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# Effects of Bisphenol A and its Analogs on Reproductive Health: A Mini Review

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## Abstract

Known endocrine disruptor bisphenol A (BPA) has been shown to be a reproductive toxicant in animal models. Its structural analogs: bisphenol S (BPS), bisphenol F (BPF), bisphenol AF (BPAF), and tetrabromobisphenol A (TBBPA) are increasingly being used in consumer products. However, these analogs may exert similar adverse effects on the reproductive system, and their toxicological data are still limited. This mini-review examined studies on both BPA and BPA analog exposure and reproductive toxicity. It outlines the current state of knowledge on human exposure, toxicokinetics, endocrine activities, and reproductive toxicities of BPA and its analogs. BPA analogs showed similar endocrine potencies when compared to BPA, and emerging data suggest they may pose threats as reproductive hazards in animal models. While evidence based on epidemiological studies is still weak, we have utilized current studies to highlight knowledge gaps and research needs for future risk assessments.

### Keywords

Bisphenol A; Bisphenol F; Bisphenol S; Bisphenol AF; Tetrabromobisphenol A; Reproductive toxicity

## 1. Introduction

Bisphenol A (BPA) is a high production volume (HPV) chemical, commonly used in food packaging materials, dental sealants, medical devices and thermal receipts [1]. Exposure to BPA is ubiquitous via ingestion, inhalation, and dermal contact [2, 3]. The Centers for Disease Control and Prevention (CDC) has reported measurable levels of BPA in urine samples in over 90% of the United States population [4, 5]. BPA has demonstrated endocrine disrupting effects by interacting with various physiological receptors, such as estrogen receptor α/β (ER α/β), estrogen-related receptor γ, androgen receptor (AR), and thyroid hormone receptor [6-13]. Numerous studies have investigated the reproductive toxicity of BPA, and extensive reviews were conducted to address the strength of the

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evidence regarding BPA toxicity [14]. In 2006, an expert panel composed of the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Dental Craniofacial Research (NIDCR), the U.S. Environmental Protection Agency (EPA), and Commonweal, reviewed human exposure to BPA *in vivo* and *in vitro* [15]. The subpanel of experts that focused on *in vivo* animal studies found contradictory results among the studies. However, they were confident that BPA impacted the male and female reproductive system [14]. Peretz et al. summarized studies published from 2007 to 2013 to examine the associations between BPA and adverse reproductive outcomes [14]. Based on the evidence from experimental animals and human exposure from 2007–2013, the authors concluded that BPA at doses below the LOAEL (50 mg/kg/day) impacted female reproduction and had potential adverse effects on the male reproductive system [14]. Furthermore, recent epidemiological studies have indicated that BPA exposure may potentially be associated with alterations in hormone levels, impairment of ovary and uterine function, and reduction of sperm quality [16-20]. Current data from experimental studies have suggested that BPA exposure adversely affected oocyte quality and maturation, decreased sperm production and quality, damaged testicular cells, perturbed hormone levels, and disrupted ovary function and uterine morphology in animal models [21-28].

Due to widespread exposure and concerns that BPA is a reproductive toxicant, the public drove manufacturers to abandon the use of BPA and introduce analogous chemicals in baby bottles, sippy cups, and infant formula packaging [29, 30]. The U.S. Food and Drug Administration then ruled that BPA would no longer be used in the products mentioned above [29, 30]. BPA analogs are being used as crosslinking reagents and flame retardants in the plastics industry to produce “BPA-free” products. However, the usage of these chemicals is expected to rise globally despite a lack of production data for these analogs. Recently, the prevalence of BPA analogs in the environment, foods, consumer products, and human urine samples have been reported [31-35]. With high degrees of structural similarities to BPA, these analogs may potentially have a similar endocrine disrupting capacity and the potential to exert adverse effects on the reproductive system. Emerging evidence suggests that BPA analogs interact with various physiological receptors, such as estrogen receptors α and β, androgenic receptors, and aryl hydrocarbons receptors [36, 37]. Compared to BPA, little is known about the reproductive toxicity of these analogs. Here, we have reviewed the current literature on BPA, its analogs, and male/female reproduction to summarize the current state of knowledge and the gaps in that knowledge, and to highlight future research directions that could provide valuable information for toxicity evaluation and risk assessment. In addition, the environmental occurrences, human biomonitoring data, toxicokinetics, and the endocrine disrupting capacity of BPA analogs have also been included. This review is structured into 7 topics: (1) BPA and female reproductive health; (2) BPA and male reproductive health; (3) BPS and reproductive health; (4) BPF and reproductive health; (5) BPAF and reproductive health; (6) TBBPA and reproductive health; (7) conclusion and research needs. This review of recent literature focuses on the effects of BPA and its analogs on the male and female reproductive system. We hope the information and conclusions in this review could direct future studies and be useful in risk assessment and in the formation of regulations regarding BPA and its analogs.

## 2. Search Strategy

We performed a literature search to identify journal articles related to BPA, BPS, BPF, BPAF, and TBBPA exposure and reproduction. The research included articles published between 2014 and 2017 for BPA and all years up to 2017 for BPA analogs. An electronic search was performed in Pubmed (http,//www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.com/). Pubmed was selected to identify journal articles as it is considered a main and reliable literature source. Google Scholar was used as a much broader search engine to collect and analyze any literature that may not have been included in Pubmed. Search terms included:

{‘Bisphenol A’ OR ‘BPA’ OR ‘bisphenol S’ OR ‘BPS’ OR ‘4,4’-sulfonyldiphenol’ OR ‘bisphenol F’ OR ‘BPF’ OR ‘4,4’-dihydroxydiphenyl-methane’ OR ‘bisphenol AF’ OR ‘BPAF’ OR ‘hexafluorobisphenol A’ OR ‘tetrabromobisphenol A’ OR ‘TBBPA’ OR ‘2,2’, 6,6’-Tetrabromo-4,4’-isopropylidenediphenol’} AND { ‘reproductive’ OR ‘oocyte’ OR ‘ovary’ OR ‘uterus’ OR ‘testes’ OR ‘sperm’ OR ‘Leydig cell’ OR ‘Sertoli cell’ OR ‘steroidogenesis’ OR ‘estradiol’ OR ‘testosterone’ OR ‘follicle-stimulating hormone’ OR ‘luteinizing hormone’ OR ‘thyroid’ OR ‘pregnenolone’}.

## 3. BPA and female reproductive health

### 3.1 Oocyte production and quality

Experimental studies conducted prior to 2014 provided compelling evidence that BPA had the potential to affect two stages of oogenesis. The onset of meiosis in fetal ovaries, germ cell nest breakdown, and follicle formation were concluded to be the main causes of BPA adversely affecting maturing oocytes. Three studies found that gestational exposure to low-dose BPA in mice induced increased expression of *Stra8* and a variety of meiotic genes in C57BL/6 mice [38], where longer gestational exposure down-regulated the expression of *Stra8, Dazl*, and *Nobox* in CD-1 mice [39]. These results suggested that BPA exposure can cause alterations of gene expression in germ cells and early meiocytes. In neonatally exposed lambs, low-dose BPA was reported to increase the number of multi-oocyte follicles [40], where another study using macaques with low-dose dietary BPA exposure also showed increased numbers of oocytes present in secondary and antral follicles at birth, and continuous exposure (<1 ng/mL in maternal serum) led to the increased incidence of unenclosed oocytes [41]. Prior to 2014, there was some evidence in an *in vitro* study that BPA altered spindle formation at a dose of 43.8 μM in MF-1 mouse oocytes [42], and in a study of follicle-enclosed oocytes, BPA at a dose of 30 μM impaired spindle alignment and caused meiotic arrest [43]. Experimental animal studies conducted after 2014 reported that BPA exposure affected oocyte quality, fertilization, and maturation (overview in Table 1), which is consistent with previous studies [14]. In a more recent study, low-dose BPA (50 μg/kg) was given orally to adult C57BL/6J mice and significantly decreased the percentage of fertilized oocytes without any ovulation changes [25]. In an *in vitro* study, it was reported that BPA treatment decreased meiosis progression and increased spindle abnormalities, including abnormal spindle morphology and chromosome alignment at doses of 15 and 30 ng/ml [44]. Additionally, bovine oocytes exposed to BPA at a dose of 130 nM showed significant increases in DNA damage and apoptosis, while gene expression in the blastocysts

was not altered after oocyte fertilization [24]. Wang et al. reported that porcine oocytes exposed to BPA at a dose of 250 μM showed a decrease in maturation rate, increases in reactive oxygen species (ROS), abnormal cytoskeletons, increases in apoptosis/autophagy rates, and alteration of the epigenetic pattern [28]. Similarly, Nakano et al. reported that BPA (2 μg/ml) decreased the maturation rate and induced cell cycle delay and spindle abnormalities in ICR mouse oocytes [45]. The data from the most recent experimental studies further strengthen the evidence that BPA affects oocyte quality, number, maturation and induced meiotic arrest of oocytes.

### 3.2 Steroidogenesis

Prior to 2014, multiple epidemiological studies analyzed associations between BPA exposure and ovarian steroid hormone production in women. Three studies conducted examined women undergoing *in vitro* fertilization (IVF) and concluded that prior to oocyte retrieval, there was a decrease in peak serum estradiol levels [46-48]. However, in a study conducted by Galloway et al. on adults living in Chianti, Italy, BPA was not associated with changes in estradiol or testosterone levels in women [49]. Therefore, in 2014, the authors concluded that further studies are needed to examine the association between exposure to BPA and steroidogenesis in women [14]. Since 2014, several epidemiological studies have investigated the association between BPA exposure and hormone production in women (overview in Table 2). More recently, a study examined Korean girls with precocious puberty, and found urinary BPA levels were associated with higher levels of testosterone (T), estradiol (E2), progesterone (P4), and the alterations of steroid metabolism among individuals with high levels of BPA. However, the authors concluded that the BPA levels were not directly associated with the onset of precocious puberty [19]. However, Akin et al. reported that BPA levels were associated with a high level of serum T in polycystic ovary syndrome (PCOS) patients in Turkey [50]. Miao et al. found that urinary BPA concentrations were positively associated with higher prolactin, E2, and P4 levels in Chinese female workers with occupational BPA exposure [51]. Additionally, in the National Health and Nutrition Examination Survey (NHANES) conducted between 2011–2012, BPA was associated with higher total T levels in female adolescents [20]. However, a prospective cohort study conducted by Minguez-Alarcon et al. showed that BPA was not associated with peak E2 levels in women with at least one *in vitro* fertilization (IVF) cycle [52]. Zhou et al. also reported that no association between BPA levels and serum follicle-stimulating hormone (FSH) levels was observed in infertile women with PCOS [53]. While there are inconsistencies across studies, multiple epidemiological studies have indicated that urinary or serum BPA levels were associated with alterations of hormone levels in females. It must be noted that many of these studies examined women with impaired reproductive functions and used single-spot urine analysis. Therefore it is important for future studies to examine the associations between long-term BPA exposure and hormone levels of the general population.

Prior to 2014, experimental studies examined the effects of BPA exposure on female steroidogenesis in laboratory animals. In two studies utilizing Sprague-Dawley rats and ICR mice, low-dose exposure to BPA induced increased levels of testosterone and progesterone [54, 55]. While studies used a variety of strains of rats, mice, and lambs exposed

gestationally or gestationally and neonatally, no effect on steroidogenesis was observed [40, 56-58]. *In vitro* studies demonstrated that exposure to 44 and 440 μM BPA inhibited estradiol, testosterone, androstenedione, estrone, dehydroepiandrosterone, and progesterone production, and decreased *StAR* and *Cyp11a1* expression in cultured intact murine antral follicles [59, 60]. Another *in vitro* study examined the effects of BPA at doses 0.1, 1 and 10 μM on porcine granulosa cells; in this study, the lowest dose increased estradiol levels, whereas the higher doses decreased them [61]. At this point in time, the studies indicated BPA exhibited dose-dependent adverse effects on steroidogenesis. Since 2014, experimental studies have examined the effects of BPA exposure on female steroidogenesis using the rodent model (overview in Table 3). In one study of Wistar rats, low-dose neonatal BPA exposure via intraperitoneal injection decreased serum P4 levels without any changes in E2 levels [62]. On the other hand, BPA increased serum P4 levels coupled with high mRNA expression of 3β-hydroxysteroid dehydrogenase (3β-HSD) in Wistar rats with prenatal and neonatal exposure via drinking water [63]. Furthermore, low-dose BPA exposure via drinking water increased serum luteinizing hormone (LH), E2 levels, and follicle numbers, while there were no changes in serum FSH levels observed in Wistar rats [64]. In other strains of rats, Delclos et al. reported that SD rats with prenatal and neonatal oral exposure to BPA showed increased E2 and prolactin levels while decreased P4 levels were observed only at the highest dose group (300000 μg/kg) [23]. Sadowski et al. reported that Long-Evans rats exposed to low-dose BPA during the prenatal and neonatal period showed a decrease in FSH levels but no changes in other hormone levels or maze behavior [65]. Low-dose BPA (50 μg/kg) given orally to adult C57BL/6J mice during 3 estrous cycles did not affect serum E2, FSH, and LH levels [25]. Only one *in vitro* study reported that BPA exposure (2 or 20 mg/ml) decreased P4 synthesis and the protein expression levels of steroidogenesis enzymes (3β-HSD, CYP11A1, and CYP19A1) in human granulosa cells [66]. Collectively, the current data indicate that BPA adversely affects female steroidogenesis, but its effects vary by animal species, strain, exposure route, and exposure window *in vivo*, while *in vitro* studies have indicated that BPA has adverse effects on steroidogenesis depending on the concentration tested.

### 3.3 Ovary and Uterine

In 2014, there was a shortage of epidemiological studies examining the associations between PCOS and BPA exposure. In a case-control study of 71 women with PCOS and 100 without, an association was observed between serum BPA levels and increased testosterone and androstenedione levels in PCOS patients [67]. Prenatal and neonatal low-dose exposure to BPA in rodents led to the disruption of estrous cyclicity, increased testosterone production and ovarian cysts [54, 68, 69]. High-dose exposure in rodents, on the other hand, led to increased ovarian cysts and accumulation of large antral follicles [54, 68]. In the BPA-treated rodents, cystic appearing follicles differ from the ovarian phenotype in women with PCOS, while the ovarian phenotype of BPA-treated rodents differed from the ovarian phenotype in women with PCOS[54, 68]. Due to the differences in ovarian phenotypes between women with PCOS and the rodent models with PCOS, the report concluded that additional studies were needed to determine why the outcomes differ in animal models and women when exposed to BPA. There have been a limited number of studies conducted investigating the effects of BPA on the ovaries in women (overview in Table 2). Since 2014,

one case-control study of 112 women between the ages of 13 and 19 suggested that urinary BPA levels were associated with a higher risk of PCOS [50]. Additionally, in 268 infertile women diagnosed with PCOS, urinary BPA levels were associated with a significant decrease in antral follicle count (AFC) [53]. In a study conducted on 62 market cashiers diagnosed with PCOS, the serum levels of BPA and the LH/FSH ratio were significantly increased, whereas TSH levels were decreased compared to healthy women with similar jobs [70]. On the other hand, a case-control study of 52 women found no association between urinary BPA concentrations and risk of PCOS [71]. Given the limited number of studies and participants in each study, it appears there is an association between BPA exposure and PCOS symptoms; however, further studies are required to validate these current findings.

Since then, experimental studies in rodents (summarized in Table 4.1) have indicated that prenatal and postnatal exposure to low-dose BPA resulted in decreased ovarian weights, follicle numbers, and primordial follicle recruitment in Wistar rats, as well as increasing the number of corpora lutea and causing a delay in vaginal opening [62, 63, 72]. Additionally, very high-dose BPA exposure (300 mg/kg) in SD rats led to an increase in cystic follicles and decreases in corpora lutea and antral follicles [23]. Zhou et al. reported that BPA exposure decreased germ cell nest breakdown and altered the expression of key genes involved in apoptosis and anti-oxidation in CD-1 mice ovaries *in vitro*, though the effects varied by ovary collection times and exposure doses [73]. Furthermore, BPA has been reported to reduce small and large primary and secondary follicle numbers, and to increase DNA damage markers (γ-H2AX, ATM,) and DNA repair genes in the F344 rat ovary *in vitro* [74]. These data suggested that DNA damage may be one of the potential mechanisms of ovarian toxicity induced by BPA [74]. A study regarding BPA exposure on the ovaries of F1 generation mice resulted in a non-monotonic dose-relationship with several transgenerational effects found in the F3 generation [22]. These data indicated the possibility that BPA is capable of causing epigenetic alterations, which are passed transgenerationally, and can impact fertility, spermatogenesis and social and behavioral activity [75].

Prior to 2014, there were limited data regarding BPA exposure and uterine endometrium in women. In a case-control study on a population of 69 women, it was suggested that BPA concentration may have an association with the occurrence of endometriosis [76]. Buck Louis et al., in their study of 495 individuals as an operative cohort and 131 women in a population cohort, reported no association between exposure and endometriosis; however, the authors point out that the study was not designed to investigate BPA exposure nor powered to assess endometriosis [77]. Therefore, the panel in 2014 saw fit to declare more epidemiological studies were required before concluding whether BPA had adverse impacts on the uterine endometrium. Since 2014, more epidemiological data has been released. Three studies have reported the impact of BPA exposure on uterine morphology in women (overview in Table 2). In a case-control study of women with endometriosis, Upson et al. found that urinary BPA levels were associated with non-ovarian pelvic endometriosis, but had no relation to ovarian endometriosis [78]. Conversely, Minguez-Alarcon et al. reported that there was no association between urinary BPA levels and endometrial wall thickness in 256 women undergoing IVF. Younger women (<37 years old) were found to have a thicker endometrial wall as urinary BPA concentrations increased, while older women (≥37 years old) had a thinner endometrial wall [52]. Additionally, urinary BPA levels were significantly

higher in 68 patients with endometriosis compared to the BPA levels in the control group [79]. Given the limited number of studies and lack of BPA exposure data during endometriosis development, future studies are needed to elucidate the association between chronic BPA exposure and uterine morphology alterations in the general population.

Prior to 2014, experimental animal studies supported the premise that BPA exposure had adverse effects on the uterus. Adult female Balb-c mice prenatally and neonatally exposed to low-dose BPA developed endometrial-like structures which expressed *Hoxa10*, a transcription factor responsible for the mediation of the proliferation of stromal tissue [80]. Increased expression of *Hox10* was further supported by studies that examined low- and high-dose prenatal exposure in adult CD-1 and ICR mice [81, 82]. This finding was further supported by studies utilizing low- and high-dose exposure on prenatally exposed CD-1 and ICR mice, wherein prenatal low-dose BPA exposure to adult mice had been reported to induce benign and malignant lesions and endometrial polyps in the uterus, as well as perturb the Wölffian duct [69, 80]. Since 2014, multiple experimental studies have added to our understanding of the effects of BPA exposure on the uterus in rodent models (overview in Table 4.2). In two studies conducted on CD-1 mice, low-dose BPA exposure increased gland nest density, periglandular collagen accumulation, and abnormal endometrial epithelial and stromal functions [83, 84]. Additionally, Calhoun et al. reported that postnatal exposure to BPA via food consumption (400 μg/kg) altered three genes (HOXA13, WNT4, and WNT5A) involved in reproductive organ development in rhesus macaque uterus, while fetal uteri did not show any notable changes in uterus histology, proliferation, or expression of hormone receptors [85]. In one study on Wistar rats, prenatal and postnatal exposure to low-dose BPA resulted in decreased glandular proliferation rates and α-actin expression at PND90, along with increased abnormal luminal and glandular epithelium at PND360 [27]. In addition, low-dose uterine BPA exposure in SD rats *ex vivo* decreased the force of uterine contractions [86]. Kim et al. reported that short-time exposure to high-dose BPA led to a rapid and transient increase in Egr1 via the ER-ERK1/2 pathway in ICR mice [87]. Prior *in vitro* studies supported the hypothesis that BPA exposure had adverse effects on the uterus. Exposure to 50 μM BPA was found to decrease the proliferation of cultured human endometrial endothelial cells after 48 hours [88]. In another study examining culture primary heterogeneous populations of uterine cells, a dose of 10 μM BPA inhibited uterine cell contractions, increased oxytocin-related pathways and decreased prostaglandin-related signaling after 48 hours [89]. Since 2014, more *in vitro* studies have been conducted. One study found that BPA (2.28 ng/mL) upregulated genes involved in cell differentiation and proliferation and downregulated genes involved in mitosis and adhesion in uterine smooth muscle cells [90]. It is important to note that in human endometrial endothelial cells and uterine leiomyoma, BPA exposure increased expression of vascular endothelial growth factor (IVGF) at the micromolar level [91, 92]. Wang et al. reported BPA exposure increased growth rate and colony-forming efficiency via CoX-2 in an endometrial carcinoma cell line [93]. Collectively, these studies have provided compelling evidence suggesting that BPA adversely affected the uterine both *in vivo* and *in vitro*, though the assessment endpoints varied across all studies.

## 4. BPA male reproductive toxicities

### 4.1 Sperm production and quality

Epidemiological data conducted prior to 2014 examined the associations between BPA exposure and sperm quality and production. While these studies provided consistency among results, the studies were limited by lack of evidence associating exposure and quality of semen. Occupationally exposed men [94] and patients recruited from infertility clinics [95] had higher urinary BPA levels, which were associated with decreased sperm count and motility. Another study examined fertile men and found no association between urinary BPA concentrations and changes in semen parameters [96]. Since 2014, many epidemiological studies have built on our understanding of how BPA affects sperm production and quality, but many limitations are still prevalent (overview in Table 2). In a prospective cohort study of male partners undergoing IVF treatments, the natural log-transformed urinary BPA concentrations were associated with a lower natural log-transformed sperm count, concentration, and motility [97]. Additionally, a study of young men from Denmark reported that men in the highest quartile of urinary BPA levels also had significantly lower sperm progressive motility when compared to the men in the lowest quartile [18]. On the other hand, in a study of male partners trying to conceive without any intervention methods, urinary BPA levels were associated with lower sperm DNA fragmentation [17]. This lower fragmentation rate may be explained by the low BPA levels detected in the study population when compared to NHANES data or the data obtained from sperm analysis conducted the day after sample collection [17]. Given the limited information and discrepancies among results, additional studies using more sensitive and reliable measurements to capture continuous BPA exposure and conduct semen analysis are required to determine if there is any association between BPA exposure and sperm quality in the general population. One potential reason why this data may not be currently available is that the cost per sample can be quite expensive. While this may work for small sample size, the data may not be indicative of the general population.

The earliest animal experimental studies on the effects of BPA on sperm suggested adverse consequences on spermatogenesis in adulthood following either prenatal or early postnatal exposure. Multiple studies analyzed the effects of gestational exposure to low-dose BPA and found decreased numbers of elongated spermatids in the seminiferous tubules of pubertal ICR mice and reduced sperm counts in Holtzman rats [98, 99]. In 2010, Minamiyama reported that BPA-induced decreases in rat sperm motility had been prevented by co-administering antioxidant *n*-acetylcysteine [100]. The lab suggested that the impaired sperm motility may be related to the increased levels of reactive oxygen species. In more recent animal studies examining BPA exposure and male reproduction (overview in Table 5), prenatal and postnatal exposure to low-dose BPA adversely affected sperm production and quality. Despite the variations in exposure windows, duration, species or strains, and endpoints examined, several findings in the previous literature were commonly observed: decreased sperm number, induction of sperm apoptosis and oxidative stress, and the alteration of seminiferous tubule morphology. Many studies reported that both prenatal and postnatal exposure to low-dose BPA decreased sperm numbers in mice and rats [101-108]. Additionally, induction of testicular oxidative stress or apoptosis was observed in mice and

rats exposed to low-dose BPA during the prenatal or postnatal periods [106, 108-112]. Low-dose BPA exposure was reported to delay meiosis, as well as inducing the accumulation of chromosomal abnormalities and meiotic DNA double-strand breaks (DSBs) in the late meiotic stage [113]. Few studies have indicated that low-dose BPA exposure potentially altered the epigenetic pattern in testes, including increased rates of methylation of Igf2 and decreased protein lysine acetylation levels in rats [114, 115]. In multiple strains of mice, however, exposure to BPA did not affect chromosome pairing and synapsis [115, 116]. Overall, the strength regarding current evidence for risk assessment regarding low-dose BPA exposure is still limited. The relevance of the doses in the experimental animal studies to human exposure is still unclear since the internal (urinary or serum) BPA levels in tested animals were not examined, therefore making extrapolation of these findings to humans difficult.

Several *in vitro* studies have further investigated the modes of action that BPA utilizes for testicular toxicity (overview in Table 5). In two studies using the mouse spermatocyte GC-2 cell line, BPA exposure (20 μM) induced germ cell apoptosis via the $Ca^{2+}$/CaM/CaMKII signaling pathway and the PERK/EIF2α/chop pathway [111, 117]. Increases in tyrosine phosphorylation via PKA were observed in the primary spermatozoa isolated from mice and rats [118, 119]. Additionally, BPA exposure (50 μM) induced early DNA damage responses and perturbed cytoskeleton in the C18–4 spermatogonial cell line [120]. BPA exposure at a very high concentration (300 μM) to human spermatozoa decreased the mitochondrial membrane potential and increased both apoptosis and DNA oxidative damage marker (8-hydroxy-2'-deoxyguanosine) [121]. Another study found that short-time BPA exposure at an extremely high-dose (1 mM) increased velocity straight linear, homogeneity of progressive movement velocity and intracellular free $Ca^{2+}$ concentration in human spermatozoa [122]. Collectively, this *in vitro* data suggests that BPA exposure may impact male germ cells through perturbation of $Ca^{2+}$ homeostasis and cytoskeleton structure, induction of apoptosis, and DNA damage.

### 4.2 Sertoli and Leydig Cells

Sertoli and Leydig cells play crucial roles in maintaining the normal functions of spermatogenesis. The functions of the Sertoli cells include the formation of the blood-testis barrier, secretion proteins, and growth factors that nurture and regulate apoptosis and mitosis of germ cells [123, 124]. Leydig cells are responsible for synthesizing and secreting T to support spermiogenesis [125]. Prior to 2014, few studies had analyzed the effects of BPA exposure on Leydig and Sertoli cells to determine whether BPA had a direct effect on these cells and to see if there was an effect on steroid hormone production. Continuous high-dose pubertal exposure to male Wistar/ST rats was reported to decrease the cell number and steroidogenic enzyme expression in Leydig cells [126]. However, gestational plus neonatal exposure to low dose BPA increased Leydig cell numbers in Long-Evans rats in adulthood via the up-regulation of mitogenic factors [127]. Nanjappa et al. also reported that adult-exposed Leydig isolates to low-dose BPA decreased testosterone production and the expression of steroidogenic enzymes [127]. Since 2014, multiple *in vitro* studies have examined the effects of BPA on Sertoli and Leydig cells (overview in Table 6). In three studies using the Sertoli cell line TM4, nanomolar BPA increased proliferation via

promoting energy metabolism, GPR 30, and ER α/β, while micromolar BPA decreased cellular proliferation via inducing oxidative stress and activating CaM-CaMKII-ERK and mitochondrial apoptotic pathways [128-130]. In studies conducted on primary rat Sertoli cells, BPA (~50 μM) induced cellular apoptosis via ROS, mitochondrial dysfunction, and activated HNKs/p38 MAPK, NF-kB, and Pten/Akt pathways [26, 93, 131]. An important finding was that in human primary Sertoli cells, BPA exposure significantly decreased cell viability, expression levels of occludin, ZO-1, β-catenin, and AR at a dose of 20 μM without changes in F-actin expression or localization [132]. Another study concluded that BPA treatment perturbed actin filaments starting at 0.4 μM and induced improper localization of actin regulatory proteins Arp3 and Eps8 at a dose of 200 μM [133]. An *in vivo* study demonstrated that high-dose BPA exposure decreased Leydig cell numbers and StAR protein levels in the adult rat testis [127, 134]. On the other hand, low-dose BPA exposure induced Leydig cell proliferation with increased protein expression of proliferating cell nuclear antigen, MAPK, AR, and ER α/β. Low-dose BPA was found to increase secretion of the anti-Mullerian hormone in the adult rat testis [127, 134]. In another *in vitro* study, BPA exposure decreased T biosynthesis and E2 levels, mRNA expression of aromatase, and the steroidogenic enzyme 17α-hydroxylase/17–20 lyases in rat primary Leydig cells [135]. In Leydig cell line TM3, micromolar doses of BPA decreased cellular proliferation rates and increased cell migration and invasion [136]. Given the current *in vitro* and *in vivo* studies, BPA exposure affected the proliferation and steroidogenesis of rodent Sertoli and Leydig cells. Furthermore, the results of the experimental studies indicated that BPA exposure may be associated with decreased hormone levels in male animals and suggested direct effects of BPA on Sertoli and Leydig cells [14].

### 4.3 Steroidogenesis

Before 2014, the epidemiological studies conducted regarding BPA exposure and male steroidogenesis had conflicting reports. The INChianti study noticed an association between increased urinary concentrations of BPA and increased serum testosterone levels but noticed no association with estradiol levels in males [49]. However, cross-sectional studies of 167 and 302 fertile men reported no associations between BPA exposure and testosterone levels [96, 137]. One of these studies conducted by Mediola et al. found that urinary BPA concentration was associated with decreased free androgen index (the ratio of free androgen index to luteinizing hormone) and a decrease in the ratio of free testosterone to luteinizing hormones in the male partners of pregnant women [96]. In contrast, Meeker et al. found associations between high concentrations of BPA and increased serum levels of follicle-stimulating hormone, and decreased levels of inhibin B and the ratio of estradiol to testosterone [137]. Since 2014, five more epidemiological studies have examined the association between urinary BPA levels and hormone levels in men (overview in Table 2). A study conducted on young men from Denmark reported that those with BPA levels above the lowest quartile had higher levels of T, LH, and E2 as compared to the men in the lowest quartile [18]. In two cross-sectional studies of male workers occupationally exposed to BPA, urinary BPA concentrations were associated with higher sex hormone-binding globulin (SHBG) and lower androstenedione (AD) [138, 139]. In male children and adolescents in the NHANES 2011–2012 study, BPA was associated with lower total T levels [20]. However, a retrospective cohort study determined that there was no association between

maternal (3rd trimester) or childhood BPA exposure on hormone levels in boys ages 8–14 [140]. These data indicated that BPA exposure have the capability of perturbing the hormone levels in men. However, the strength of the study was limited by the study population with occupational exposure, the use of single spot urine samples, and the lack of a co-exposure assessment. Many occupational exposure studies on BPA have already been conducted. For instance, Hines et al. found that 1.4% of workers involved with industries that manufacture and use BPA in the United States exceeded the US EPA oral reference dose for BPA (50 μg/kg-day) [141]. Another study conducted in Finland showed that the highest occupational exposure levels were found in the manufacturing of thermal paper, and that increased urinary levels were noticed in liquid paint factories [142]. These studies provide insight into occupational exposure to BPA. However, these studies do not provide any health analysis of the participants, which weakens their strength. For future studies, it is imperative to analyze both occupational exposure and subsequent health of the participants to determine whether BPA exposure has any effects on male steroidogenesis.

Data prior to 2014 regarding experimental studies suggested that BPA exposure decreased hormone levels in male animals. However, this conclusion was considered contradictory. One study examined gestational through neo-natal exposure to low-dose BPA in CD-1 mice, and reported that there was a decrease in testosterone levels [143]; but this was not reported in a study examining the effects of *in utero* exposure on adult C57BL/6 mice [144]. Studies examined low-dose exposure to gestationally or neonatally exposed Holtzman rats [99, 145], adult-exposed albino rats[146], and adult-exposed Wistar rats [147] and concluded that these species experienced decreased testosterone levels. However, when examining gestational and neonatal exposure of low-dose BPA in Long Evans rats [148] or SD rats [56, 149], testosterone levels were not affected. Therefore, there was conflicting evidence in 2014 that associated BPA with decreased expression of steroidogenic enzymes and even affected the levels of follicle-stimulating hormone, which are required to start steroidogenesis. Recent experimental studies have assessed prenatal exposure to low-dose BPA, and it has been reported to alter the hormone levels in mice and rats, but the data are not consistent (overview in Table 7). Gamez et al. reported that low-dose BPA exposure led to increased serum LH and FSH levels in young Wistar rats [150]. On the contrary, a study conducted on adult Wistar rats found that BPA exposure decreased serum T, LH, and FSH levels and increased the E2 level [104]. In two studies using SD rats, findings reported decreased serum T and E2 levels with postnatal low-dose BPA exposure [101]. BPA at an extremely high dose (300 mg/kg) significantly increased serum thyroxine (T4) levels without changes in serum triiodothyronine (T3) and FSH levels [23]. BPA exposure was reported to decrease serum T levels in Swiss albino and C57BL/6 mice, but these doses varied between 0.5 μg/kg to 100 mg/kg [151, 152]. Additionally, Sadowski et al. reported that Long-Evans rats exposed to low-dose BPA showed a decrease in FSH levels at weaning [65]. An *in vitro* study examined fetal testis explants from rats, mice, and humans, and concluded that BPA exposure reduced basal T secretion at a concentration of 10 μM in rats, 1 μM in mice, and 10 nM in human explants, respectively [153]. These data suggested that BPA exposure could impair male steroidogenesis in rodents, but the effects vary by species, strain, exposure window, and duration.

## 5. BPA analogs and reproductive health

### 5.1 BPS and reproductive health

BPS is structurally similar to BPA and is now used in a variety of common consumer products as a BPA alternative. BPS has been detected in food, indoor dust, personal care products, sediment, and paper products such as currency and cashier's receipt [32, 154-156]. BPS exposure frequently occurs through ingestion, inhalation, and dermal contact. BPS was detected in 81% of the human urine samples in the United States and in seven Asian countries with a mean concentration of 0.654 ng/mL, which was comparable to BPA [33]. Neither the metabolic nor biological fate of BPS has been fully examined. An *in vitro* study indicated that glucuronidation was the major metabolic pathway for BPS [157]. As a potential EDC, BPS has been examined in the National Toxicology Program (NTP) Tox21 High Throughput Screening (HTS) Program and was classified as an estrogen agonist with a weak affinity for the ER [158, 159]. In addition, Rochester and Bolden reviewed the endocrine activity of BPS by comparing BPS's estrogenic binding potency against estradiol ($EE_2$), a positive control, on a plethora of estrogenic receptors. They then ran an experiment to examine BPA's estrogenic potency and compared this value to $EE_2$'s potency. The average estrogenic potency for BPS was calculated to be $0.32 \pm 0.28$ by dividing the estrogenic potency of BPA from the estrogenic binding potency of BPS, indicating BPS had a similar affinity to ER receptors as BPA [160]. This study also indicated that BPS was in the same order of magnitude as BPA regarding its androgenic, antiandrogenic, antiestrogenic and aryl hydrocarbon binding affinity, and in inhibitory hormone signaling of adipocytes[160]. A study conducted by Rosenmai et al. found that BPS bound to estrogen receptors and affected estrogenic and antiandrogenic activity in a similar manner to BPA [161].

However, there have only been a few *in vivo* studies that have examined the effects of BPS exposure on female and male reproductive systems (overview in Table 1). Yamasaki et al. reported that in the immature rat utero-trophic assay, BPS exposure significantly increased absolute and relative uterine wet weights and blotted weights at doses of 20 and 500 mg/kg, but not at a dose of 200 mg/kg [162]. In SD adult rats, BPS exposure induced testicular reactive oxygen species (ROS) and lipid peroxidation, altered seminiferous epithelium morphology, and decreased antioxidant enzyme activity and plasma T levels in the highest dose group (50 μg/kg) in spermatogonia, spermatocytes, and spermatids [163]. However, there were no significant changes in the populations of these testicular cells [163]. As vertebrates, zebrafish have conserved pharmacological targets and nervous system structures, which is comparable with mammals. This therefore makes zebrafish an ideal specimen to study, as they have a large genetic database, short lifespan, and high fecundity. Zebrafish have been widely used as a model to identify targets as well as modes of the action of EDCs [12]. In two studies that examined zebrafish, both adult and developmental exposure to BPS resulted in increased plasma estradiol (E2) levels in both sexes, while adult exposure altered the E2 levels at lower doses when compared to developmental exposure. Additionally, male fish exhibited more sensitive responses when compared to the female fish [164, 165]. BPS exposure in male zebrafish at different points in their lifespan had decreased T levels [164, 165]. Chen et al. reported that *Caenorhabditis elegans* exposed to BPS showed

increased germline apoptosis and activation of DNA damage checkpoint kinase CHK-1. BPS is also known to cause distinct alterations of gene expression at the whole transcriptome level compared to BPA [166]. Consequentially, these current studies have provided compelling evidence that BPS exposure altered hormone homeostasis and impaired reproductive organs in different sexes, exposure windows, and species. More *in vivo* studies are needed to validate these current findings and examine the effects of BPS exposure on multiple rodent strains.

In an *in vitro* study, Eladak et al. reported that BPS exposure decreased basal testosterone (T) secretion in mouse or human fetal testis explants, starting at doses of 100 nM and 1000 nM, respectively [153]. When compared to BPA, BPS treatment induced more significant changes in T secretion in the mouse explants, but fewer changes in human explants [153]. In an *in vitro* test on the Leydig cell line, MA-10, a dose of 10 μM BPS significantly increased P4 and P5 levels and increased gene expression levels of CYP51 and 5α-Red1 [167]. In addition, BPS exposure also decreased cell viability and increased early DNA damage responses and abnormal cytoskeleton structure at a dose of 50 μM in a mouse spermatogonial cell line C18–4 [120]. The dose responses obtained of cell viability, cell cycle alteration, DNA damage, and cytoskeleton were comparable to BPA, but less drastic when compared to BPAF or TBBPA [120].

### 5.2 BPF and reproductive health

BPF is a component of epoxy resins widely used in tank and pipe linings, industrial floors, coatings, dental sealants, and food packaging materials [160]. BPF has been found in indoor dust and various food items such as beverages, dairy products, meats, seafood, cereals, fruits, and vegetables [32, 155]. It has had been reported that BPF was metabolized and transformed to nonactive sulfates, rather than glucuronides, and excreted through urine in pregnant rats. A study found that active BPF was distributed to multiple tissues, including the liver, uterus, placenta and fetus [168]. In the United States population, BPF was found in approximately 60% of urine samples, and the concentrations ranged from 0.15 to 0.54 μg/L [169]. The average estrogenic hormonal potency for BPF, as compared to BPA, was reported to be 1.07 ± 1.20, calculated in the same manner as BPS [160]. Therefore, BPF may have an effect on the endocrine system equal to or possibly more potent than that of BPA.

Limited data are available for BPF exposure and reproductive outcomes in experimental animals (overview in Table 2). Two studies conducted on female Wistar rats suggested that short-time postnatal exposure to BPF at doses over 100 mg/kg increased uterine relative weight [162, 170]. However, another study did not find any changes in reproductive organ weights in young adult female SD rats exposed to BPF at concentrations reaching 500 mg/kg [171]. Meanwhile, in male SD rats, BPF exposure increased testis weight without significant spermatological changes at a dose of 500 mg/kg. In the same study, rats in both sexes showed decreased serum triiodothyronine (T3) levels and increased thyroxine (T4) levels. The opposite trends in T3 and T4 levels and no changes to serum thyroid-stimulating hormone (TSH) levels suggested that these observed effects were not related to the endocrine-mediated effects of BPF [171].

According to the results of recent *in vitro* studies, BPF's effects on steroidogenesis are equivocal to BPA. BPF has been reported to increase T secretion and expression of steroidogenic genes (Cyp51 and 5αRed1) at a dose of 100 μM in MA-10 Leydig cells [167]. Eladak et al. reported that BPF exposure decreased basal T secretion in mouse fetal testis explants starting at a dose of 1000 nM, which followed a similar dose-response curve as BPA. In human fetal testis explants, BPF treatment reduced T levels at a dose of 10 nM with a non-monotonic dose-response curve (10 nM) [153]. The discrepancy in the current data could be the result of different biotransformations of BPF into its metabolites the *in vitro* models and the different species and strains tested. Collectively, the data suggest that BPF exposure may alter steroidogenesis both *in vitro* and *in vivo*, but its effects on the reproductive organs, oogenesis, spermatogenesis, and embryonic development remain inconclusive. Future studies are necessary to fully validate the current findings in multiple rodent models and determine the consequences of BPF-induced hormone alterations on reproductive functions.

### 5.3 BPAF and reproductive health

BPAF is used widely as a crosslinking agent and a monomer in the plastics industry. There is limited information available on the occurrence of BPAF in consumer products and human urine or blood samples. In the United States, BPAF has been found in various food items with lower detection rates (6% - 30%) compared to BPA [155]. BPAF was found to be metabolized primarily through glucuronidation and excreted through feces and urine in SD rats [172, 173]. In humans, BPAF was detected in urine samples at concentrations ranging from below the detection level to 3.93 μg/L in China and Saudi Arabia [174, 175]. It is important to note that BPAF exhibited estrogenic binding potencies greater than those of BPA [36, 37]. Additionally, BPAF exhibited a preferential affinity (three times stronger) for ER β compared to ER α [176].

Relatively few studies have examined the effects of BPAF exposure on steroidogenesis *in vivo* (overview in Table 3). Two studies performed on zebrafish demonstrated that exposure to BPAF during development led to increases in E2 levels in the female fish [177, 178]. The gonadal examination carried out on the zebrafish indicated that exposure to 1 mg/L BPAF induced acellular areas in the testis and retarded oocyte development [178]. In those same studies, BPAF exposure decreased T levels in male fish and also altered testicular morphology [177, 178]. In contrast, no decreases in T production were observed in SD rat dams prenatally exposed to BPAF at a dose of 750 mg/kg [179]. Furthermore, Li et al. reported that BPAF could be transferred via cord blood and lactation, finally accumulating in the offspring's testes [137]. Offspring exposed to BPAF prenatally and postnatally showed a significant increase in testicular T levels and alterations of genes involved in cell differentiation and meiosis [180]. Feng et al. reported that BPAF exposure decreased serum T level and T biosynthesis (200 mg/kg), and increased serum luteinizing hormone (LH) (50 mg/kg) and follicle-stimulating hormone (FSH) (10 mg/kg) levels in adult male SD rats [181]. Recently, a study revealed that BPAF exposure uniquely impaired pregnancies and sexual development in rats at doses of ~80 and ~280 mg/kg, whereas BPA exposure did not alter these reproductive endpoints at similar concentrations [182]. These data suggest that BPAF might be a more potent endocrine disruptor than BPA.

In *in vitro* studies, exposure to BPAF inhibited mouse oocyte maturation at concentrations of 50 and 100 μg/mL and induced cell cycle arrest by the activation of spindle assembly checkpoints [45]. In a recent multi-parametric high-content analysis (HCA) of mouse spermatogonial cells, BPAF exhibited the highest spermatogonial toxicity when compared to TBBPA, BPA, and BPF [86]. Exposure to 1 μM BPAF altered the nuclear morphology and induced cell cycle arrest, while a concentration of 10 μM caused cytoskeleton perturbation and multinucleation of cells, with DNA damage recognized at a concentration of 25 μM [120]. This *in vitro* study indicated that BPAF exposure may target the spermatogonia cells as observed *in vivo* in a fertility study [182]. The effects of BPAF on steroidogenesis are still unclear and likely differ depending on different exposure windows. Additionally, further studies should be conducted to examine the effects of BPAF exposure on hormone levels and multiple reproductive endpoints in various experimental strains, species, and exposure windows.

### 5.4 TBBPA and reproductive health

TBBPA's primary use is as a reactive flame retardant in plastics, paper, textiles, and circuit boards. The general population can be exposed to TBBPA through inhalation, dermal contact, and ingestion of fish and shellfish [183]. TBBPA is absorbed by the gastrointestinal tract, then metabolized to glucuronides and sulfates, which in turn are excreted through feces in animal models [184]. Several studies have examined TBBPA exposure levels on the general population. Serum TBBPA levels were below the level of detection (0.03 ng/L) in pregnant Canadian women, but detectable in 5% of Inuit adults with concentrations up to 480 ng/L [185]. In the United States, TBBPA was found in approximately 35% of human breast milk samples at levels between 50–350 pg/kg/day [186]. However, the current data demonstrated that TBBPA did not interact with ER α/β or AR in a panel of *in vitro* bioassays [187].

Van der Ven et al. established a one-generation reproduction study and a subacute toxicity study to examine dose-response relationship of TBBPA and its effects on the endocrine system [188]. The subacute toxicity test was conducted as a 28-day repeat dose study according to OECD407 guidelines, including doses of 0, 30, 100, 300 mg TBBPA/kg body weight. In the two-generation study, exposure started 10 weeks or 2 weeks before mating and was continued during mating, pregnancy and lactation. No exposure-related histopathological changes were observed in any of the assessed organs in either experiment. There were also no effects on endpoints of reproduction -- i.e., mating success, number of implantation sites, and litter size. The cauda epididymis sperm count and morphology were not affected in either experiment. However, a significant dose-dependent increase of the weight of the testis and pituitary weight were observed in F1 male animals. Decreased circulating thyroxine (T4) levels were observed in both the subacute and one-generational study [188].

Similarly, another two-generation reproductive study was performed on SD rats exposed to TBBPA at doses of 0, 10, 100 or 1,000 mg/kg/day in corn oil by oral gavage [189]. The F0 generation was treated during a premating period of 10 weeks and the 2-week mating period. The only significant decrease occurred in serum T4 levels in both the F0 and F1 generations

at a dose of 1000 mg/kg [189]. Cope et al. reported a two-generation reproduction study on reproductive, developmental and neurobehavioral effects of TBBPA at oral doses of 10, 100, and 1000 mg/kg BW/day in SD rats [190]. These findings are consistent with other multi-generational studies, as there were no marked effects on various reproductive parameters including time to the vaginal opening and anogenital distance, sperm motility, concentration, and morphology in F1 or F2 generations. The decrease in T4 levels in SD rats exposed to a dose of 1000 mg/kg of TBBA was the only change observed [190].

Zatecka et al. conducted a two-generational study focused on the trans-generational effects of TBBPA in CD1 outbred mice [191]. Gestational exposure to TBBPA was through drinking water (35 μg/kg) to generate the F1 offspring. Experimental and control animals of the F1 generation were bred in various conditions to evaluate the trans-generational effects on the reproductive system. Significantly reduced testicular weight, increased prostate weight, and increased seminal vesical weights were observed in the F2 generation when both parents (F1) were treated with TBBPA. However, no changes in sperm parameters were observed, and decreased the thickness of the seminiferous epithelium and increased apoptotic cells in the testes by TUNEL staining were observed in both F1 and F2 males [191]. Utilizing C57BL/6J mice exposed to the same level of TBBPA during the gestation, lactation, pre-pubertal, and pubertal periods up to the age of 70 days, Zatecka, et al. found TBBPA treatment did not induce significant changes in any of the general reproductive system parameters such as the anogenital distance, reproductive organ weight, and sperm count and morphology. However, significant reductions in T and T3 levels, and ratios of protamine 1/protamine 2, and increased total protamine/DNA ratio in sperm and apoptotic spermatozoa were observed [192].

A study of B6C3F1/N mice exposed to TBBPA for two years (500 mg/kg) showed an increased incidence of uterine epithelial tumors including adenomas, adenocarcinomas, and malignant mixed Mullerian tumors [193]. In an experiment utilizing zebrafish, TBBPA exposure decreased egg production (0.047 μM) and increased premature egg production (1.5 μM) [194]. In contrast, there were no changes in the ovary or uterine weight observed in ICR mice exposed to 1.0% TBBPA in their diet [195].

In two *in vitro* studies, TBBPA exposure was reported to increase T secretion in Leydig cell line MA-10 at micromolar levels [167, 196]. Ogunbayo et al. reported that TBBPA induced Sertoli cell death via disruption of $Ca^{2+}$ signaling and through affecting $Ca^{2+}$ transport proteins [197]. In a recent study with the mouse spermatogonia cell line C18–4, TBBPA exposure exhibited a dose-dependent induction of nuclear morphological changes from the high content analysis (HCA), including nuclear area and nuclear shape (LWR and P2A). TBBPA also induced significant increases of LWR at concentrations of 5, 10 and 25 μM and a significant increase of P2A at a concentration of 25 μM for 72 h. TBBPA treatments of 25 μM for 48 h, and of 10, 25 μM for 72 h led to an increase of cells in the G2/M phase accompanied by an increase of apoptotic cells. Additionally, TBBPA exposure (25 μM) induced DNA damage responses and perturbed cytoskeleton structure [120]. Compared to BPA and BPS, TBBPA exhibited higher spermatogonial toxicity, including dose- and time-dependent alterations impacting nuclear morphology, cell cycle progression, DNA damage responses, and perturbation of the cytoskeleton [120]. Taken collectively, current studies

indicated that the effects of TBBPA on reproduction varied in a limited number of studies. No severe reproductive dysfunctions were consistently observed, even at the higher doses. Some studies of TBBPA revealed alterations in T3 or T4 levels, though those changes did not accompany any histological changes in the thyroid gland or other reproductive organs. In *in vitro* studies, TBBPA exposure impacted testicular cells at relatively low doses compared to BPA. Future *in vivo* animal studies are needed to determine TBBPA's reproductive toxicity and molecular mechanism.

## 6. Discussion and Conclusion

This review performed a literature search of epidemiological and experimental animal studies, which examined the reproductive toxicities of BPA analogs. While there were several studies that monitored urinary or serum levels of BPA analogs, the association between BPA analog exposure and reproductive dysfunction have not been explored. Emerging evidence from animal models suggests that exposure to these chemicals could adversely affect reproductive functions, including oocyte and sperm quality, steroidogenesis, and ovary and testis functions. These adverse effects might vary based on different testing species, exposure periods, and duration.

It is also worth noting that our lab's previous study using mouse spermatogonial cells combined with high-content analysis (HCA) revealed BPAF exhibited the highest testicular toxicity (20% maximal effect concentration EC20≈ 10 μM), followed by TBBPA, BPA, and BPS [120]. BPAF induced a dose-dependent increase of multinucleated germ cells (MNGs). Induction of MNGs has been reported following gestational exposure to di-(n-butyl) phthalate (DBP) [198-201]. The accumulation of MNGs in the testis has been associated with the formation of carcinoma *in situ* (CIS) cells, the known precursor to testicular germ cell cancer (TGCC) in humans [202]. Additionally, a recently published *in vivo* study showed consistent data that BPAF exposure uniquely impaired pregnancies and sexual development in rats compared to BPA at similar doses [182]. BPS uniquely reduced the reproductive lifespan of, and induced distinct transcriptome changes in, *C. elegans* [166]. Therefore, given the similarities of their estrogenic potencies to BPA, current data indicates that BPA analogs, especially BPAF and TBBPA, may disrupt reproductive functions in an ER-independent manner.

The studies reviewed here provide insufficient toxicological and epidemiological data to characterize and determine the reproductive effects of BPA analogs. In animal models, absorption, distribution, metabolism, and excretion of BPA analogs, as well as their estrogenic potencies, should be determined and evaluated. The effects of developmental and adult exposure should be characterized in multiple species. Currently, the NTP is in the process of carrying out toxicological studies of BPS and BPAF on rodents, and toxicokinetic studies of BPS following oral and intravenous exposure. In *in vitro* studies, adverse signaling pathways need to be elucidated. As endocrine disruptors, the potential interactions of bisphenols and hormone receptors on different testicular cell lines and their toxic consequences need to be determined, using gain- and loss-of-function approaches. Human studies analyzing the associations between analog exposure levels and hormone levels, oocyte and sperm quality, and pregnancy outcomes should be examined. The single urine

spot sample is usually used in BPA studies, but it does not reflect the long-term chemical exposure or determine the real exposure level the progression of a disease's development. Future epidemiological studies need to employ an advanced exposure assessment to monitor long-term BPA analog exposure on individuals. These multifaceted data will potentially allow for comparing information across BPA analogs and a better risk assessment of bisphenols in general.

Given the current data gap, the following types of research studies are needed in the future:

- Environmental studies are needed to better elucidate the environmental occurrence of BPA analogs and determine sources and pathways of human exposure.
- Epidemiological studies should be conducted in the general population with precise measurement of chronic exposure level. Co-exposure should also be considered.
- *In vivo* studies are needed to better elucidate the metabolic pathways of BPA analogs and target the internal doses and exposure times that are relevant to human exposure.
- *In vitro* studies are needed to elucidate the unique mechanisms and the mode of actions of BPA analogs on the reproductive systems, especially the molecular mechanism of the formation of MNGs by BPAF.

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## Abbreviations:

| | |
|---|---|
| **3β-HSD** | 3β-hydroxysteroid dehydrogenase |
| **AR** | androgen receptor |
| **BPA** | bisphenol A |
| **BPAF** | bisphenol AF |
| **BPF** | bisphenol F |
| **BPS** | bisphenol S |
| **CDC** | the US Centers for Disease Control and Prevention |
| **E2** | estradiol |
| **EC20** | 20% maximal effect concentration |
| **ER α/β** | estrogen receptor α/β |

| | |
|---|---|
| **ER** | endoplasmic reticulum |
| **EPA** | the United States Environmental Protection Agency |
| **FDA** | the U.S. Food and Drug Administration |
| **FSH** | follicle-stimulating hormone |
| **GD** | gestational day |
| **HTS** | high throughput screening |
| **LH** | luteinizing hormone |
| **LOAEL** | the lowest adverse effect level |
| **NHANES** | the National Health and Nutrition Examination Survey |
| **NTP** | the National Toxicology Program |
| **P4** | progesterone |
| **PF** | post-fertilization |
| **PND** | postnatal day |
| **ROS** | reactive oxygen species |
| **T** | testosterone |
| **T3** | triiodothyronine |
| **T4** | thyroxine |
| **TBBPA** | tetrabromobisphenol A |
| **TSH** | thyroid-stimulating hormone |

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**Table 1.**

BPA and oocyte outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Moore-Ambriz et al., 2015 | Mouse | C57BL/6 J | Oral dose[a] | 3 estrous cycle | 50 μg/kg | After the 3 estrous cycles | Young (PND 28-32) female rats were exposed to BPA at a dose of 50 μg/kg during the first estrous cycle. In *in vivo* and *in vitro* fertilization assay, BPA exposure significantly decreased the percentage of fertilized oocytes. No changes of ovulation were observed | [25] |
| Ferris et al., 2015 | Bovine | | *In vitro* oocyte | 24 h | 15 and 30 ng/ml | | In bovine oocyte, exposure to 30 ng/ml BPA (130 nM) decreased meiosis progression and increased spindle abnormalities, including abnormal spindle morphology and chromosome alignment | [44] |
| Wang et al., 2016b | Porcine | | *In vitro* oocyte | | 250 μM | | BPA exposure (250 μM) increased ROS abnormal cytoskeletons, apoptosis/autophagy rate and altered epigenetic pattern in porcine oocytes | [28] |
| Ferris et al., 2016 | Bovine | | *In vitro* cumulus oocyte complexes | 8 days | 65 and 130 nM | | Bovine oocytes exposed to BPA were fertilized in embryo culture and showed significant DNA damage and apoptosis at 130 nM, while gene expression in blastocysts was not altered. | [24] |
| Nakano et al., 2016 | Mouse | ICR | *In vitro* oocyte | 6, 9, 12, 15 and 18 h | 2, 20, 50 and 100 μg/ml | | BPA exposure inhibited oocyte maturation at concentrations of 50 and 100 μg/ml and delayed the cell cycle at a dose of 2 μg/ml. Further BPA treatment caused spindle abnormalities and activated the spindle assembly checkpoint at a dose of 50 μg/ml | [45] |

[a]Placing a pipette tip with the dosing solution in the corner of the animal mouth.

**Table 2.**

BPA and human reproductive outcomes.

| Source | Study design | Study Population | Sample Size | Measurement Time | BPA concentrations | Summary | Reference |
|---|---|---|---|---|---|---|---|
| Ferguson et al., 2014 | Retrospective cohort | Boys ages 8–14 (ELEMENT) [a] | 118 | At the time of hormone measurement | NA | In 118 boys during the peripubertal period, parental (3rd trimester) or childhood BPA exposure was not associated with hormone levels, adrenarche or puberty. | [140] |
| Knez et al., 2014 | Prospective cohort | Male partners undergoing IVF treatments (Slovenia) | 149 | Same day as follicle aspiration | Geometric mean 1.55 ng/mL | In 149 couples undergoing IVF, the natural logarithm transformed urinary BPA concentration was associated with lower natural logarithm transformed sperm count (b 1/4 0.241, 95% CI 0.470 to 0.012), natural logarithm transformed sperm concentration (b 1/4 0.219, 95% CI 0.436 to 0.003), and sperm vitality (b 1/4 2.660, 95% CI 4.991 to 0.329) in male partner, while the embryo development parameters were not associated with BPA exposure. | [97] |
| Lassen et al., 2014 | Cross-sectional | Young men from general population (Denmark) | 308 | Same day as blood sample collection | Median 3.25 ng/mL | In 308 young men from Denmark's general population, Men with BPA concentrations above the lowest quartile had higher serum T, LH, E2, and free T levels, as compared with the lowest quartile ($p \leq 0.02$). Men in the highest quartile of BPA had lower sperm progressive motility compared with men in the lowest quartile (−6.7 percentage points, 95% CI, −11.76, −1.63). | [18] |
| Lee et al., 2014 | Case-control | Girls with central precocious puberty (Korea) | 40 Peripheral PP/42 Central PP/32 Controls | Same day as blood sample collection | 8.7 ± 7.6 μg/g creatinine (peripheral-PP), 8.0 ± 9.9 μg/g (central-PP), 6.6 ± 7.3 μg/g (control) | In 82 PP patients, BPA levels were slightly higher compared with 32 age-matched healthy girls but not associated with the onset of PP. Altered steroid metabolism was associated with urinary BPA levels, and levels of T, E2, and P4 were significantly increased in individuals with higher BPA level. | [19] |
| Upson et al., 2014 | Case-control | Women with confirmed endometriosis (WREN) [c] | 143 Cases/287 Controls | After disease diagnosis | Median 1.32 ng/mL(cases), 1.24 ng/mL (control) | In 143 endometriosis cases and 287 population-based controls, total urinary BPA concentrations was associated with non-ovarian pelvic endometriosis (second versus lowest quartile, OR 3.0; 95% CI, 1.2, 7.3; third versus lowest quartile, OR 3.0; 95% CI, 1.1, 7.6), but not assicated wtih ovarian endometriosis. | [78] |
| Vagi et al., 2014 | Case-control | Female PCOS patients from an urban academic medical center in Los Angeles | 52 Cases/50 Controls | Same day as blood sample collection | Geometric mean 1.6 μg/L (PCOS case), 2.1 μg/L (control) | In 52 patients diagnosed with PCOS, the urinary BPA concentrations were not associated with increased risk of PCOS. | [71] |
| Akin et al., 2015 | Case-control | Female PCOS patients from a Paediatric Endocrinology Outpatient Clinic (Turkey) | 112 Cases/61 Controls | During the early follicular phase | Geometric mean 1.61 ng/mL (PCOS case), 0.8 ng/mL (control) | Among 112 girls with PCOS and 61 controls between 13 and 19 years of age, serum bisphenol A levels markedly increased in PCOS cases. Bisphenol A was significantly correlated with total T ($r = 0.52$), free T ($r = 0.44$) ($p < 0.05$). | [50] |
| Goldstone et al., 2015 | Prospective cohort | Male partners of couples trying to become pregnant (LIFE) | 418 | Two days before semen collection | Geometric mean 0.55 ng/mL | In 418 males from Michigan and Texas, 2005–2009, BPA was negatively associated with DNA fragmentation in adjusted linear regression (˜ = −0.0544, p = 0.035). No | [17] |

| Source | Study design | Study Population | Sample Size | Measurement Time | BPA concentrations | Summary | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | | associations between BPA exposure and other sperm parameters were observed. | |
| Liu et al., 2015 | Cross-sectional | Male workers with occupational exposure (China) | 592 | Pre and post-shift | Median 685.9 μg/g creatinine (exposed), 4.2 μg/g creatinine (unexposed) | Among 592 male workers, urine BPA level was associated with increased prolactin ($p<0.001$), E2 ($p < 0.001$), sex SHBG level ($p = 0.001$), and a reduced androstenedione ($p < 0.001$) and free androgen index level ($p = 0.021$). | [138] |
| Miao et al., 2015 | Cross-sectional | Female workers with occupational exposure (China) | 356 | Pre and post-shift | Geometric mean 22 μg/g creatinine (exposed), 0.4 μg/g creatinine (unexposed) | In 106 exposed and 250 unexposed female workers, urinary BPA levels were positively associated with higher PRL and PROG levels ($p<0.05$). The BPA levels were positively associated with E2 levels among exposed workers ($p = 0.05$) and negatively associated with FSH levels among the unexposed group ($p<0.005$). | [51] |
| Minguez-Alarcon et al., 2015 | Prospective cohort | Female completed at least one IVF cycle (Massachusetts General Hospital Fertility Center) | 256 | Same day of oocyte retrieval | Geometric mean 1.87 ng/mL | In 256 women undergoing IVF, Urinary BPA concentrations were not associated with endometrial wall thickness or peak E2 levels. Younger women (<37 years old) had thicker endometrial thickness across increasing quartiles of urinary BPA concentrations, while older women (≥37 years old) had thinner endometrial thickness across increasing quartiles of urinary BPA concentrations. | [52] |
| Zhuang et al., 2015 | Cross-sectional | Male workers with occupational exposure (China) | 559 | Pre-shift | Median 18.75 ng/mL (exposed) 3.37 ng/mL (unexposed) | In 281 exposed and 278 unexposed male workers, serum BPA levels were increased after occupational exposure. The serum BPA level was associated with lower serum AD level (0.18 ng/mL; 95 % CI −0.22 to −0.13) and higher serum SHBG level (2.79 nmol/L; 95 % CI 2.11–3.46).104 | [139] |
| Scinicariello et al., 2016 | Cross-sectional | Male and female children (6-11 years) and adolescents (12-19 years) from general population (NHANES 2011-2012) | 588 | NA | Geometric mean 1.40-1.94 ng/mL | In 558 child and adolescent participants, urinary BPA concentrations were associated with significantly lower TT in male adolescents, and significantly higher TT in female adolescents (p-trend=0.01). | [20] |
| Vahedi et al., 2016 | Case-control | Female PCOS patients who worked as marketing sellers (Iran) | 62 Cases/62 Controls | NA | 0.48 ng/mL (PCOS case), 0.16 ng/mL (control) | In 62 marketing professionals with PCOS and 62 healthy women with a similar job, serum BPA levels, LH-FSH ratio were significantly increased in PCOS cases, while TSH levels were significantly decreased. | [70] |
| Zhou et al., 2016 | Cross-sectional | Infertile women with PCOS (China) | 268 | NA | Median 2.35 ng/mL | In 268 infertile women diagnosed with PCOS, urinary BPA level was associated with a significant decrease in AFC ($\beta = -0.34$, 95% CI = −0.60, −0.08; $p = 0.01$). But no association between BPA level and FSH was observed. | [53] |
| Simonelli et al., 2017 | Case-control | Female endometriosis patients | 68 Cases/60 Controls | During the consultation | Mean 5.31 ng/mL(cases), 1.64 ng/mL (control) | In 68 patients with endometriosis, urinary BPA level was significantly higher as compared with BPA level in the control group. | [79] |

[a]The Early Life Exposure in Mexico to Environmental Toxicants project

[b] The Longitudinal Investigation of Fertility and the Environment Study

[c] The Women's Risk of Endometriosis Study

[d] The Environment and Reproductive Health Study

[e] The Health Outcomes and Measures of the Environment Study

[f] The Maternal-Infant Research on Environmental Chemicals Study

[g] The North Carolina Early Pregnancy Study

**Table 3.**

BPA and female steroidogenesis in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Delclos, et al., 2014 | Rat | SD | Oral gavage | GD 6-PND 90 | 2.5–300000 μg/kg | PND 80 | SD female rats were exposed to BPA orally from GD 6 through PND 90. The chronic BPA exposure resulted in increases in serum E2 and prolactin level only at 100000 and 300000 μg /kg groups. Progesterone was significantly decreased at 300,000 μg BPA/kg BW/day groups. | [23] |
| Li et al., 2014 | Rat | Wistar | Intraperitoneal injection | PND 28-PND 35 | 10, 40 and 160 mg/kg | PND 35 | Pre-puberty female Wistar rats were exposed to BPA for one week. BPA exposure decreased at 40 and 160 mg BPA/kg BW/day, while serum E2 level was not altered. | [62] |
| Sadowski et al., 2014 | Rat | Long-Evans | Oral gavage | GD 0-PND 9 | 4, 40 and 400 μg/kg | PND 23 | Long–Evans rats received oral administration of BPA at 4 μg/kg, 40 μg/kg, or 400 μg/kg throughout pregnancy, and the pups received direct oral administration of BPA between PND 1–9. Rats in both genders had decreased levels of FSH at weaning at doses of 4 and 400 μg/kg. But no changes in other hormone levels or maze behavior were observed. | [65] |
| Gamez et al., 2015 | Rat | Wistar | Drinking water | GD 0-PND 21 | 3 μg/kg | PND 30 | Wistar mated rats were treated with BPA in their drinking water (estimated 3 μg/kg) until their offspring were weaned at 21 days after birth. Serum LH and E2 levels were significantly increased in the treatment group with increased follicle number, while no changes in serum FSH level were observed. | [64] |
| Moore-Ambriz et al., 2015 | Mouse | C57BL/6 J | Oral dose | 3 estrous cycle | 50 μg/kg | After the 3 estrous cycles | Young (PND 28-32) female rats were exposed to BPA at a dose of 50 μg/kg during the first estrous cycle. In *in vivo* and *in vitro* fertilization assay, BPA exposure significantly decreased the percentage of fertilized oocytes. No changes of ovulation and hormone levels were observed. | [25] |
| Santamaria et al., 2016 | Rat | Wistar | Drinking water | GD 9-PND 21 | 0.5 and 50 μg/kg | PND 90 | In adult female rat offspring with gestational and lactational exposure, serum P4 levels were significantly increased in BPA 0.5 and 50 μg/kg groups coupled with high mRNA expression of 3b-hydroxysteroid dehydrogenase (3b-HSD). | [63] |
| Mansur et al., 2016 | Human | | *In vitro* granulosa cells | 48 h | 0.2, 0.02, 2.0, 20 mg/ml | | Treatment of human granulosa cells after[?] 48 h resulted in significantly lower progesterone biosynthesis at doses of 2 or 20 mg/ml and lowered E2 level at a dose of 20 mg/ml. These two concentrations significantly reduced the mRNA and protein levels of 3b-HSD, CYP11A1, and CYP19A1 without affecting StAR and 17b-hydroxysteroid dehydrogenase mRNA expression. | [66] |

**Table 4.1.**

BPA and ovary outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Delclos, et al., 2014 | Rat | SD | Oral gavage | GD 6-PND 90 | 2.5–300000 μg/kg | PND 21 | SD rats exposed to BPA orally from GD 6 through PND 90. Adverse effects of BPA exposure on the ovary, including increased cystic follicles, depleted corpora lutea, and antral follicles at two BPA high dose (100000 or 300000 μg/kg). | [23] |
| Li et al., 2014 | Rat | Wistar | Intraperitoneal injection | PND 28-PND 35 | 10, 40 and 160 mg/kg | PND 35 | Pre-puberty female Wistar rats were exposed to BPA for one week. BPA exposure significantly decreased rat ovarian weights and follicle numbers at doses of 40 and 160 mg/kg. In addition, the mRNA and protein levels of the germline alpha (FIGLA) and oocyte-specific histone H1 variant (H1FOO) genes decreased at 160 mg/kg and 10-160 mg/kg, respectively. | [62] |
| Patisaul et al., 2014 | Rat | Wistar | Dietary exposure and Drinking water | GD 6-PND 40 | 0.18-0.44 mg/kg | PND 120 | Wistar rats exposed to BPA during GD 6-PND 40 showed delayed vaginal opening. But no changes in corpora lutea and cystic follicles were observed. | [72] |
| Berger et al., 2016 | Mouse | FVB | Oral dose | GD 11-PND 0 | 0.5, 20, and 50 μg/kg | PND 4 and 21 (F1-F3) | To examine the transgenerational effects of BPA on the ovary, FVB mice exposed to BPA in utero and ovaries of F1-3 generations were collected at PND 4 and PND 21 to examine expression levels of multiple genes in apoptosis, antioxidant, igf family, hormone receptor, and steroidogenesis. Overall, more significant changes in gene expression were observed at PND 21, while no clear dose-dependent responses showed. | [22] |
| Santamaria et al., 2016 | Rat | Wistar | Drinking water | GD 9-PND 21 | 0.5 and 50 μg/kg | PND 90 | In adult female rat offspring with Maternal exposure to low doses of BPA during gestation and breastfeeding, ovaries from both BPA-treated groups showed decreased ovaries weight, primordial follicle recruitment, and a greater number of corpora lutea. | [63] |
| Gamez et al., 2015 | Rat | Wistar | Drinking water | GD 0-PND 21 | 3 μg/kg | PND 30 | No changes in ovarian weight and its relative weight. | [64] |
| Zhou et al., 2015 | Mouse | CD-1 | *In vitro* ovary | 24-192 h | 0.1, 1, 5, and 10 μg/mL | PND1, 2, 4 and 8 | In ovaries of newborn mice, BPA exposure increased germ cells and decreased primordial follicle in ovaries. Further, BPA exposure altered the expression of key genes involved in apoptosis and antioxidation, while the effects varied by ovary collection times and exposure doses. | [73] |
| Ganesan and Keating, 2016 | Rat | F344 | *In vitro* ovary | 48-192 h | 440 μM | PND 4 | In F344 rat ovaries, BPA reduced small primary, large primary and secondary follicle numbers and increased DNA manage markers, γ-H2AX, ATM, and DNA repair genes. | [74] |

**Table 4.2.**

BPA and uterine outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Calhoun et al., 2014 | Monkey | Rhesus Macaque | Dietary exposure | GD 100-GD 165 | 400 μg/kg | GD 165 (F1) | The pregnant rhesus macaques were exposed orally to BPA. Fatal uteri did not show notable changes in uterus histology, proliferation, expression of hormone receptors. At GD 165, BPA exposure altered expression levels of three genes (HOXA13, WNT4, and WNT5A) involved in reproductive organ development. | [85] |
| Kim et al., 2014 | Mouse | ICR | Intraperitoneal injection | 0.5, 1, 2, 4, 6 and 12 h | 10, 20, 50, 100, 200 and 500 mg/kg | Adult | Egr1 (early growth response 1) was rapidly and transiently induced by BPA (starting at 20 mg/kg) in stromal cells surrounding implanting blastocyst via nuclear estrogen receptor (ER)-ERK1/2 pathway. | [87] |
| Kendziorski and Belcher, 2015 | Mouse | C57Bl/6N and CD-1 | Dietary exposure | 4 weeks | 0.004, 0.04, 0.4, 4, and 40 mg/kg | Adult | In adult C57Bl/6N and CD-1 mice, BPA non-monotonically increased gland nest density and periglandular collagen accumulation, collagen I and III expressions, decreased matrix metalloproteinase 2 (MMP2) and MMP14 expression, and increased immune response were observed in 4 mg/kg BPA CD-1 group only. | [84] |
| Camacho et al., 2015 | Rat | SD | Oral gavage | GD 6-PND 90 | 2.5, 8, 25, 80, 260, 840, 2700, 100,000 and 300,000 μg/kg | PND 4, PND 90 | In SD rats exposed to BPA orally, no changes in global genomic DNA methylations in uterus were observed. Changes in prostate and female mammary glands were only observed in BPA-high dose groups (100,000 and 300,000 μg/kg). | [203] |
| Salleh et al., 2015 | Rat | SD | Ex-vivo | 3-5 min | 1×10-8-1×10-4 M | Adult | In *ex-vivo* uterus contraction assay, uterine contractile force decreased with increasing doses of BPA. | [86] |
| Vigezzi et al., 2015 | Rat | Wistar | Drinking water | GD 9-PND 21 | 0.5 and 50 μg/kg | PND 90, PND 360 | Wistar rats were exposed to BPA via drinking water through GD 9 to PND 21. The female offspring showed decreased glandular proliferation (0.5 and 50 μg/kg) and alpha-actin expression (50 μg/kg) at PND 90 and increased the incidence of abnormalities in the luminal (50 μg/kg) and glandular epithelium (0.5 and 50 μg/kg) at PND 360. | [27] |
| Li et al., 2016 | Mouse | CD-1 | Oral | PND 22-GD 9 | 60 and 600 μg/kg | GD 9 | In CD-1 mice, BPA exposure affected puberty and estrous cyclicity, decreased embryo implantation, PGR and HAND2 expression in uterine with enhanced activation of fibroblast growth factor and MAPK signaling in the epithelium, and increased improper endometrial epithelial and stromal functions. | [83] |
| Kang et al., 2014 | | | *In vitro* uterine smooth muscle cells | 48 h | 2.28 ng/mL | | In uterine smooth muscle cells, BPA treatment upregulated genes involved in cell differentiation, cellular metabolic processes, cell proliferation and smooth muscle contraction and decreased the genes involved in mitosis, lipid metabolism, regulation of muscle cell differentiation and cell adhesion. | [90] |

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Helmestam et al., 2014 | Human | | *In vitro* endometrial endothelial cell | 24 h | 0.01, 1, 100, 10000 nM | | The HECC cells were co-cultured with primary endometrial stromal cells to mimic the *in vivo* situation and treated with environmentally relevant doses of BPA. BPA exposure did not alter the HEEC viability and proliferation, and increased tube formation and vascular endothelial growth factor (VEGF)-D protein expression at a dose of 10000 nM. | [91] |
| Shen et al., 2014 | Human | | *In vitro* uterine leiomyoma | 24, 48 and 72 h | 1, 2.5, 5, 10 and 20 μM | | The BPA exposure increased the protein expression level of ERα, IGF-1, and VEGF at doses of 2.5, 5 and 10 μM in uterine leiomyomas. | [92] |
| Wang et al., 2015 | Human | | *In vitro* endometrial carcinoma cells line (RL95-2) | 7 days | 1×10-10-1×10-4 M | | The BPA exposure increased gene expression of cyclooxygenase-2 (COX-2) and epithelial-mesenchymal transition (EMT), promote growth rate and colony-forming efficiency in a nonmonotonic manner in human endometrial carcinoma cells line. | [93] |

**Table 5.**

BPA and sperm outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Gurmeet et al., 2014 | Rat | SD | Oral gavage | PND 28-70 | 1, 5 and 100 mg/kg | PND 70 | In prepubertal SD rats, 6-week BPA oral exposure increased intercellular junction disruptions, sloughing of germ cells, and immature germ cells and cellular debris. No testis weight change was observed. Further BPA exposure decreased plasma T and E2 levels in all treatment groups. | [101] |
| Liu et al., 2014 | Rat | Wistar | Oral gavage | 60 days | 20 μg/kg | Adult | In Wistar rats, a 60-day exposure to BPA at an environmentally relevant dose resulted in significant increase in the proportion of stage VII seminiferous epithelium and the decrease in stage VII. Further, BPA exposure induced the expression level of γ-H2AX, ATM and SCP3, suggesting DNA damage and early meiosis inhibition. | [138] 80 |
| Vilela et al., 2014 | Mouse | Vesper | Oral gavage | GD 0-PND 0 | 40, 80 and 200 μg/kg | PND 70 | In vesper mice received utero BPA exposure, BPA treatment significantly reduced the sperm with normal morphology at a dose of 200 μg/kg, mitochondrial integrity at doses of 80 and 200 μg/kg, and *in vitro* penetration rate starting at 40 μg/kg, whereas no changes in DNA integrity and acrosome integrity were observed. | [102] |
| Wang et al., 2014 | Rat | SD | Oral gavage | 4 weeks | 50, 100, and 200 mg/kg | Adult | In SD rat, BPA exposure increased germ cell apoptosis in testes and decreased sperm concentration at doses of 100 and 200 mg/kg. Further, BPA exposure significantly increased protein and mRNA levels of cytochrome C, apoptosis-inducing factor, caspase-3/9, Bas, and decreased protein and gene levels of Bcl-2 in all treatment groups. Also, the abnormal structure of mitochondria was observed at a dose of 200 mg/kg. | [112] |
| LI et al., 2015 | Mouse | C57BL/6J | Intraperitoneal injection | PND 21-28 | 50 mg/kg | PND 56 | In C57BL/6J mice receiving BPA exposure, a decrease in epididymal sperm number and increase in sperm deformity rate were observed. Abnormal seminiferous tubules with sloughing of germ cells were observed, while male fertility was not affected. | [103] |
| Mao et al., 2015 | Rat | SD | Oral gavage | GD 0-PND 21 | 40 μg/kg | PND 56 (F1) | The paternal BPA exposure induced Igf2 DMR2 methylation and decreased mRNA expression of IGH2 in F1 sperm, which potentially associated with hypermethylation of Igf2 observed in islets of male F2 offspring. | [116] |
| Vrooman et al., 2015 | Mouse | Cd-1; C57BL/6J ; C3H/HeJ | Oral gavage | PND 1-PND 12 | 20 and 500 μg/kg | PND 12/84/365 | In multiple strains of mice, BPA exposure did not alter the chromosome pairing and synapsis in spermatogonial stem cells. | [115] |
| Wisniewski et al., 2015 | Rat | Wistar | Oral gavage | PND 50-90 | 5 and 25mg/kg | PND 105 | In Wistar rats exposed to BPA orally, serum T, LH, and FSH levels were decreased, and the E2 level was increased in both treatment groups. In addition, the gene expression levels of hormone receptors were increased in the hypothalamus. BPA exposure reduced sperm production, reserves and transit time in both treatment groups. | [104] |
| Hass et al., 2016 | Rat | Wistar | Oral gavage | GD 7-PND 22 | 25, 250, 5000 and 50000 μg/kg | 3 months | Prenatal and postnatal BPA exposure significantly decreased the sperm count only at a dose of 25 μg/kg in Wistar rat. No changes in reproductive organ were observed. | [105] |

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Kalb et al., 2016 | Mouse | Swiss Albino | Oral gavage | PND 0-PND 21 | 300, 900, and 3000 μg/kg | Adult | During the breastfeeding period, maternal BPA exposure altered sperm parameters (sperm motility; normal morphology; membrane integrity; acrosomal integrity; DNA integrity; and mitochondrial functionality) at all treatment groups. BPA 3000 μg/kg treatment also induced Testicular degeneration. In addition, the total antioxidant capacity was impaired at doses of 900 and 3000 μg/kg. | [106] |
| Quan *et al.*, 2016a | Rat | SD | Intraperitoneal injection | 20 days | 2, 10, 50 mg/kg | 6 months | In SD rats, BPA exposure induced oxidative stress (SOD activity, GSH-Px activity, and MDA level) at a dose of 50 mg/kg and sperm malformation rate and apoptosis in testis at all treatment groups. The mRNA expression of genes in Akt/mTOR pathway were altered in the different treatment groups. In addition, the serum T (2, 10, 50 mg/kg), FSH (10 and 50 mg/kg) and LH (50 mg/kg) levels were decreased. | [109] |
| Quan et al., 2016b | Rat | SD | Oral gavage | GD 14-21 | 1, 10, 100 mg/kg | PND 21 | In SD rat male offspring, utero BPA exposure induced oxidative stress (MDA level) at doses of 10 and 100 mg/kg and apoptosis in testis, and altered seminiferous tubules morphology at all treatment groups. The mRNA and protein expression of genes in Akt/mTOR pathway were altered in the different treatment group. In addition, the serum T (100 mg/kg), FSH (100 mg/kg) and LH (1, 10, 100 mg/kg) levels were decreased. | [110] |
| Rahman et al., 2016 | Mouse | CD-1 | Oral gavage | GD 7-14 | 50, 5000 and 50000 μg/kg | PND 120 | Gestational exposure to BPA inhibited sperm count, motility parameters, and intracellular ATP levels in a dose-dependent manner. BPA exposure reduced numbers of stage VIII seminiferous epithelial cells in testis at doses of 5000 and 50000 μg/kg and decreased PKA activity and tyrosine phosphorylation in spermatozoa at doses of 5000 and 50000 μg/kg. Further, BPA exposure altered the expression levels multiple proteins involved in ATP production, oxidative stress response, and fertility. | [107] |
| Wang et al., 2016 | Mouse | C57BL/6 | Oral gavage | 8 weeks | 10, 50 and 250 μg/kg | Adult | In C57BL/6J mice, BPA exposure decreased sperm viability at a dose of 250 μg/kg and motility at all treatment groups. Sperm-specific $Ca^{2+}$ channel currents were reduced in at all treatment groups. And the mRNA and protein levels of CatSper subunits were reduced at doses of 50 and 250 μg/kg. Similar results were observed *in vitro* sperm treated with BPA. | [108] |
| Yin et al., 2016 | Mouse | Kunming | Oral gavage | 5 weeks | 3, 30 and 300 mg/kg | Adult | In Kunming mice, BPA exposure induced spermatogenic cellular apoptosis, sloughing of germ cells, and seminiferous tubules vacuolation in all treatment groups. | [111] |
| Chen et al., 2017 | Rat | Wistar | Oral gavage | 35 weeks | 50 μg/kg | Adult | In Wistar rats receiving 50 μg/kg BPA exposure for 35 weeks, no apoptosis or sperm deformation was observed. BPA exposure decreased protein lysine acetylation levels and increased the expression of histone deacetylase Sirt1, ERβ expression and its binding with caveolin-1 (Cav-1) in testes. | [114] |
| Qian et al., 2015 | Mouse | | *In vitro* spermatocyte GC-2 cell line | 0.5-48 h | 0.02–20 μM | | In mouse spermatocyte GC-2 cell line, BPA treatment decreased cell viability, the release of mitochondrial cytochrome c and the activation of caspase-3 at doses from 0.2 to 20 μM. Further, BPA exposure impaired $Ca^{2+}$ homeostasis and induced $Ca^{2+}$ sensor proteins (CaM and CaMKII) expressions starting at 0.02 and 0.2 μM, respectively. The pretreatment with Ca chelator or sensor protein inhibitor could partially attenuate BPA-induced cellular injury. | [117] |

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Rahman et al., 2015 | Mouse | ICR | *In vitro* spermatozoa | 6 h | 0.0001, 0.01, 1, and 100 μM | | BPA exposure significantly affected sperm motility, fertilization rate, and intracellular ATP levels at a dose of 100 μM. Also, BPA induced the protein kinase A (PKA) activity, tyrosine phosphorylation and fertility-related proteins (peroxiredoxin-5, glutathione peroxidase 4, glyceraldehyde-3-phosphate dehydrogenase, and succinate dehydrogenase), except bate-actin in spermatozoa. | [118] |
| Barbonetti et al., 2016 | Human | | *In vitro* spermatozoa | 4 and 20 h | 10–800 μM | | In human spermatozoa, BPA exposure decreased the sperm motility, viability and mitochondrial membrane potential, and increased apoptosis, DNA oxidative damage marker, 8-hydroxy-2'-deoxyguanosine starting at 300 μM. | [121] |
| Kotwicka et al., 2016 | Human | | *In vitro* spermatozoa | 5-60 min | 10–10, 10–8 and 10–6 M | | In human spermatozoa, BPA treatment induced a transient increase of velocity straight linear (VSL) and homogeneity of progressive movement velocity (HPMV) at 15 min after stimulation. 1h BPA exposure did not alter vitality phosphatidylserine membrane translocation, for all doses. BPA at a dose of 10–6 mol/L induced a rapid and transient increase of intracellular free calcium ions concentration. | [122] |
| Wan et al., 2016 | Rat | SD | *In vitro* mature sperm | 10-300 min | 1-600 μg/ml | | In rat sperm, exposure to BPA significantly decreased sperm motility in a dose and time-dependent manner. Further, capacitation-associated protein tyrosine phosphorylation was induced by BPA treatment, while the induction could be blocked by PKA inhibitor. | [119] |
| Yin et al., 2016 | Mouse | | *In vitro* spermatocyte GC-2 cell line | 24 and 48 h | 20, 40 and 80 μM | | In mouse spermatocyte GC-2 cell line, BPA exposure decreased cell viability starting at 50 μM for 24 h hand 5 μM for 48 h and induced apoptosis, ER stress, ROS mitochondrial damage and the mitochondrial apoptotic pathway starting at 20 μM for 48 h. Knocking down the PERK/EIF2α/chop pathway (one of the ER stress pathways) partially recovered the BPA-induced cell apoptosis. | [111] |
| Liang et al., 2017 | Mouse | | *In vitro* Spermatogonial cell line C18-4 | 24, 48 and 72 h | 0.1, 1, 10, and 50 μM | | The BPS exposure significantly decreased cell viability, altered nuclear morphology, increased gamma-H2AX expression level, and perturbed cytoskeleton and cell cycle progression at d dose of 50 μM in spermatogonial cell line C18-4. | [120] |

**Table 6.**

BPA and Sertoli/Leydig cells in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Ge et al., 2014a | Mouse | | *In vitro* Sertoli cell line TM4 | 24 and 48 h | 10–8 M and 10–5 M | | Exposure to 10– 5 M BPA induced oxidative stress and inhibited cell proliferation. Exposure to 10– 8 M BPA increased intercellular ATP, activities of mitochondria, and proliferation in Sertoli cell line TM4. | [128] |
| Ge et al., 2014b | Mouse | | *In vitro* Sertoli cell line TM4 | 24 and 48 h | 10–8 M and 10–3 M | | Exposure to 1 and 10 nM BPA significantly induced the Sertoli cell proliferation via activating ERK1/2 through GPR30 and ER alpha/beta. | [129] |
| Qi et al., 2014 | Rat | | *In vitro* primary Sertoli cell culture | 24 h | 30, 50, 70 and 90 μM | | In primary rat Sertoli cells, BPA exposure significantly reduced cell viability and induced apoptosis starting at a dose of 50 μM. Further, BPS exposure activated JNKs/p38 MPAK and Fas/FasL signaling pathways and induced translocation of NF-kappa B at doses of 50 and 70 μM. | [26] |
| Qian et al., 2014 | Mouse | | *In vitro* Sertoli cell line TM4 | 12, 24 and 48 h | 0.02, 0.2, 2.0 and 20 μM | | In primary rat Sertoli cells, BPA exposure significantly reduced cell viability and induced apoptosis starting at a dose of 50 μM. Further, mitochondrial mass loss, membrane potential decrease, cytochrome c release, Bcl-2 family members down-regulation and caspases-3 up-regulation were observed in TM4 cells treated with BPA. Additionally, the expression of CaM, ERK1/2, and phosphorylation of CaMKII significantly increased after BPA treatment. Treatments with CaM, ERK1/2 and CaMKII inhibitor attenuated BPA-induced cell damage. | [130] |
| Xiao et al., 2014 | Human | | *In vitro* primary Sertoli cell culture | 24, 48 and 72 h | 0.4, 4, 40 and 300 μM | | In human Sertoli cells, BPA exposure significantly decreased the cell viability, expression levels of ZO-1, N-Cadherin and beta-Catenin at a dose of 200 μM. BPA treatment also increased truncation and depolymerization of actin microfilaments starting at 0.4 μM and improper localization of actin regulatory proteins Arp3 and Eps8 at a dose of 200 μM. | [133] |
| Wang et al., 2015 | Rat | | *In vitro* primary Sertoli cell culture | 24 h | 30, 50, and 70 μM | | In primary rat Sertoli cells, BPA exposure decreased cell viability and induced apoptosis at doses of 50 and 70 μM. BPA exposure caused the elevation of Pten expression and the inactivation of Akt, and then triggered the caspase3, which led to apoptosis of Sertoli cells. | |
| de Freitas et al., 2016 | Human | | *In vitro* primary Sertoli cell culture | 6 and 24 h | 20 μM | | In human Sertoli cells, BPA exposure significantly decreased the cell viability, expression levels of occludin, ZO-1, β-catenin, and AR at a dose of 20 μM for 6 and 48 h without changes in F-actin expression or localization. | [132] |
| Wang et al., 2016 | Rat | | *In vitro* primary Sertoli cell culture | | 30, 50, and 70 μM | | In primary rat Sertoli cells, BPA exposure induced ROS, intracellular $Ca^{2+}$ release at doses of 50 and 70 μM and cellular apoptosis at a dose of 70 μM. Pretreatment with N-acetyl-L-cysteine attenuated the BPA-induced cellular apoptosis. | [131] |
| Akingbemi et al., 2004 | Rat | Long-Evans | *In vitro* primary Leydig cell culture | 18 h | 0.01 nM | | Treatment of adult Leydig cells with 0.01 nm BPA decreased T biosynthesis and E2 level, mRNA expression of aromatase and the steroidogenic enzyme 17α-hydroxylase/17–20 lyases. | [135] |
| Nakamura et al., 2010 | Rat | Wistar/ ST | Intraperitoneal injection | 6 weeks | 0, 20, 100 and 200mg/kg | Adult | 200 mg/kg BPA significantly decreased Leydig cell numbers with decreases in the StAR protein level in the rat testis | [134] |

*Reprod Toxicol*. Author manuscript; available in PMC 2019 August 11.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Nanjappa et al., 2012 | Rat | Long-Evans | Oral gavage | GD 12-PND 21 | 2.5 and 25 μg/kg | Adult | BPA exposure (2.5 and 25 μg/kg) significantly promoted Leydig cell division during the prepubertal period and increased Leydig cell numbers at PND 90. In Leydig cells, BPA treatment induced the protein expression of proliferating cell nuclear antigen, MAPK, AR, and ER, increased secretion of the anti-Mullerian hormone. Also, BPA suppressed protein expressions of the LH receptor and the 17beta-hydroxysteroid dehydrogenase enzyme. | [127] |
| Chen et al., 2016 | Mouse | | *In vitro* Leydig cell line TM3 | 24, 48 and 72 h | 10–8 to 10–3 M | | In Leydig TM3 cells, BPA greater than 10–6 M inhibited the proliferation of Leydig TM3 in a dose-dependent manner. The proteomic study revealed BPA could modulate the expression of proteins related to cell structure and motility and cellular metabolism. Further, BPA induced cell migration at a dose of 10–5 M via galectin-1 and ERK1/2. | [136] |

**Table 7.**

BPA and male steroidogenesis in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Delclos et al., 2014 | Rat | SD | Oral gavage | GD 6-PND 90 | 2.5–300000 μg/kg | PND 15 | In male offspring, BPA exposure significantly increased serum T4 level at the highest BPA dose group. No changes in serum T3 and FSH levels and testicular descent were observed. | [23] |
| Gamez et al., 2014 | Rat | Wistar | Drinking water | GD 6-PND 21 | 3 μg/kg | PND 35 | In Wistar rats exposed to BPA, a decrease in testicular weight was observed, while seminal vesicles weight, relative weights of testes and seminal vesicles were not changed. | [150] |
| Gurmeet, et al., 2014 | Rat | SD | Oral gavage | PND 28-70 | 1, 5 and 100 mg/kg | PND 70 | In prepubertal SD rats, 6-week BPA oral exposure increased intercellular junction disruptions, sloughing of germ cells, and immature germ cells and cellular debris. No testis weight change was observed. Further BPA exposure decreased plasma T and E2 levels in all treatment groups. | [101] |
| Sadowski et al., 2014 | Rat | Long-Evans | Oral gavage | GD 0-PND 9 | 4, 40 and 400 μg/kg | PND 23 | Long–Evans rats received oral administration of BPA at 4 μg/kg, 40 μg/kg, or 400 μg/kg throughout pregnancy, and the pups received direct oral administration of BPA between postnatal days 1–9. Rats had decreased levels of FSH at weaning at doses of 4 and 400 μg/kg but no changes in other hormone levels and maze behavior. | [65] |
| Chouhan et al., 2015 | Mouse | Swiss albino | Intraperitoneal injection | 60 days | 0.5, 50 and 100 μg/kg | Adult | In Swiss albino mice, 60-day intraperitoneal BPA exposure significantly decreased sperm count, StAR expression in the testis and serum T level in all treatment groups. | [151] |
| Quan *et al.*, 2016a | Rat | SD | Intraperitoneal injection | 20 days | 2, 10, 50 mg/kg | 6 months | In SD rats, BPA exposure induced oxidative stress (SOD activity, GSH-Px activity, and MDA level) at a dose of 50 mg/kg and sperm malformation rate and apoptosis in testis at all treatment groups. The mRNA expression of genes in Akt/mTOR pathway were altered in the different treatment group. In addition, the serum T (2, 10, 50 mg/kg) FSH (10 and 50 mg/kg) and LH (50 mg/kg) levels were decreased. | [109] |
| Quan et al., 2016b | Rat | SD | Oral gavage | GD 14-21 | 1, 10, 100 mg/kg | PND 21 | In SD rat male offspring, utero BPA exposure induced oxidative stress at doses of 10 and 100 mg/kg and apoptosis in testis, altered seminiferous tubules morphology at all treatment groups. The mRNA and protein expression of genes in Akt/mTOR pathway were altered in the different treatment group. In addition, the serum T (100 mg/kg), FSH (100 mg/kg) and LH (1, 10, 100 mg/kg) levels were decreased. | [110] |
| Wisniewski, et al., 2015 | Rat | Wistar | Oral gavage | PND 50-90 | 5 and 25mg/kg | PND 105 | In Wistar rats exposed to BPA orally, serum T, LH, and FSH levels were decreased, and the E2 level was increased in both treatment groups. Also, the gene expression levels of hormone receptors were increased in the hypothalamus. BPA exposure reduced sperm production, reserves and transit time in both treatment groups. | [104] |
| Zang et al., 2016 | Mouse | C57BL/6 | Intraperitoneal injection | 21 days | 10, 50 and 100 mg/kg | Adult | In C57BL/6 mice, BPA exposure significantly impaired sexual behavior and decreased testis weight in all treatment groups and epididymis at 100 mg/kg group. Further BPA exposure decreased serum T levels at a dose of 100 mg/kg and intratesticular T at doses of 50 and 100 mg/kg. | [152] |

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Eladak *et al.*, 2015 | Human/ Mouse/R at | | *In vitro* fetal testis explants | 24-72 h | 0.001-10000 nM | | BPA exposure significantly reduced basal T secretion levels in rat fetal testis explants at a dose of 10000 nM, in mouse at 1000 and 10000 nM, and in human starting at 10 nM. | [153] |

**Table 8.**

BPS and reproductive outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Yamasaki et al., 2004 | Rat | Wistar | Subcutaneous injection | 3 days | 20, 100 and 500 mg/kg | PND 24 | BPS showed weaker estrogen receptor binding capacity as compared with E2 (0.0055%). In the immature rat uterotrophic assay, BPS treatment significantly increased absolute and relative uterine wet weight and blotted weight at doses of 20 and 500 mg/kg. | [162] |
| Ji et al., 2013 | Fish | Danio ratio | Water | 21 days | 0.5, 5, and 50 μg/L | Adult | Adult zebrafish were exposed to 0.5, 5, and 50 μg/L of BPS for 21 days. Egg production and the gonad somatic index in female fish was significantly decreased at ≥0.5 μg/L BPS. Plasma concentrations of E2 were Significantly increased in both genders. In male fish, significant decreases of T level were observed with up-regulation of cyp19a and down-regulation of cyp17 and 17βhsd transcripts at 50 μg/L BPS. In an F1 generation, parental BPS exposure resulted in delayed and decrease in hatching rate. Continuous BPS exposure in the F1 further increased malformation rates. | [164] |
| Naderi et al., 2014 | Fish | Danio ratio | Water | 75 days | 0.1, 1, 10 and 100 μg/l | Adult | Zebrafish embryos were exposed to various concentrations of BPS for 75 days. The plasma E2 Levels were significantly increased in both genders starting at a dose of 100 μg/l. In male fish, BPS exposure decreased plasma T, T3, T4 levels and sperm count at doses of 10 and 100 μg/l. In female fish, BPS exposure decreased T3 and T4 levels at a dose of 100 μg/l and egg production at doses of 10 and 100 μg/l | [165] |
| Ullah et al., 2016 | Rat | SD | Oral gavage | 28 days | 1, 5, 25 and 50 μg/kg | Adult | In adult rats exposed to various concentrations of BPS, a significant increase in the testicular ROS and lipid peroxidation was observed at a dose of 50 μg/kg with reduced antioxidant enzyme activity. Further BPS decreased plasma T level and altered the testicular morphology (thin seminiferous epithelium; reduction the tubular epithelium area; empty lumen) at a dose 50 μg/kg. No changes in spermatogenesis were observed. | [163] |
| Eladak *et al.*, 2015 | Human/ Mouse/Rat | | *In vitro* fetal testis explants | 24-72 h | 10, 100, 1000 and 10000 nM | | BPS exposure significantly reduced basal T secretion levels in mouse fetal testis explants starting at 100 nM, and in human starting at 1000 nM. | [153] |
| Chen et al., 2016 | *Caenorhabditis Elegans* | | | 4 days | 125, 250 and 500 μM | | BPS exposure increased embryonic lethality, germline nuclear loss and apoptosis at doses of 125, 250 and 500 μM in *C. Elegans*. 500 μM BPS exposure induced DNA damage and impaired homologous chromosome synapsis. Further BPS show distinct alterations of gene expression at whole transcriptome level as compared with BPA. | [166] |
| Roelofs et al., 2015 | Mouse | | *In vitro* Leydig cells MA-10 | 48 h | 10 μM | | BPS exposure significantly increased P4 levels sand gene (5aRed1) in the MA-10 cells at a dose of 10 μM. | [167] |
| Liang et al., 2017 | Mouse | | *In vitro* Spermatogonial cell line C18-4 | 24, 48 and 72 h | 0.1, 1, 10, and 50 μM | | The BPS exposure significantly decreased cell viability, altered nuclear morphology, increased gamma-H2AX expression level, and perturbed cytoskeleton and cell cycle progression at a dose of 50 μM in spermatogonial cell line C18-4. | [120] |

**Table 9.**

BPF and reproductive outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Stroheker et al., 2003 | Rat | Wistar | Oral gavage | 4 days | 25, 50, 100, and 200 mg/kg | PND 26 | In immature Wistar rats, BPF exposure increased vaginal cornification and uterus relative weight at a dose of 200 mg/kg. | [170] |
| Yamasaki et al., 2004 | Rat | Wistar | Subcutaneous injection | 3 days | 100, 300 and 1000 mg/kg | PND 24 | BPF showed weaker estrogen receptor binding capacity as compared with E2 (0.0719%). In the immature rat heterotrophic assay, BPF treatment significantly increased absolute and relative uterine wet weight and blotted weight at all treatment group in a dose-dependent manner. | [162] |
| Higashihara et al., 2007 | Rat | SD | Oral gavage | 28 days | 20, 100 and 500 mg/kg | Adult | In SD rats exposed to BPF orally, serum T3 levels increased, and serum T4 levels decreased in both genders at a dose of 500 mg/kg. In male rats, the testis weight significantly increased at a dose of 500 mg/kg. | [171] |
| Roelofs et al., 2015 | Mouse | | *In vitro* Leydig cells MA-10 | 48 h | 0.01–100 μM | | BPF exposure significantly increased T levels at a dose of 100 μM, P4 levels and genes (Cyp51 and 5aRed1) at a dose of 10 μM in the MA-10 cells. | [167] |
| Eladak *et al.*, 2015 | Human/ Mouse/Rat | | *In vitro* fetal testis explants | 24-72 h | 10, 100, 1000 and 10000 nM | | BPF exposure significantly reduced basal T secretion levels in mouse fetal testis explants starting at 1000 nM, and in human starting at 10000 nM. | [153] |

**Table 10.**

BPAF and reproductive outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| Feng et al., 2012 | Rat | SD | Oral gavage | 14 days | 2, 10, 50 and 200 mg/kg | Adult | In adult rats, orally to BPAF at doses from 2 to 200 mg/kg, the concentration of BPAF in testes increased in a dose-dependent manner. In addition, 14 days of exposure decreased serum T level and the expression levels of genes and proteins in T biosynthesis pathway, and increased serum LH and FSH levels in rats given a dose of 200 mg/kg. | [181] |
| Furr et al., 2014 | Rat | SD | Oral gavage | GD 14-GD 18 | 200, 300, 400,500 and 750 mg/kg | GD 18 | The prenatal exposure to BPAF (200-750 mg/kg) did not alter T secretion in dams on GD 18. | [179] |
| Shi et al., 2015 | Fish | Danio ratio | Water | PF 4h - PF 140d | 5, 25 and 125 μg/L | PF 140d | Zebrafish were exposed to BPAF at 5, 25 and 125 ug/L, from 4-hour pf to 120 pf, representing the period from embryo to adult. The increases in E2 levels were observed in both genders, while decreases in T levels were only observed in the male fishes. In offspring, increase in malformation and decrease in survival rate were observed only at maternal exposure to BPAF at 125 ug/L. | [177] |
| Li et al., 2016 | Rat | SD | Oral gavage | GD 3-GD 19 PND 3-PND 19 | 100 mg/kg | PND 23 PND 23 | Female rats were exposed to BPAF (100 mg/kg) orally during gestation or lactation. HPLC-MS/MS analysis showed that BPAF was transferred via cord blood and lactation, finally bio-accumulating in the offspring testes. Offsprings exposed to BPAF both prenatally and postnatally showed a significant increase in testis T levels and alterations in genes involved in cell differentiation and meiosis in testes. | [180] |
| Yang et al., 2014 | Fish | Danio ratio | Water | 28 days | 0.05, 0.25 and 1 mg/L | ~ PF 80d | Zebrafish exposed to BPAF at a concentration of 1 mg/L showed the acellular area in the testis with an increase in T levels in males and retardation of oocyte development in females. | [178] |
| Nakano et al., 2016 | Mouse | ICR | *In vitro* oocyte | 6, 9, 12, 15 and 18 h | 2, 20, 50 and 100 μg/ml | | BPAF exposure inhibited oocyte maturation at concentrations of 50 and 100 μg/ml and delayed the cell cycle at a dose of 2 μg/ml. Further BPAF treatment caused spindle abnormalities, activated the spindle assembly checkpoint but showed no difference in the MAD2 localization at a dose of 50 μg/ml. | [45] |
| Liang et al., 2017 | Mouse | | *In vitro* Spermatogonial cell line C18-4 | 24, 48 and 72 h | 0.1, 1, 5, 10, and 25 μM | | The BPAF exposure significantly decreased cell viability, altered nuclear morphology, increased gamma-H2AX expression level, and perturbed cytoskeleton and cell cycle progression with EC 20 ≈10 μM. Further, BPAF treatment at 25 μM induced the formation of multinucleated cells with active DNA synthesis and cells with dot-like structure. | [120] |

**Table 11.**

TBBPA and reproductive outcomes in experimental studies.

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| ECB., 2006 | Rat | SD | Oral gavage | 10 weeks premating period, 2 weeks mating period, gestation and lactation | 10, 100 and 1000 mg/kg | After mating/ weaning | In SD rats, TBBPA exposure showed no effects on organ weight and sperm quality. Serum T4 levels were decreased in males and females of the F0, and F1 generations and serum T3 levels were decreased in F0 males only at high dose groups. No change in FSH level was observed. | [189] |
| Tada et al., 2006 | Mice | ICR | Dietary exposure | GD 0-PND 27 | 0.01%, 0.1% or 1.0% in diet | PND 27 | In ICR mice receiving maternal dietary exposure through GD 0 to PND 27, no changes in testes, ovary or uterine weight were observed. | [195] |
| Kuiper, et al., 2007 | Fish | Danio ratio | Water | 30 days 47 days | 0.023-1.5 μM | Adult Offspring ph 47 d | Adult zebrafish were exposed to waterborne TBBPA for 30 days, and their offspring received TBBPA exposure up to 47 days. In F0 female fish, TBBPA exposure decreased egg production starting at 0.047 μM and increased premature oocytes at a dose of 1.5 μM. In offspring, exposure to 6 μM TBBPA resulted in embryo malformation. | [194] |
| Van der Ven, et al., 2008 | Rat | Wistar | Dietary exposure | Paternal and maternal exposure started 10 and 2 weeks before mating and ended in lactation | 3, 10, 30, 100, 300, 1,000 and 3,000 mg/kg | Adult | Maternal and paternal TBBPA exposure resulted in decreases in circulating T4 level and testes weight, increase in circulating T3 level at male offspring, and a decrease in circulating T4 in female offspring. In addition, the concentrations of TBBPA metabolites in plasma increased with increasing exposure levels. | [188] |
| Saegusa, et al., 2009 | Rat | SD | Dietary exposure | GD 10-PND 20 | 100, 1000 or 10,000 ppm | PND 77 | In SD rats receiving the prenatal and postnatal exposure to TBBPA, no changes of testes, ovaries and uterus weights were observed. Decreases in serum T3 levels were observed only at low [high?] exposure levels. | [204] |
| Zatecka, et al., 2013 | Mouse | CD1 | Drinking water | Life time | 35 μg/kg | PND 70 | In CD-1 mice, two-generation exposure to TBBPA resulted in decreases in testes weight, seminal vesicles weight and expression of the gene for the androgen receptor. Further, TBBPA exposure increased in apoptotic cells and apoptotic genes expressions in seminiferous tubules. However, no changes in sperm parameters were observed. | [191] |
| Zatecka, et al., 2014 | Mouse | C57BL/6J | Drinking water | GD 0-PND 70 | 35 μg/kg | PND 70 | C57Bl/6J mice were exposed to TBBPA during the GD 0 to PND 70. The TBBPA treatment significantly decreased protamine 1/ protamine 2 the ratio increased total protamine/DNA ratio and increased number of TUNEL positive spermatozoa. | [192] |
| Cope, et al., 2015 | Rat | SD | Oral gavage | GD 0-GD 9 | 100, 300 and 1000 mg/kg | PND 60 | In SD rats, exposure to ≥100 mg/kg TBBPA resulted in a decrease in circulating, T4 levels in rats. No changes in sperm motility, concentration, abnormal sperm percentage were observed in F0/1/2 generations. | [190] |
| Dunnick, et al., 2015 | Mouse | Wistar Han rats / | Oral gavage | 2 years | 250, 500 and 1000 mg/kg | Adult | In 2-year TBBPA oral exposure, TBBPA increased uterine epithelial tumors including adenomas, adenocarcinomas, and | [193] |

| Source | Animal | Strain | Exposure route | Time of exposure | Doses | Age at collection | Summary | Reference |
|---|---|---|---|---|---|---|---|---|
| | | B6C3F1/N | | | | | malignant mixed Mullerian tumors in rats at doses of 500 and 1000 mg/kg. In the testes of treated male rats, atrophy of the germinal epithelium and testicular interstitial cell adenomas was observed (no significance). | |
| Ogunbayo et al., 2008 | Mouse | | *In vitro* Sertoli cell line TM4 | 0-18 h | 0-60 μM | | In mouse Sertoli cells TM4, TBBPA treatment significantly increased cell death starting at a dose of 10 μM and cellular $Ca^{2+}$ levels starting at a dose of 5 μM. Further, TBBPA treatment inhibited sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPases starting at a dose of 0.4 μM and activated the Ryanodine receptor $Ca^{2+}$ channel starting at a dose of 2 μM. | [197] |
| Dankers et al., 2013 | Mouse | | *In vitro* Leydig cell line MA-10 | 24 h | 0-30 μM | | TBBPA exposure significantly increased T levels at a dose of 10 and 30 μM via multidrug resistance proteins. Further, 10 μM TBBPA exposure significantly induced the expression levels of StAR, Cyp11A1, and Cyp17 in Leydig cell line MA-10. | [196] |
| Roelofs et al., 2015 | Mouse | | *In vitro* Leydig cell line MA-10 | 48 h | 0.01–100 μM | | TBBPA exposure significantly increased T levels at a dose of 30 μM, P4 levels and gene (5aRed1) at a dose of 10 μM in the MA-10 cells. | [167] |
| Liang et al., 2017 | Mouse | | *In vitro* Spermatogonial cell line C18-4 | 24, 48 and 72 h | 0.1, 1, 5, 10, and 25 μM | | The TBBPA exposure significantly decreased cell viability, altered nuclear morphology, increased gamma-H2AX expression level, and perturbed cytoskeleton and cell cycle progression at a dose of 25 μM in spermatogonial cell line C18-4. | [120] |