently, many systematic and meta-analysis studies have been focusing on the influences of BPS on the human body, such as its influence on the cardiovascular system and neurobehaviors.[53] Nevertheless, based on our investigation, only a few studies have evaluated the oxidative potential of BPA and BPS on the male and female reproductive systems. Besides, no systematic review was performed on the potential of BPS for oxidative stress induction as well as endocrine disruption in male fertility.

Detrimental potential of bisphenol-S on male fertility and reproductive system function

Spermatozoa are very susceptible to oxidative stress due to cytoplasmic loss after puberty. Proper levels of oxidative factors are critical for appropriate sperm function, but excessive oxidation status has deleterious effects on male fertility by damaging lipids, proteins, and DNA integrity in spermatozoa.[54]

It is noteworthy that BPA was suggested to induce spermatozoa malfunction and apoptosis promoted by genomic and non-genomic receptors.[55] After the replacement of BPS with BPA, Eladak *et al*. compared the effects of BPS and BPF with BPA on the reproductive system. This was the first study explaining the detrimental potential of BPS in human and rodent male reproductive systems. In the aforementioned study, BPS showed less endocrine disruption, compared to BPA; however, significant dose- and time-dependent reduction was reported due to BPS exposure.[56]

Ullah *et al*. first indicated that the toxic potential of BPS on male reproduction was not only induced by hormonal alteration, but also by oxidation induction.[52] Results of their next study revealed the detrimental effects of BPS on rat spermatozoa based on the examination of SOD, TBARS, and ROS activity as well as the hazardous influence of sub-chronic exposure on daily sperm production, DNA integrity, and sperm motility. The above-mentioned study suggested the genotoxic potential as well as oxidative stress-inducing capability of BPS in rat sperm, in both *in vivo* and *in vitro* studies.[51] In addition, they compared BPS and another BPA analogue in terms of their harmful potential effects on male hormonal status, reproductive function, and antioxidant capacity through *in vitro* and *in vivo* approaches in another study. Their findings were inconsistent with those of their previous studies.[50]

Furthermore, SOD and ROS could be considered the main mechanisms involved in BPS oxidative stress induction in the male reproductive system due to the linear and non-linear dose-response effect. However, further studies with larger sample sizes are needed to clarify the exact mechanism of BPS oxidation induction and the main indicator for oxidative stress assessment. To the best of our knowledge, no study has been conducted on the linear and non-linear dose-response assessment of BPS in oxidative induction of the male reproductive system.

On the other hand, meta-analysis studies have been performed to evaluate the effect of the bisphenols family on the reproductive system. In previous meta-analysis studies, adult men with a history of postnatal exposure to EDCs were systematically evaluated, and also the LH, progressive motility, and normal morphology were compared between high-exposed and non-exposed groups. It is noteworthy that postnatal exposure to EDCs was correlated with semen quality and hormonal status reduction, which is inconsistent with the results of LH assessment in our study.[57]

In another study, a comparison of the toxicity of BPS and BPA was reviewed and it was concluded that BPS had the potential for oxidative stress induction, hormonal status disruption, and reproductive disability, which is in line with the findings of the present study.[58,59] Besides, the possible indication of testosterone disorder as the main mechanism of BPS hormonal alteration in the male reproductive system could be suggested due to the strong linear and non-linear correlation that was found in the present research. However, further studies with larger sample sizes are recommended to determine testosterone as the key factor influenced by BPS in the male reproductive system.

Altogether, based on the above-mentioned studies and findings of the present meta-analysis, it can be suggested that BPS, as a new alternative to BPA, might induce toxic effects in the male reproductive system, compared to BPA and other BPA analogues. However, BPS was reported to have different detrimental effects based on the route of administration, and there has been an increased new public health concern about BPS safety and BPA-free labeled products, especially on the next-generation testis and male accessory gland development.

Based on oxidative stress parameters evaluation, it could be suggested that BPS-induced oxidative stress in the male reproductive system. Moreover, significant dose-dependent reduction of different testosterone as well as estrogen status was shown. Linear and non-linear associations were observed in hormonal and oxidative stress parameters, which could be assessed further in future studies. It is suggested that further studies be performed on the influence of BPS and its analogues on the next-generation male accessory gland and infant testis development as well as its age-dependent effects based on oxidative stress and hormonal parameters.

Detrimental potential of bisphenol-S on *in vitro* fertilization outcome, female fertility, and reproductive system function

The female reproductive tract is a multi-functional system designed for the production of the female primary oocytes, granulosa cells, hormonal balance, and sexual behavior management.[60] The EDCs detrimental influence on the female reproductive system has been reported for decades and the folliculogenesis process has been suggested as the main target of EDCs.[61] To the best of our knowledge, only a few studies have been carried out on the influences of BPA analogues on female fertility.

The detrimental effects of low BPS concentrations on *in vitro* fertilization (IVF) outcomes were first suggested by our study performed in 2017. Results of the aforementioned study revealed that the cooperation of oxidative stress with low dosages of BPS damages the female reproductive system and reduces the rate of IVF success.[46] It should be noted that many studies have supported our above-mentioned hypothesis. The BPS potential for the reduction of *in vitro* blastocyte and cleavage rate was found in low BPS concentration, while no oxidative stress potential was observed in the blastocyte and cleavage cells,[62] which is inconsistent with the detrimental effect of BPS on the early developmental stage of the oocyte in ewe.[63]

Prokešová *et al*. evaluated the *in vivo* influence of different BPS dosages on oocytes harvested from mature females by *in vitro* maturation which showed the toxic potential of acute BPS administration.[64] Moreover, results of another study indicated that the *in vivo* prenatal exposure to BPS altered the female reproductive system and that also the transmission of epigenetic alterations in germ cells could cause reproductive disorders/dysfunction until F3 generation.[65]

In agreement with the aforementioned studies, BPS detrimental influence was reported on bovine oocyte maturation and early embryo development; however, no oxidative stress status was evaluated in exposed oocyte.[66] Results of a meta-analysis systematic review conducted on the association between BPA and polycystic ovarian syndrome revealed that patients with polycystic ovarian syndrome had significantly higher BPA concentrations. Moreover, a positive association was detected between BPA with body mass index in the aforementioned meta-analysis.[67]

According to the findings of the present systematic review, BPS had dose-dependent effects on the oxidative and hormonal parameters in the female reproductive system. In addition, the linear and non-linear association was detected between female testosterone, LH, POD, ROS, and TBARS. Berni *et al*. evaluated the influence of different dosages of BPS on cultured granulosa cells. In agreement with the results of this study, they found that BPS (0.1-1-10 μM) could disrupt metabolic effects and therefore induce harmful effects on the female reproductive tract.[42]

Recently, a histopathological examination of the ovary after *in vivo* BPS exposure was performed to evaluate the number of antral and corpus luteum follicles. Results of this examination indicated oxidative stress induction in different groups based on CAT, SOD, and POD examination.[43] Furthermore, Nevoral *et al*. performed an *in vivo* evaluation of low doses of BPS administration on folliculogenesis and oocyte quality. They found that the BPS-reduced ovarian follicle numbers and histological quality as well as oxidative stress induction in ovarian tissue.[45] Results of both histopathological examinations of the ovary are in agreement with those of the present analysis and showed that pre- and post-pubertal stage BPS exposure induced oxidative stress and histopathological alteration during follicular development and reservation in female rats.[43,45]

Possible indication of LH, POD, ROS, and TBARS disorder as the main mechanism of BPS hormonal and oxidative stress alteration could be suggested since strong linear and non-linear correlations were found in our data. However, further studies with larger sample sizes are suggested to clarify the exact mechanism of BPS hormonal disruptions. To the best of our knowledge, no study has indicated the linear and non-linear dose-response effects of BPS in oxidative induction and hormonal disruptions of the female reproductive system. Only one study has evaluated the influence of BPA exposures on sexual behavior in a linear manner which indicated the induction of developmental problems by low doses of bisphenol-A.[68]

In conclusion, based on our studies and previous research, BPS could be considered a toxic material for the female reproductive system. To the best of our knowledge, this is the first study to indicate linear and non-linear associations of different dosages of BPS with oxidative and hormonal parameters. Further studies are recommended to examine the effects of exposure to low doses of BPS on female reproductive oxidative stress parameters and determine the main mechanisms of BPS that lead to oxidation reduction. However, no study has been designed for the evaluation of the detrimental effects of BPS on the female accessory gland and its histopathological alteration as well as vaginal and uterus secretion. Moreover, the correlation between BPS concentration (in human blood and urine) and female fertility parameters (i.e. uterus diameter and ovarian reserve) has not been studied yet.

Association of BPA with fat and body weight was meta-analyzed in animal modeling which suggested that BPA exposure in neonates may increase adiposity and circulation of lipid level.[69] Furthermore, the correlation between maternal exposure to BPA and birth weight was examined in male neonates which indicated the detrimental effect of BPA on weight outcome.[70] The collected studies

in the present research did not detect weight alteration of samples after the administration of different dosages of BPS. However, further studies are suggested to find the exact mechanism and detrimental effect of the Bisphenol family on fat circulation and body weight.

Conclusions

In conclusion, based on our research and mentioned articles, BPS could be suggested as a toxic material for the female and male reproductive systems. To the best of our knowledge, this is the first study to indicate the linear and non-linear associations of different dosages of BPS with oxidative and hormonal parameters.

Finally, it appears necessary to inform sub-fertile couples, pregnant women, and immature children to moderate BPS exposure due to its potential harmfulness that could influence reproductive system development and function as well as infant maturity. Therefore, this meta-analysis provides further support for previous recommendations regarding the association between BPS dosage and reproductive system malfunction. Further studies are suggested for the evaluation of the detrimental influences of BPS on the accessory gland and infant testis development as well as its age-dependent effects, based on oxidative stress and hormonal parameters.

Consent to publish

The manuscript has been read and approved by all authors.

Acknowledgments

This work is part of military service research project of Dr. Alireza Nourian under supervision of Drs. Abouhamzeh, Zare, Mohammadi and Moosazadeh. Alireza Nourian would like to thankfully appreciate for all supports received from AJA university of Medical Sciences.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 15 Jun 21 **Accepted:** 27 Oct 22
Published: 21 Mar 23

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