Adverse Effects of Bisphenol A on Male Reproductive Function

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Contents

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1   Introduction

Infertility is one of the major health problems that affect human sociocultural life. It affects 8–15% of couples around the world, and about 50% of infertility cases are attributed to male factors (WHO 1991; Cui 2010; Hamada et al. 2011). Among the factors that cause male infertility are exposures to environmental toxicants (Akingbemi et al. 2004). Bisphenol A ([2,2-bis(4-hydroxyphenyl)propane]: BPA) is among the most prominent of toxic environmental contaminants worldwide. The original synthesis of BPA is attributed to two scientists: Dianin, who is thought to have been the first to design the molecule in 1891, and Zincke, who reportedly synthesized the molecule in 1905 (Huang et al. 2011). Since then, BPA has been widely produced and used as a common ingredient in the manufacture of plastics. Plastics are broadly integrated into today's lifestyle and make a major contribution to almost all product areas (Olea et al. 1996; Völkel et al. 2011; Hammer et al. 2012). The wide and heavy use of plastics has contributed to BPA having been spread throughout the environment.

Humans are mainly exposed to BPA through food ingestion (Yamada et al. 2002), and increasing evidence supports its association with impairment of male reproductive function, as well as other health problems and diseases; such diseases include diabetes, obesity, cardiovascular diseases, and cancer (Li et al. 2010a, 2011; Salian et al. 2011; Batista et al. 2012; Shankar and Teppala 2012; Lee et al. 2012; Wang et al. 2012a). BPA acts primarily by mimicking the effect of estrogen hormones, modifying DNA methylation, and modulating enzyme activities in utero and in vivo, resulting in metabolic diseases, spermatogenesis defects, and/or infertility in males. The deleterious effect of BPA on male reproductive function may occur during embryonic, pubertal, and/or adult life. The fact that BPA is a causal agent in such effects is supported by its repeated detection in human biological samples (Sun et al. 2004; He et al. 2009a; Li et al. 2010a).

In this review, we address the topic of BPA effects on male reproductive function and emphasize its effects on testicular steroidogenesis, spermatogenesis, and sperm function.

2   Sources and Routes of Bisphenol A Exposure

BPA is a man-made industrial chemical that is used as a component of plastics. The USA, Japan, and Europe are the areas in which the majority of BPA is produced. BPA's annual production capacity now exceeds six billion pounds, and this high production level is sustained and encouraged by the widespread use of plastics to manufacture food containers, water bottles, medical devices, and other objects that must be made of materials that are both flexible and durable. More than 100 t of the annual BPA production volume is released into the atmosphere (Vandenberg et al. 2009; Cao et al. 2011). This volume of release has made BPA environmentally ubiquitous; BPA residues are found in air, drinking water, lakes, the seas, sewage sludge, soil, house

dust, foodstuffs, paper currency, among other objects and media (Ignatius et al. 2010; Liao and Kannan 2011; Geens et al. 2012; Hammer et al. 2012; Liao et al. 2012; Molina-García et al. 2012; Rudel et al. 2011; Wang et al. 2012b; Rocha et al. 2013).

BPA enters the human body mainly via consuming contaminated food and drinking water, although exposure via environmental (from polluted air and water), domestic (household products, cosmetics), medical (from contaminated equipment and devices), and occupational sources (inhalation, dermal contact, and ingestion during manufacturing processes or industrial use) also occurs (Toppari et al. 1996; Demierre et al. 2012; Cho et al. 2012). Intake by the oral route may be enhanced when certain food preparation practices are used, such as wrapping food in plastic bags prior to thermal treatment or cooking—processes that enhance leakage of BPA from the bag into the food. BPA is known to be used in the manufacture of microwave oven ware, from which it may be released to food (EFSA 2006; Geens et al. 2012). Oral exposure to BPA may also be enhanced from the presence in the mouth of dental composites (Olea et al. 1996; Doerge et al. 2012), or from using epoxy resin-based food cans, water bottles, or plastic baby bottles (Cao et al. 2011; Kang et al. 2011; Völkel et al. 2011; Cho et al. 2012).

Absorption of BPA may also be indirect, as occurs when the fetus absorbs the chemical from maternal blood plasma (after maternal exposure). Indeed, BPA is transported across the human placenta (Mørck et al. 2010), and BPA's effect on the fetus may be exacerbated, because the production of toxic effects is inversely correlated with age (Kline and Ruhter 2012). Transdermal BPA exposure and inhalation are of greater concern because such exposure routes avoid the first-pass metabolic effect that occurs with oral intake (Welshons et al. 2006; Mørck et al. 2010; Demierre et al. 2012).

Occupational exposure to BPA occurs in those countries where the compound is manufactured. Although most intake occurs from ingestion, people who are engaged in the manufacturing or use of BPA (or related chemicals) can easily absorb it through the skin, or take it up via inhalation (He et al. 2009b; Kaddar et al. 2009; Geens et al. 2012).

Absorption or uptake of BPA into the human body is ascertained by analyzing for the presence of the chemical or its metabolites in biological fluids such as blood, breast milk, urine, etc. (Zhang et al. 2011; Geens et al. 2012). For instance, a study conducted in a reference human population of the United States showed the presence of BPA in ≥95% of urinary samples collected from urban and rural residents (Calafat et al. 2005). Similarly, BPA was detected in spot samples of urine collected from both urban and rural girls in Egypt (Nahar et al. 2012). Urinary levels of BPA, detected in children and adolescents, were reported to be higher than in adults (Calafat et al. 2009; Zhang et al. 2011).

High levels of BPA have been measured in human placental tissue, in maternal urine, and in maternal and fetal plasma. Maternal BPA levels were positively correlated with BPA concentrations detected in the fetal umbilical cord (Schönfelder et al. 2002; Lee et al. 2008; Callan et al. 2012; Ünüvar and Büyükgebiz 2012). In utero exposure appears to be more harmful in humans, since BPA accumulates in amniotic fluid of pregnant women (Schönfelder et al. 2002; Sun et al. 2004).

BPA concentrations in maternal plasma were found to be fivefold lower than levels measured in amniotic fluid (Ikezuki et al. 2002), indicating that the fetus is more highly exposed than is the mother. These observations suggest that BPA exposure is higher during fetal life, and diminishes as age increases.

Urinary BPA levels detected in workers were also consistent with degree of occupational exposure to the chemical. He et al. (2009b) reported high levels of BPA in urine and blood of people working in epoxy-resin and BPA manufacturing factories in China.

Several researchers have noted that BPA produces estrogenic and antiandronenic activity, thus emphasizing the importance of its potential harmful effects on human health upon entry into the organism (Olea et al. 1996; Lee et al. 2003; Wetherill et al. 2002, 2007; Alonso-Magdalena et al. 2012). In males, such endocrine disruption may also affect the regulation of the hypothalamic–pituitary–gonadal axis, resulting in reproductive disorders and infertility.

3 Effects of In Utero Exposure to Bisphenol A on Male Reproductive Function

The harmful effects of BPA on male reproductive function, following in utero exposure, have been widely studied in laboratory animals such as rodents. vom Saal et al. (1998) studied prenatal BPA exposure on male mice and found increased size for preputial glands and reduced epididymides size, as well as decreased efficiency of sperm production (daily sperm production). A decrease in fertility, daily sperm production, sperm count and motility in BPA-exposed male offspring during adulthood was also reported (Salian et al. 2009a, 2011). Oral administration of 2–20 ng BPA/g body weight (bwt) to female mice on gestational day (GD) 11–17 resulted in a significant decrease of relative testis weight of male pups at 8 and 12 weeks of age (Kawai et al. 2003). When female mice were concomitantly administered BPA and di(2-ethylhexyl) phthalate (another plastic component), the expression level of Anti-Müllerian hormone (AMH) and Steroidogenic Acute Regulatory Protein (StAR) was reduced in the testes of the exposed male pups, and the pups' testicular size was reduced. Importantly, the adverse effects were persistent in the sexually mature pups at postnatal day (PND) 42, and were consistent with significant reductions of epididymal sperm counts (Xi et al. 2012). Analysis of RNA samples from the hypothalamus, testes, and epididymides of rat fetuses, exposed to BPA in utero from GD 11–20, or GD 6–21, revealed modification of the gene expression profile, including hypothalamic estrogen receptors (ERs), testicular luteinizing hormone receptor (LHR), cholesterol side chain cleavage enzyme (Cyp11a1), and StAR (Naciff et al. 2005; Cao et al. 2013). BPA exposure affects hypothalamic development in the embryo. This was evidenced by enhanced dendritic and synaptic development in cultured hypothalamic cells from fetal rats, as manifested by increases in the area of dot-like staining of synapsin I and MAP2-positive area (Iwakura et al. 2010). Treatment of Ishikawa cell cultures with BPA also modulated the expression of the INSIG1 and FOS genes, which are implicated in regulating transcription and steroid metabolic processes, respectively (Naciff et al. 2010).

In pregnant female rats exposed to BPA from GD 1 throughout parturition, serum testosterone levels were decreased in male fetuses and pups (Tanaka et al. 2006). Exposures of the dams from GD 12 to PND 21 also resulted in decreased testosterone levels in the testicular interstitial fluid of male pups in adulthood (Akingbemi et al. 2004). The testosterone inhibition is probably induced by the BPA-suppressive effect on testicular Leydig cell steroidogenic proteins. In fact, BPA inhibits expression of the StAR protein, and the 17-β-hydroxysteroid dehydrogenase enzyme (17β-HSD) (Horstman et al. 2012; Nanjappa et al. 2012). Protein expression of the LHR is also compromised following BPA exposure, and may lead to decreasing androgen secretion by testicular Leydig cells (Nanjappa et al. 2012). The testosterone concentration increased in 9-week-old male pups exposed to BPA in utero and through lactation (Watanabe et al. 2003), and this could be attributed to in utero BPA-induced proliferative activity (mitogenic effect) on testosterone-producing Leydig cells (Nanjappa et al. 2012). In addition to modulating the Leydig cells, BPA also induced down-regulation of several genes associated with Sertoli cell function (Msi1h, Ncoa1, Nid1, Hspb2, and Gata6) in 6-week-old male mice after prenatal exposure (Tainaka et al. 2012), thereby disrupting the blood–testis barrier (BTB) and impairing spermatogenesis (Cheng et al. 2011; Su et al. 2011). Perturbation of BTB (reduction in the expression of Connexin 43 and increases in the expression of N-cadherin and Zona Occludin-1) and spermatogenesis were also observed in 45/90-day-old rats neonatally exposed to BPA (≥400 µg/kg bwt/day, during PND 1–5) (Salian et al. 2009b).

The biological effect of thyroid hormones that act on male reproductive function by modulating germ cell development (Krassas and Pontikides 2004) can also be compromised by BPA exposure during fetal life. BPA affects the expression of thyroid specific genes that have been implicated in thyroid development, as well as control of gene expression in rat thyroid cells and zebra fish embryos in vitro (Gentilcore et al. 2013). BPA antagonizes triiodothyronine (T3) action at the transcriptional level in human TSA201 cells, through displacement of T3 from the hormone receptor (TSH) and recruitment of a transcriptional repressor (a T3- negatively regulated TSHalpha promoter), resulting in gene suppression (Moriyama et al. 2002). A BPA antithyroid effect in rats was also observed in vivo. In fact, feeding pregnant Sprague-Dawley rats a BPA-containing diet during pregnancy and lactation caused an increase in serum total thyroxin in male pups on PND 15, with up-regulation of the expression of the thyroid hormone-responsive gene RC3/neurogranin in the dentate gyrus. This suggests a thyroid-hormone antagonist effect of BPA on the beta-thyroid receptor, which mediates the negative feedback effect of the hormone on the pituitary gland (Zoeller et al. 2005). In utero exposure of CD-1 pregnant mice to BPA (50 µg BPA/kg/day, during GD 16–18) also resulted in increasing the anogenital distance (AGD: distance from the center of the anus to the anterior base of the penis, an androgen-dependent variable, used as a sensitive marker of androgenic and antiandrogenic effects of in utero chemical exposure) in male pups (Gupta 2000; Foster and McIntyre 2002). This contrasted with studies of Talsness et al. (2000), who reported shortening of the AGD, following prenatal BPA exposure. Notwithstanding, these two studies indicated that BPA has the ability to modulate AGD during prenatal life.

These in utero effects are likely to also occur in BPA exposed human males. Such evidence has been derived from a recent epidemiological study conducted by Braun et al. (2012), who detected BPA in urine samples of pregnant women, suggesting gestational exposure. Moreover, Miao et al. (2011a) demonstrated an association between parental occupational BPA exposure during pregnancy and shortened AGD in male offspring. The latter association was stronger for maternal exposure, and the authors found a dose–response relationship between increased BPA levels in pregnancy and greater magnitude of shortened AGD. In Table 1, we summarize data from selected studies that addressed BPA's male reproductive effects.

Because of its accumulation in amniotic fluid of pregnant women, BPA exposure appears to be more harmful in utero (Schönfelder et al. 2002; Sun et al. 2004), a critical hormonally dependent step in development of the individual. BPA acts as an endocrine disruptor (estrogenic, antiandrogenic, or antithyroid). It has been shown to reduce total blood T4 levels in pregnant women, with associated decreased TSH in their respective male neonates (Olea et al. 1996; Moriyama et al. 2002; Lee et al. 2003; Zoeller et al. 2005; Wetherill et al. 2007; Chevrier et al. 2013). BPA binds to ERs, inhibits androgen-induced androgen receptor (AR) transcriptional activity and androgen (dihydroxytestosterone) binding to AR (Lee et al. 2003; Alonso-Magdalena et al. 2012). However, recent findings support an additional BPA action mechanism, through a non-genomic pathway, initiated at membrane receptors, including classical ERs and/or G protein-coupled receptor 30 (reviewed by Iwakura et al. 2010). The estrogenicity of BPA can also prevent AMH action on the Müllerian ducts in the male (Pryor et al. 2000), leading to the feminization of male fetus (Hutson et al. 1994). Such feminization may be triggered by up-regulation of genes required for ovary development (*Foxl2* and *Wnt4*), with concomitant repression of genes responsible for testis development (*Sox9* and *Fgf9*) in the embryo, as reported elsewhere (Aoki and Takada 2012). By disrupting hormone levels or receptor activity, the detrimental effect of BPA may be to alter male reproductive-organ development during fetal life (Miao et al. 2011a, b). Moreover, the BPA effect may be more pronounced and irreversible during this development stage, unlike in adults, who have a matured and functional sex-specific physiology, in which the deleterious effect is potentially reversible once exposure ends (Kline and Ruhter 2012).

4   Effects of Bisphenol A on Spermatogenesis and Sperm Function Following Postnatal Exposure

4.1   Effects on the Hypothalamic–Pituitary–Testicular Axis

The spermatogenesis process in mammals is coordinated by the hypothalamic–pituitary–testicular axis and the thyroid gland (Zoeller et al. 2005; Moriyama et al. 2002). Dysfunction of the axis, triggered by endocrine disruptors such as BPA, may result in arrest or alteration of spermatogenesis (Table 1).

Table 1 Investigations that have addressed the effects of BPA on male reproductive function

Experimental model	BPA dose or concentration	Major findings	Reference(s)
In vitro (rat and human testis microsomes)	10^{-8}–10^{-4} M, 3 h incubation	Decrease of 3β-HSD, and 17β-HSD activities	Ye et al. (2011)
In vitro exposure (Leydig cells from adult rats)	0.01 nM, 18 h incubation	Inhibition of CYP19 expression, and estradiol release	Akingbemi et al. (2004)
In vitro exposure (human spermatozoa)	1 µM, 2 h incubation	Absence of effect on calcium fluxes, and acrosome reaction	Luconi et al. (2001)
Ex vivo (Leydig cells from BPA-treated male rats)	2.4 µg/kg/day, PND 21–35	Inhibition of testosterone release	Akingbemi et al. (2004)
In utero exposure (Male rats)	2 and 20 µg/kg dam/day, GD 11–17	Enlargement of the prostate	Nagel et al. (1997)
In utero exposure (Male mice)	2–20 ng/g dam, GD 11–17	Decrease of testis weight	Kawai et al. (2003)
In utero exposure (CD-1 mice)	50 µg/kg dam/day, GD16–18	Enlargement of the prostate, increase of AGD, and reduction of epididymal weight	Gupta (2000)
In utero (male rat fetuses)	0.002–400 mg/kg dam/day, GD11–20	Modulation of LHR, Cyp11a1, and StAR	Naciff et al. (2005)
In utero (male rat fetuses), and postnatal exposures	2.4 µg/kg dam/day, GD12–PND35; 20 and 200 µg/kg dam/day, GD 1–PND 0	Decrease in serum testosterone	Akingbemi et al. (2004); Tanaka et al. (2006)
In utero and postnatal exposures	1.2–2.4 µg/kg dam/day, G6–PND21	Spermatogenesis inhibition, reduction of fertility of male offspring	Salian et al. (2009a)
In vivo (male mice and rats) and in utero exposures	6.25–125 ng/mouse; 12.5–500 ng/rat; 1.2–2.4 µg/kg/day dam from GD 6–21	Disruption of BTB	Toyama and Yuasa (2004); Salian et al. (2009b)
In vivo (adult male rats)	1 mg/rat, 14 days 10 mg/kg/day (14 days) 0.005–500 µg/kg/day, 45 days	Decrease in serum testosterone, and testicular antioxidant enzymes	Tohei et al. (2001); El-Beshbishy et al. (2012); D'Cruz et al. (2012a)
In vivo (adult male rats)	1 mg/rat/day, 14 days	Increase in plasma LH	Tohei et al. (2001)
In vivo (3-week-old male rats)	200 mg/kg/day, 5 days/week, 6 weeks	Decrease in serum LH	Nakamura et al. (2010)
	2.1 µg/kg/day, 70 days (PND 21–90)	Decrease in seminal vesicles size	Akingbemi et al. (2004)

Table 1 (continued)

Experimental model	BPA dose or concentration	Major findings	Reference(s)
In vivo (young mice)	50 μg/mL (in drinking water), 8 weeks	Decrease in serum testosterone	Takao et al. (1999)
In vivo (male mice)	10–40 mg/kg/day, 2 weeks	Induction of DNA standard breaks in germ cells, decrease of sperm count and motility	Dobrzyńska and Radzikowska (2013)
In vivo (adult male rats)	20 μg–2 mg/kg/day, 6 days	Decrease in sperm production	Sakaue et al. (2001)
In vivo (male rats)	0.2–20 μg BPA/kg/day, 45–60 days	Increase of ventral prostate weight, decrease of epididymal and testicular weights	Chitra et al. (2003a, b)
In vivo (male chicks)	2 μg–200 mg/kg/day, 3–23 weeks	Decreased testis size	Furuya et al. (2006)
In vivo (brown trout, prespawning and spawning exposures, in aquarium)	1.75–2.40 μg/L, late prespawning and spawning periods	Decrease of semen quality	Lahnsteiner et al. (2005)
In vivo (male rats, oral; and male goldfish, in aquarium)	200 mg/kg, 10 days; 0.2 and 20 μg/L, 20-90 days	Alteration of sperm motility and velocity, increase of sperm DNA damage	De Flora et al. (2011); Hatef et al. (2012a, b)
In vivo (adult male guppies, in aquarium)	274–549 μg/L, 21 days	Decline in total sperm counts	Haubruge et al. (2000)
Male workers (humans) exposed to high levels of BPA at work	ND (exposure ascertained by higher BPA levels in blood, urine, or personal air)	Erectile and ejaculatory difficulties, reduction of sexual desire and sperm morphology and density	Xiao et al. (2009); Li et al. (2010b)
Men occupationally exposed to BPA diglycidyl ether	ND (exposure ascertained by higher urinary BPA levels)	Decrease of plasma FSH	Hanaoka et al. (2002)

Available data relating to the deleterious effect of BPA on male reproductive function were gathered and tabularly summarized from studies on rodents (rats and mice). Fish and chicks have also been included as experimental (animal) models; results gathered for all examined species support the view that BPA causes an endocrine-disrupting effect, i.e., decreased testosterone levels, altered sperm quality, etc. Moreover, altered sperm quality effects were confirmed in men who were occupationally exposed to BPA

3β-HSD 3-β-hydroxysteroid dehydrogenase, *17β-HSD* 17-β-hydroxysteroid dehydrogenase enzyme, *AGD* anogenital distance, *BTB* blood–testis barrier, *CYP19* aromatase, *Cyp11a* Cytochrome P450, subfamily 11A, *GD* gestational day, *FSH* follicular-stimulating hormone, *LHR* luteinizing hormone receptor, *ND* not determined, *PND* postnatal day, *StAR* steroidogenic acute regulatory protein

One adverse effect attributable to BPA is atrophy of the testes, as reported to have occurred in adult male Swiss mice treated with BPA glycerolate dimethacrylate (BISGMA, 100 μg/kg/day) for 60 days (Al-Hiyasat and Darmani 2006). White Leghorn male chicks treated with BPA (2 μg-200 m/kg/day) from 2 to 25 weeks of age also showed decreased testes size, and growth inhibition of androgen-dependent organs such as comb and wattle. The chicks receiving a higher BPA dose (≥20 μg/kg) showed inhibition of seminiferous tubuli development and spermatogenesis (Furuya et al. 2006), conditions more likely attributed to inhibition of testosterone synthesis. BPA's modulatory effect on testosterone synthesis has been reported in several studies (Table 2).

Oral administration of BPA to young mice for 4–8 weeks resulted in a dramatic decrease of plasma free-testosterone levels (Takao et al. 1999). BPA exposure also decreased the serum testosterone level in adult male rats, and suppressed human chorionic gonadotropin (hCG)-induced testosterone release by the testis (Tohei et al. 2001; El-Beshbishy et al. 2012; D'Cruz et al. 2012a). This antiandrogenic activity results from the BPA inhibitory effect on testicular Leydig cell StAR protein and steroidogenic enzymes, such as 3-β-hydroxysteroid dehydrogenase (3β-HSD), and 17β-HSD (D'Cruz et al. 2012a; Hatef et al. 2012a).

Decreased activity of 3β-HSD and 17β-HSD, following BPA exposure, was also observed in both rat and human testis microsomes, together with inhibition of 17α-hydroxylase/17,20-lyase (CYP17A1) (Ye et al. 2011). Similarly, Akingbemi et al. (2004) reported that BPA inhibited Leydig cell CYP17A1. The inhibitory effect of BPA on CYP17 is likely a competitive-type inhibition, as demonstrated in *Escherichia coli* that expressed steroidogenic CYP17 (Niwa et al. 2001). Aromatase (CYP19) catalyzes conversion of androgens (testosterone) to estrogens (Carreau and Hess 2010; Carreau et al. 2010), and BPA exposure increased its expression in testes of male chicks, or in rat testicular Leydig cells (Furuya et al. 2006; Kim et al. 2010). This induction of testicular aromatase by BPA may thus contribute to decreased serum levels of androgens. However, Akingbemi et al. (2004) reported that postnatal BPA exposure of rats resulted in inhibited Leydig cell CYP19 expression and decreased serum 17β-estradiol levels. The latter authors exposed Long-Evans rats to BPA during perinatal period (PND 21–35) and noticed that serum estradiol was inhibited in the animals treated with the lower doses of BPA (0.2 μg–100 mg/kg bwt/day). The inhibitory effect was not observed at the highest dose (100 mg BPA/kg bwt/day), suggesting a dose-dependent effect of BPA on aromatase.

The fact that BPA causes an antisteroidogenic effect is further sustained by its ability to inhibit cAMP formation by preventing adenylate cyclase coupling to the luteinizing hormone (LH) receptor in vitro in mLTC-1 Leydig tumor cells (Nikula et al. 1999). Secretion of LH was also compromised in male animals exposed to BPA (Nakamura et al. 2010). The suppressed serum LH was associated with decreased LHbeta, decreased hypothalamic KiSS1 mRNA levels, and increased pituitary and testicular estrogen receptor (ER) mRNA levels (Akingbemi et al. 2004; Furuya et al. 2006; Navarro et al. 2009; Bai et al. 2011; Hatef et al. 2012a). An increased excretion (vs. matched controls) of BPA and decreased plasma

Table 2 Selected data relating to BPA effects on androgen/estrogen synthesis and action

Experimental model	Doses of BPA	Effect (estrogenic/antiandrogenic)	Mechanism of action/endpoint	Reference(s)
Perinatal exposure (male rat fetuses and pups)	2.4 µg/kg dam/day, GD12–PND35	Antiandrogenic	Decrease of testosterone levels	Akingbemi et al. (2004); Tanaka et al. (2006)
Perinatal exposure, male rat fetuses and pups	400 mg/kg dam/day GD6–PND20	Androgenic	Increase of testosterone levels Induction of AR in Leydig cells	Watanabe et al. (2003); Nanjappa et al. (2012)
In utero, and ex-vivo (Leydig cell cultures, from perinatally BPA-exposed rats) exposures	2.5 and 25 µg/kg dam/day, GD12–PND21; 10 µg/ kg dam/day, GD11–20	Antiandrogenic/estrogenic	Inhibition of testosterone release, LH receptor, StAR, and 17β-HSD expression in Leydig cells Induction of ERs (ER1) in Leydig cells	Horstman et al. (2012); Nanjappa et al. (2012)
In utero exposure (CD-1 male mice fetuses)	50 µg BPA/kg dam/d, GD16–18	Antiandrogenic	Increase of AGD and prostate, reduction of epididymal weight	Gupta (2000)
Perinatal exposure (male rat pups)	1.2–2.4 µg/kg dam from GD6–PND21	Antiandrogenic	Decrease in testicular steroid receptors	Salian et al. (2009a)
In vivo exposure (male chicks)	2 µg–200 mg/kg/day, from 2 to 25 weeks of age	Antiandrogenic	Decrease of testis size, inhibition of spermatogenesis	Furuya et al. (2006)
In vivo exposure (male mice)	50 µg/mL (in drinking water), 8 weeks	Antiandrogenic	Decrease of plasma testosterone	Takao et al. (1999)
In vivo exposure (adult male rats)	1 mg/rat (≈3 mg/kg/day), 14 days; 10 mg/kg/day, 14 days	Antiandrogenic	Decrease of serum testosterone	Tohei et al. (2001); El-Beshbishy et al. (2012)
In vivo exposure (adult male rats)	0.005–500 µg/kg/day, 45 days	Antiandrogenic	Decrease in testicular activities of 3β-HSD, 17β-HSD, and serum testosterone	D'Cruz et al. (2012a)

In vivo exposure (male goldfish)	0.2 and 20 µg/L, 30–90 days	Antiandrogenic and estrogenic	Reduction of StAR, increase of testicular ERβ2 mRNA transcript at 0.2 µg BPA/L; Increase of AR, ERβ1 and CYP19 mRNA transcript in testis at 20 µg BPA/L	Hatef et al. (2012a)
In vitro (rat Leydig cells, rat and human testis microsomes)	0.01 nM; 10^{-8}–10^{-4} M	Antiandrogenic	Decreased activity of 3β-HSD, and 17β-HSD	Akingbemi et al. (2004); Ye et al. (2011)
In vivo (male chick), and in vitro (rat Leydig cells)	2 µg/kg–200 mg/kg; 0.1–10 nM	Estrogenic	Increases of CYP19 activity	Furuya et al. (2006); Kim et al. (2010)
In vivo (pubertal and adult rats)	≥ 0.2 µg BPA/kg/day, 45–60 days	Antiandrogenic	Decreased epididymal and testicular weights; Increased ventral prostate weight	Chitra et al. (2003a, b)

17β-HSD 17-β-hydroxysteroid dehydrogenase, *3β-HSD* 3-β-hydroxysteroid dehydrogenase, *AGD* anogenital distance, *AR* androgen receptor, *CYP19* aromatase, *ERs* estrogen receptors (e.g., ERβ2, ERβ1), *GD* gestational day, *LHR* LH receptor, *PND* postnatal day, *StAR* steroidogenic acute regulatory protein

follicle-stimulating hormone (FSH) was reported in men occupationally exposed to epoxy-resin hardening agents containing BPA diglycidyl ether (Hanaoka et al. 2002), suggesting inhibition of FSH release by the chemical (Salian et al. 2011). In contrast, Tohei et al. (2001) reported increased plasma LH, following treatment of adult male rats of the Wistar-Imamichi strain (300–350 g) with BPA (1 mg/rat/day for 2 weeks). The LH stimulatory effect was associated with decreased plasma concentrations of testosterone and prolactin, as well as testicular contents of inhibin, suggesting that BPA directly inhibits testicular functions. The increased level of plasma LH was probably due to a reduction in the negative feedback regulation of the hypothalamic–pituitary axis by testosterone. Discrepancies in modulation of LH secretion by BPA (stimulation, or inhibition) as demonstrated by Tohei et al. (2001) and Nakamura et al. (2010), emphasize that the BPA endocrine-disrupting effect may be affected by the age of the animal at the onset of exposure.

Inhibin is synthesized in adult rat testes by Sertoli cells. Any reduction of inhibin's concentration in plasma, or in the testis (Tohei et al. 2001), therefore, suggests a dysfunction of the Sertoli cells. BPA-induced apoptosis of rat Sertoli cell was reported by Iida et al. (2003), and may result from an induction of caspase-3 by BPA (Mørck et al. 2010). BPA also promotes contact between harmful substances and developing sperm cells, by inducing inter-Sertoli cell BTB impairment (Toyama and Yuasa 2004; Salian et al. 2009b; Cheng et al. 2011). Sertoli cell function is pivotal in spermatogenesis, because it coordinates the differentiation of spermatogonia to mature spermatozoa, under stimulation of the FSH. Modulation of the Sertoli cells by BPA, directly or indirectly via inhibition of FSH synthesis (Hanaoka et al. 2002), may impair reproductive function in exposed males.

4.2 Effects of Bisphenol A on Spermatogenesis

The antiandrogenic and estrogenic effects of BPA that have been described in male goldfish (*Carassius auratus*) were associated with impairment of their spermatogenesis, as illustrated by the altered sperm parameters that were observed (viz., reduction in total sperm number, volume, density, motility, and velocity) (Hatef et al. 2012a, b). Lower semen quality was also observed in brown trout exposed to 1.75–2.40 µg/L BPA during the late prespawning and spawning periods (Lahnsteiner et al. 2005). Similarly, Haubruge et al. (2000) demonstrated declines in total sperm counts in adult male guppies exposed to BPA (274–549 µg/L) for 21 days. Such adverse effects of BPA on fish spermatogenesis have been documented to occur in rodents following the postnatal and pubertal periods, and in adulthood.

In mice, BPA induced the formation of morphologically multinucleated giant cells in testicular seminiferous tubules, having greater than three nuclei each (Takao et al. 1999). Similarly, a decrease of sperm count and motility was observed, and an increase of sperm morphological abnormalities, following 2 weeks of BPA administration (10–40 mg/kg bwt) (Dobrzyńska and Radzikowska 2013). The latter sperm parameters were also affected by a BPA derivative, BPA glycerolate dimethacrylate;

this derivative induced decreased male mouse fertility (Al-Hiyasat and Darmani 2006). Administration of BPA (≥20 µg/kg bwt/day) to adult rats for 6 days decreased daily sperm production (Sakaue et al. 2001). Similarly, Chitra et al. (2003a) reported a reduction in epididymal sperm motility in adult rats exposed to BPA for 60 days.

The antispermatogenic effect of BPA demonstrated in experimental animals has been confirmed by several epidemiological studies conducted among groups of BPA-exposed human males. Examples include a study carried out in China in 2008, in which it was revealed that male factory workers exposed to high levels of BPA at work experienced a sexual dysfunction, characterized by reduced sexual desire, and greater erectile and ejaculatory difficulties (Li et al. 2010b). During a cross-sectional pilot study, Xiao et al. (2009) analyzed blood BPA and semen quantity in workers exposed to BPA, and compared results to a control group. The sperm density of exposed workers was significantly lower than that of the control group, which had a lower blood BPA concentration. Furthermore, there was a negative correlation between blood BPA concentration and the percentage of normal sperm, indicating the negative influence of BPA on the semen quality.

Meeker et al. (2010) found a positive association, though not statistically significant, between BPA exposure (urinary BPA concentration) and altered sperm parameters (viz., decreased sperm count, altered morphology and motility, and increased sperm DNA damage) among infertile men. In a study carried out in fertile men, the correlation of urinary BPA concentration with semen quality was suggestive of an inverse association with sperm count and sperm motility (Mendiola et al. 2010). The urinary BPA concentration of the subjects was inversely associated with the free androgen index (FAI) and the FAI/LH ratio, and positively correlated to sex hormone-binding globulin (SHBG), indicating a deregulation of spermatogenesis. Similarly, Wang et al. (2012c) reported an association between higher urinary BPA concentrations and clinically abnormal thyroid hormones (elevated serum free T3 levels) that also influence spermatogenesis.

Although a three-generation reproductive toxicity study of BPA exposure in CD Sprague-Dawley rats showed no treatment-related effects from BPA exposure on reproductive organs/parameters (Tyl et al. 2002), other adverse effects appeared to be consistent with those caused by BPA in previous studies. Furthermore, Tyl et al. (2002) investigated physiological parameters, but did not assess biochemical changes. Other authors have studied BPA and have reported that it caused various effects, including genotoxicity and clastogenicity in blood cells (Ulutaş et al. 2010; Dobrzyńska and Radzikowska 2013; Tiwari et al. 2012), increased susceptibility to chemically induced mammary carcinogenesis (Jenkins et al. 2012), and induced meiotic aneuploidy in oocytes (Hunt et al. 2003), suggesting possible modification of the DNA in male germ cells that may be transmitted to the next generation (Salian et al. 2011).

Further evidence that BPA causes adverse effects is provided by the results of an in vitro binding assay involving proteins that transport sex hormones (Déchaud et al. 1999). BPA is a xenoestrogen that binds to SHBG (a steroid transporter in human plasma), with a reversible and competitive binding activity for both testosterone and estradiol, and produces a dose-dependent increase in concentrations of

hSHBG-unbound testosterone and/or estradiol. BPA may thus displace endogenous sex steroid hormones from hSHBG binding sites and disrupt the androgen-to-estrogen balance that is required for normal spermatogenesis (Déchaud et al. 1999; Carreau and Hess 2010).

4.3 Effects of Bisphenol A on the Testicular and Epididymal Antioxidant System

Another important mechanism by which environmental toxicants exert their adverse effects on male reproductive function is to disturb the pro-oxidant–antioxidant balance of the testis, resulting in impairment of testicular function (Mathur et al. 2008). Testicular function is associated with production of reactive oxygen species (ROS) that are regulated by an antioxidant system, under normal physiologic conditions. Exposure to environmental toxicants such as BPA aggravates the production of ROS, leading to testicular oxidative stress (see Fig. 1). El-Beshbishy et al. (2012), orally administered BPA to male rats at a dose of 10 mg/kg bwt for 14 days, and observed a decrease of testicular antioxidant enzymes such as glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase. The levels of hydrogen peroxide (H_2O_2) and lipid peroxidation were also increased in testes and spermatozoa of BPA-treated animals. In another study, testicular antioxidant enzymes were impaired by a very low-dose (viz., 0.005 mg/kg bwt/day) of BPA following 45 days of exposure (De Flora et al. 2011; D'Cruz et al. 2012a, b). BPA also decreased antioxidant enzyme activities and induced lipid peroxidation in both epididymides and sperm cells (Chitra et al. 2003a) (Fig. 1). The latter antioxidant enzymes were negatively affected in liver (Bindhumol et al. 2003), the organ that synthesizes steroid transport proteins such as hSHBG (Pugeat et al. 2010).

BPA acts to significantly disturb the pro-oxidant–antioxidant balance; therefore, reinforcing the ROS scavenging activity in the reproductive organs may represent a promising strategy to mitigate the BPA-related disturbances. To illustrate, in a recent study, Fang et al. (2013) reported that adolescent male mice, whose diet was supplemented with vitamin E during BPA exposure, showed an enhanced antioxidant response (i.e., increased SOD activity), and vitamin E protected against the reproductive inhibition normally caused by BPA.

4.4 Effects of Bisphenol A on Sperm Function

Whether BPA directly affects spermatozoa is still unclear. Luconi et al. (2001) incubated human spermatozoa in the presence of 1 μM BPA, and the results revealed no significant modification in calcium influxes and acrosome reaction in the spermatozoa. Similarly, the DNA integrity of sperm cells, as assessed using the Comet and TUNEL assays, and redox activity were not affected by BPA treatment in vitro
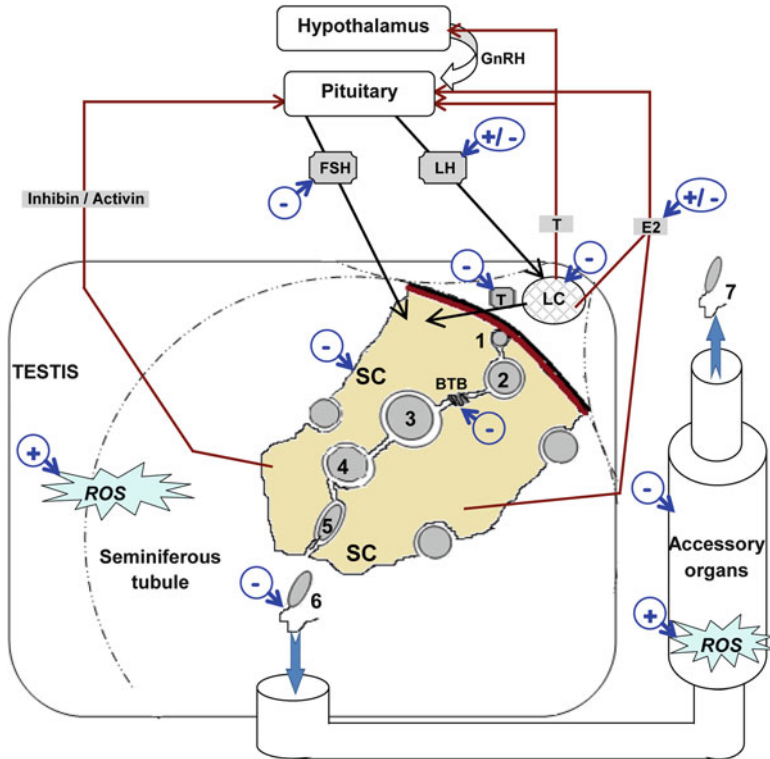
Fig. 1 A schematic diagram showing the main effects and action sites of BPA on male reproductive function: This schematic drawing depicts the hypothalamic–pituitary–testicular axis, and accessory organs. It also summarizes the spermatogenesis and sperm maturation processes. The main action sites where BPA modulates male reproductive function are indicated in the chart. The positive and negative signs indicate the following: (−): BPA disrupts cell function, reduces the weight of accessory organs, or inhibits hormone levels; (+): BPA induces increased hormone levels or reactive oxygen species (ROS), or stimulates enlargement of the prostate; (+/−): BPA exposure results in either induction (+) or inhibition (−) of hormone production. The numbers 1 to 7 refer to germ cells, at different developmental/maturation stages, viz. 1: spermatogonium; 2: preleptotene spermatocyte; 3: pachytene spermatocyte; 4: round spermatid; 5: elongated spermatid; 6 and 7: spermatozoa, before and after capacitation, respectively. Abbreviations: *BTB* blood–testis barrier, *E2* estradiol, *LC* Leydig cell, *FSH* follicle-stimulating hormone, *GnRH* gonadotropin-releasing hormone, *SC* Sertoli cell, *T* testosterone

(Bennetts et al. 2008). This suggests that the adverse effects on male reproductive function caused by BPA are mediated in vivo by other mechanisms, such as alteration of the hypothalamic–pituitary–gonadal axis and thyroid function (Akingbemi et al. 2004; Zoeller et al. 2005). Other examples of the effects caused by in vivo BPA exposure include altered sperm motility and velocity in goldfish (i.e., following 20–90 days exposure to 0.2 and 20 μg BPA/L) (Hatef et al. 2012a, b), and enhanced fragility of spermatozoa (i.e., as revealed by DNA fragmentation or sperm chromatin dispersion) in rats, following 10 days of administration of 200 mg BPA/kg bwt

(De Flora et al. 2011). Meeker et al. (2010) also studied human male partners of subfertile couples seeking treatment from the Vincent Andrology Lab at Massachusetts General Hospital, and observed increased DNA damage in sperm, and reduced semen quality that were associated with BPA exposure (Fig. 1).

5 Effects of Bisphenol A on Accessory Reproductive Organs

Secretions of male reproductive accessory organs have been implicated in the maturation, motility, and vitality of spermatozoa in the female tract. These organs represent potential targets for antifertility compounds, such as BPA. When female rats were orally dosed to 2 and 20 µg BPA/kg bwt/day on GD 11–17, their male offspring showed enlargement of the prostate in adulthood (Nagel et al. 1997). The latter effect was also reported by Gupta (2000) in CD-1 mice, whose female progenitors received 50 µg BPA/kg/day, during GD 16–18. In addition, the pups showed reduced AGD and decreased epididymal weight (Gupta 2000; Talsness et al. 2000). Exposure of rats to low doses of BPA (≥0.2 µg BPA/kg/day for 45 days) during pubertal and adult life also induced decreased epididymal and testicular weights, as well as increased weight of ventral prostate (Chitra et al. 2003a, b). BPA also affected the prostate epigenome during development, and thereby promoted prostate cancer (Ho et al. 2006). Mitogenic effects in the prostatic gland have been further affirmed by in vitro studies on human prostatic adenocarcinoma (LNCaP). In fact, BPA initiated both an androgen-independent (inappropriate proliferation, through activation of the tumor-derived androgen receptor, AR-T877A) and an estrogen/androgen-dependent proliferation signalling pathway in LNCaP (Wetherill et al. 2002; Lee et al. 2012). Moreover, treatment of Ishikawa cell cultures with BPA modulated several genes implicated in regulation of transcription (SUZ12, HES2, FST, ATF3) (Naciff et al. 2010). The increased size of the preputial glands and atrophy of epididymides were also reported in mice prenatally exposed to BPA (vom Saal et al. 1998).

6 Effects of Bisphenol A Derivatives on Male Reproduction

Because of concerns for the effects of BPA, Canada was the first country to regulate the products in which BPA could be used. Canada banned the use of BPA in baby bottles in 2008. Since this occurred, other developed countries (e.g., Japan and the USA) have also acted to restrict the use of BPA in baby bottles, and to some degree, the manufacture or production of BPA. These countries have also promoted the development of alternative BPA isomers, such as Bisphenol S ((BPS; 4,4′-sulfonyl-diphenol), Bisphenol F (BPF; 4,4′-dihydrox-ydiphenylmethane), Bisphenol AF (BPAF; 4,4′-(hexa fluoroisopropylidene)diphenol), and Bisphenol B (BPB; 2,2-bis(4-hydroxyphenyl)butane), all of which are thought to be safer (Health

Canada 2008; Liao et al. 2012). Unfortunately, the biological activity (genotoxicity and estrogenicity) of these derivatives appears to be similar to that of BPA (Liao et al. 2012). BPAF acts as an agonist or antagonist to estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ) (Matsushima et al 2010), and its administration to adult male rats for 14 days induced dysregulation of the hypothalamic–pituitary–testicular axis, characterized by increased LH and FSH levels, reduced serum testosterone, and a decline in testicular mRNA levels of inhibin B, ERα, and LHR (Feng et al. 2012).

7 Implications of Updated Data for Bisphenol A Exposure in Risk Assessment Studies

Human exposure to BPA is now of great concern, because of how widespread the chemical has become in the environment and because it is detected in human biological fluids. The harmful effects of BPA on male reproductive function have been clearly illustrated in animal-based studies, and the effects it produces appear to be more pronounced during fetal life (Lagos-Cabré and Moreno 2012). The reported data were essentially gathered from investigations that used rodents (rats and mice) as the animal model. However, BPA's kinetics within rodent and primate (chimpanzee and monkey) systems are similar (Taylor et al. 2011), and support a conclusion that BPA effects observed in rodents may well be expected to occur in humans. Moreover, although glucuronidation of BPA (prior to urinary elimination) occurs both in rat and human liver microsomes, human liver microsomes do this less efficiently than do those of rats (Elsby et al. 2001), and this can lead to BPA bioaccumulation in humans, as recently suggested by Stahlhut et al. (2009). It is also of concern that human fetal testes are more sensitive to the deleterious effects (inhibition of testosterone secretion and insulin-like 3 mRNA levels in Leydig cells) of BPA than are testes of rodents (N'Tumba-Byn et al. 2012).

Therefore, we believe that regulators should reinforce actions to prevent exposures to BPA and BPA-related products, with particular emphasis on reducing exposures during fetal life (pregnancy) and babyhood, since these are the stages that are most sensitive to toxicity by this chemical. BPA also preferentially attacks the developing (rather than adult) testis during the puberty stage.

The current BPA tolerable daily intake values (TDI) proposed by the European Food Safety Authority and by Health Canada are 0.025 and 0.05 mg/kg bwt/day, respectively (EFSA 2010; Cao et al. 2011; Hengstler et al. 2011; Geens et al. 2012). These values are respectively based on animal studies, in which the lowest-observed-effect-level (LOEL) for BPA is 0.025 μg/kg bwt and 0.05 μg/kg bwt. These TDIs were derived from LOEL values using an uncertainty factor of 1,000 (10 for interspecies differences, 10 for interindividual differences, and 10 for LOEL to no-observed-effect-level or TDI). However, recent studies included in this review have provided evidence that harmful or adverse effects result from administering very low doses of BPA. D'Cruz et al. (2012a, b) showed that

administering 0.005 μg BPA/kg bwt/day for 45 days inhibited rat testicular steroidogenic and antioxidant enzymes. This indicates that a more appropriate LOEL for BPA may be 0.005 μg/kg bwt in rats. Hence, we suggest a proper TDI to be 5 μg/kg bwt/day, instead of 25 or 50 μg/kg bwt/day (with an uncertainty factor of 1,000). Establishing a lower TDI that is more appropriate will assist in guiding authorities to limit human BPA exposure, and reduce the risk burden it places on health, and particularly on male reproductive function.

8   Summary

BPA is a ubiquitous environmental contaminant, resulting mainly from manufacturing, use or disposal of plastics of which it is a component, and the degradation of industrial plastic-related wastes. Growing evidence from research on laboratory animals, wildlife, and humans supports the view that BPA produces an endocrine-disrupting effect and adversely affects male reproductive function. To better understand the adverse effects caused by exposure to BPA, we performed an up-to-date literature review on the topic, with particular emphasis on in utero exposure, and associated effects on spermatogenesis, steroidogenesis, and accessory organs.

BPA studies on experimental animals show that effects are generally more detrimental during in utero exposure, a critical developmental stage for the embryo. BPA has been found to produce several defects in the embryo, such as feminization of male fetuses, atrophy of the testes and epididymides, increased prostate size, shortening of AGD, disruption of BTB, and alteration of adult sperm parameters (e.g., sperm count, motility, and density). BPA also affects embryo thyroid development.

During the postnatal and pubertal periods and adulthood, BPA affects the hypothalamic–pituitary–testicular axis by modulating hormone (e.g., LH and FSH, androgen and estrogen) synthesis, expression and function of respective receptors (ER, AR). These effects alter sperm parameters. BPA also induces oxidative stress in the testis and epididymis, by inhibiting antioxidant enzymes and stimulating lipid peroxidation. This suggests that employing antioxidants may be a promising strategy to relieve BPA-induced disturbances.

Epidemiological studies have also provided data indicating that BPA alters male reproductive function in humans. These investigations revealed that men occupationally exposed to BPA had high blood/urinary BPA levels, and abnormal semen parameters. BPA-exposed men also showed reduced libido and erectile ejaculatory difficulties; moreover, the overall BPA effects on male reproduction appear to be more harmful if exposure occurs in utero.

The regulation of BPA and BPA-related products should be reinforced, particularly where exposure during the fetal period can occur. The current TDI for BPA is proposed as 25 and 50 μg/kg bwt/day (European Food Safety Authority and Health Canada, respectively). Based on the evidence available, we believe that a TDI value of 5 μg/kg bwt/day is more appropriate (the endpoint is modulation of rat testicular function). Certain BPA derivatives are being considered as alternatives to BPA.

However, certain of these related products display adverse effects that are similar to those of BPA. These effects should be carefully considered before using them as final alternatives to BPA in plastic production.

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