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# The Evaluation of Evidence Bisphenol A Exposure and Human Reproductive Health: A review

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### Abstract

Infertility is widespread problem defined as the inability to conceive after one year of unprotected intercourse. One of the most notable factors causing this status is the exposure to environmental contaminants. It is now recognized that many contaminants present in the environment have the ability to interfere in the action of hormones and therefore are termed endocrine disruptors (EDs). Some of these compounds are present in nature, but the majority are artificial and released into the environment by the human activities without any prior knowledge of their impact on ecosystems, animal welfare, or wildlife and human health. Many epidemiological studies have reported a radical growth in the incidence of male infertility, accompanied by decreasing sperm quality, decline in spermatozoa motility, defect in Leydig cell morphology, insufficient activity of steroidogenesis and spermatogenesis. The similar situation was observed in female, when the increased risk for endometriosis, reproductive and other endocrine-related cancer, impaired oocytes, ovarian dysfunction, or irregular menstrual cycle was confirmed. All mentioned consequences have been associated with increasing concentration of bisphenol A (BPA) in the environment. Humans are exposed to BPA not only through specific occupational circumstance, but nowadays more generally also from the ordinary day-to-day domestic and workplace lifestyles. Almost 3.4 million tons per year of BPA is used in a variety common product such as food packaging, household products, epoxy resins, dental sealants and many others. Under these endpoints, apprehensions about the reproductive dysfunctions associated with BPA action are unquestionable. In this review, we address the topic of BPA effects on reproductive function in males and females and emphasize its effects on overall health. A considerably more detailed and systematic research in EDs toxicology is required for a better understanding of risks associated with exposure to environmental toxicants.

## 1. Introduction

Infertility is a major problem for many couples of reproductive age and currently affects around 10% of couples worldwide. In approximately 50% of the affected couples, infertility is due to male reproductive dysfunction (Quah and Cockerham, 2017). In addition, increasing prevalence of congenital abnormalities such as hypospadias and cryptorchidism has also been confirmed by many studies during the last decades. Substantial part of the problem is the disruption of essential cellular processes responsible for normal reproductive functions (Boisen et al., 2004; Boivin et al., 2007). Given the short time, genetic changes cannot explain it. We may assume that they only reflect persistently adverse changes in the environment. During the last decades, an increased occurrence of hazardous chemical present in human or wildlife environment was confirmed. Enormous production and release of industrial chemicals into the ecosystem has led the scientific community to hypothesize that current pollutants may irrefutably disrupt health conditions, leading to extensive damages of physiological

functions (Jambor et al., 2018; Kovacik et al., 2018). A huge number of different hazardous substances have been found to interact with the endocrine system of many animals, and there are increasing reports of endocrine disruption in wildlife (Tyler et al., 1998; Svechnikov et al., 2010). The group of chemicals, that may alter the hormonal and homeostatic system is called endocrine disruptors (EDs). They are able to alter functions of the endocrine system, inhibit critical cellular processes, increase the risk of the hormone-dependent cancers and may result in many other adverse health effects. According to final report of Darbre (2015), EDs are an exogenous chemical substances or mixtures that alter the structure or functions of the endocrine system and cause adverse effects at the level of the organism, its progeny, populations, or subpopulations of organisms, based on scientific principles, data, weight-of-evidence and the precautionary principle. Several reports of declines in quality and decreases in the quantity of sperm production in humans over last four decades and reported increases in incidence of certain cancers (breast, prostate, testicular) that may have an

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endocrine-related basis have led to speculation about environmental etiologies (**Rochester, 2013**).

Nowadays, questions are raising about mechanism of action or potential toxic effects of EDs. Given the complexity of the endocrine system, there are many ways in which EDs may affect physiological functions, and this makes the mechanisms of action difficult to unravel. A large number of EDs have been shown to mimic, block or modulate the actions of hormones such as estrogens, anti-estrogens, androgens and anti-androgens. All of them act through interfering with the estrogen receptors (ER) or the androgen receptor (AR). Estrogens are able to regulate processes such as development and function of the reproductive system and protection against cardiovascular diseases. The estrogenic effects are mediated through ER of which two variants ( $\alpha$ ,  $\beta$ ) regulate these physiological processes. Endogenous estrogens are primarily recognized for their role in the differentiation and growth of secondary sex-tissues. However, the endocrine system is especially vulnerable to perturbation by EDs with estrogenic properties. They can interfere with normal endogenous hormone action by binding themselves to receptors or by blocking the steroid receptor binding (**Welshons et al., 2006; Swedenborg et al., 2009**).

## 2. Sources of EDs

Humans are exposed to environmental chemicals with endocrine-disrupting properties not only through specific occupational circumstance, but nowadays more generally also from the ordinary day-to-day domestic and workplace lifestyles of the twentieth and twenty-first centuries. Occupational exposures, such as of agrochemicals on farms or of plastics in manufacturing factories, can cause specific high exposures, but the general population also uses pesticides, herbicides, paints, personal care products, solvents, detergents and industrial lubricants. Another source of EDs exposure is through pharmaceuticals, nutraceuticals and food products that are promoted as providing health or medical benefits through the prevention of treatment of disease (**Darbre et al., 2015**). Many textiles also contain contaminants, such as flame-retardants, including tetrabromobisphenol A and polybrominated diphenyl ethers (**Yonglai et al., 2002**). Although there is chronic exposure to EDs through the skin contact or inhalation, food products are the major source. **Wagner and Oehlmann (2011)** are convinced that plastic packaging is the largest source of EDs in the human diet. Repeated exposure of food – contact materials to UV light, acid and alkaline contents and heat may cause polymers to breakdown into monomers as phthalates, which then leach into the food or beverages. Phthalate esters are weakly estrogenic plasticisers used to soften plastics destined for material such as cling film and plastic wrappers. Bisphenol A (BPA) is a component of polycarbonate plastics and epoxy resins used in resins linings of food cans and water pipes. Perfluorinated compounds can be found in non-stick Teflon cookware and are also used in fast-food packaging for their stain-resistant properties. While relatively low concentrations of EDs result in harmful effect, some kinds of EDs must be consumed at relatively high concentrations to produce corresponding effect on the human endocrine system because their hormonal activities are usually five or six times lower than  $17\beta$ -estradiol. However, a combination of EDs at lower concentrations may result in additive, enhanced or low-level cocktail effect, thus posing a greater risk to the consumer. Other high-risk groups called alkylphenols persist in the environment for a long time. They are used in the production of agrochemicals, industrial and household detergents, paints or plastics (**Nimrod and Benson, 1996; Jambor et al., 2017**). Detection of ED residues in human serum, seminal plasma and follicular fluid has supported the concern that environmental

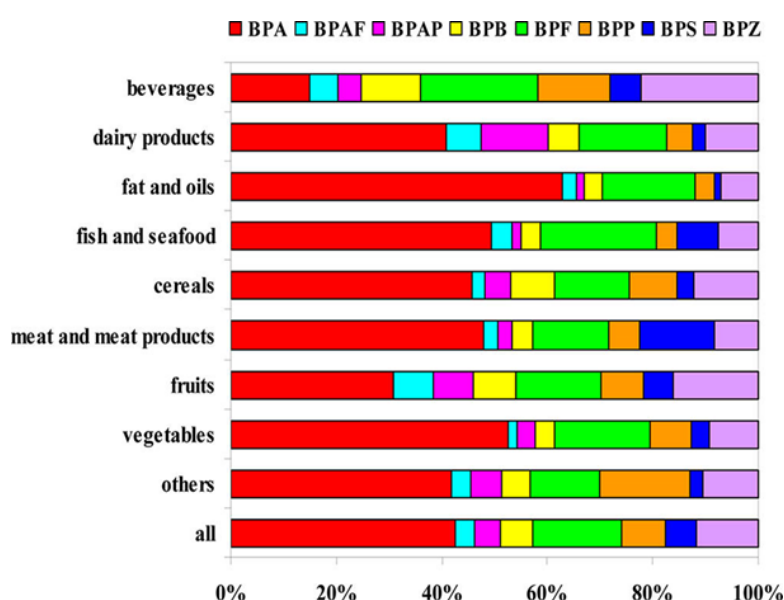
exposure to ED is affecting human fertility. Nowadays, some of them were banned or otherwise were removed from the industrial process years ago. The long-debated question remains - whether such effects might also occur in the human population in response to the EDs, and therefore whether the wildlife effects might be a forewarning of consequences for human health. A number of studies have suggested that hormone alterations in females resulting from environmental EDs exposure may represent an increased risk for endometriosis, reproductive and other endocrine-related cancer, impaired oocytes, competence or changes of ovarian function and menstrual cycle (**Toft et al., 2004; Dhooze et al., 2007**). In males, environmental or occupational exposures to EDs may be associated with declining reproductive capacity or increasing the risk of testicular or prostate cancer, as well as poor semen quality and alterations in testosterone levels (**Uhler et al., 2003; Meeker et al., 2006; Jambor et al., 2017**). In this context, possible adverse effects of EDs have been taken into focus, both regarding the effects of EDs on the male and female reproductive system and with respect to its differential susceptibility towards these compounds. Although there has been an effort to list and rank all possible EDs, the number of evaluated chemicals remains limited (**Vandenberg et al., 2007**).

## 3. Bisphenol A and “safe” alternatives

Bisphenols are one of the most studied EDs in the field of male and female reproductive system. It has been shown that BPA alter the normal function of the endocrine system, cause adverse effects on male reproductive system and irrefutably affect essential processes responsible for functional health in humans and numerous animal species (**Welshons et al., 2006**). A survey of the Pubmed database provides more than 10,000 articles on the topic, including epidemiological as well as experimental studies. The overwhelming majority of bisphenols are used as stable components of household products, epoxy resins, inner surface of food metallic cans, plastics packaging, dental sealants, and for myriad additional synthetic products (**Calafat et al., 2008**). BPA is industrially produced by condensation of phenol and acetone in the presence of an acid catalyst (hydrogen chloride) and usually a promoter such as methyl mercaptan. After reaction and recovery of acid and phenol, the BPA is washed with water, neutralized with milk or lime and distilled under vacuum. Newer processes employ distillation and extractive crystallization under pressure to purify the BPA. Two grades are produced: one for epoxy resins production and a higher purity grade for polycarbonate manufacture. Almost 70% of BPA production is primarily used to produce polycarbonate plastics used in a variety of common products (**Vandenberg et al., 2007**). BPA is ubiquitous in the environment, and humans are exposed to this chemical via dietary and nondietary sources (Figure 1). Based on the analysis of blood samples from adults found that the concentration of unconjugated BPA, which is the biologically active form, ranged from 0.2 to 10 ng/mL, with an average concentration from 1 to 3 ng/mL (**Vandenberg et al., 2012**).

Exposure to BPA has been associated with several human diseases, such as diabetes, obesity, cardiovascular, chronic respiratory and kidney diseases, breast cancer, behavioral troubles, tooth developmental defect, and reproductive disorders in both sexes (**Geens et al., 2012; Vandenberg et al., 2012; Rochester, 2013**). As we mentioned before, many studies have been shown to affect many endpoints of fertility. Exposure to high or low doses of BPA may induce adverse health effects in testis, including reduced sperm motility and viability, DNA damage or decreased sperm count. Several cohort studies examined individual undergoing infertility treatments and measured BPA in relation to various reproductive endpoints,

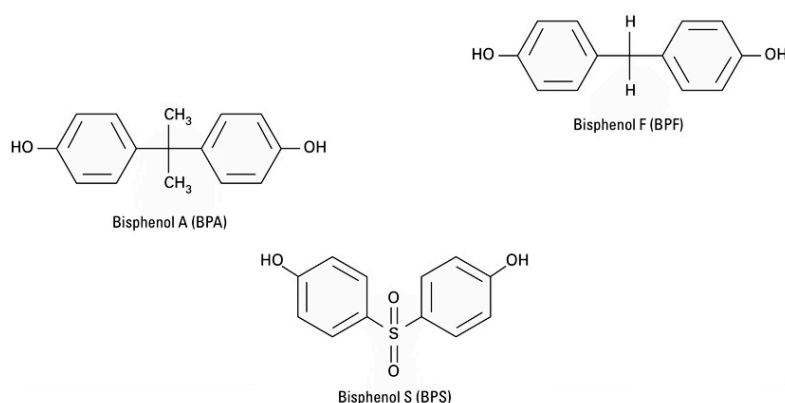
such as ovarian response, fertilization success, embryo quality and many others (Ehrlich et al., 2012). On the other hand, there are plenty of studies focused on the ability of BPA to affect the brain even at very low doses. Palanza et al. (2016) showed, that the epigenetic action of BPA on the hippocampus and hypothalamus, may disrupt normal steroid programming in the brain and subsequently affect sex-specific behavior. Several animal studies report BPA to affect synaptogenesis and neurogenesis processes which are known as the brain self-regeneration against trauma and disease. In a study of the associations between BPA and cancer in humans, Yang et al. (2009) analyzed total serum BPA of women with and without breast cancer. There was a no-significant elevation of BPA in the cancer patients. However, there exists evidence from rodent (Markey et al., 2001; Li et al., 2009) and primate (Tharp et al., 2012) studies that prenatal exposure to BPA cause disruption of the mammary tissue and increases the susceptibility of the tissue to environmental carcinogens. Diabetes – type II has been also associated with BPA in many human studies. Lang et al. (2008) found that higher total urinary BPA was significantly associated with increased diagnosis of type-II diabetes (defined as fasting serum glucose greater than 126 mg/dL, non-fasting greater than 200 mg/dL, glycosylated hemoglobin greater than 6.5%). This positive association between BPA and diabetes was present among normal weight and overweight patients, and smokers as well as non-smokers. In another study, Ning et al. (2011) assessed Chinese adults. Higher urinary BPA was non-significantly associated with increased diabetes and measured by blood glucose. Cardiovascular disorders and hypertension are other adult onset diseases that have been associated with adult BPA exposure. Lang et al. (2008) reported that higher urinary BPA was associated with a more frequent diagnosis of cardiovascular disease (coronary heart attack, angina). Meanwhile, Melzer et al. (2010) assessed individuals 18-74 years of age and found a significant increase in myocardial infarction, coronary heart disease together with increased urinary BPA. The decomposition of BPA takes place in the liver by uridine5'-diphospho-glucuronyl transferase (Yokota et al., 1999) and the half-time of BPA is about 5.4 hours (Stahlhut et al., 2009).



**Figure 1.** Composition profiles of bisphenols in foodstuffs (Liao and Kannan, 2013)

Due to many negative effects, toxicity and widespread exposure, the general public has drawn considerable attention to BPA.

Based on many negative effects on human health restrictions on the use of certain consumer products have been suggested. For example, BPA has been prohibited from manufacture, sale, or distribution in some consumer products, such as reusable food or beverage containers, infant formula containers, and thermal receipt paper. The U.S. Food and Drug Administration (FDA) also banned the use of BPA in baby bottles and children's drinking cups in July 2012 (Eladak et al., 2015). At this point, alternatives to BPA have started to develop which can be used to replace it in food plastics packaging or epoxy resins. However, we are convinced that common analogues of BPA are not entirely "safe" as indicated by industrial companies. Nowadays, there are recognized several "safe" analogues to BPA such as bisphenol S (BPS; 4,4'-sulfonyldiphenol), bisphenol F (BPF; 4,4'-dihydroxydiphenylmethane), bisphenol B (BPB; 2,2-bis(4-hydroxyphenyl)butane), bisphenol AF (BPAF; 4,4'-(hexafluoroisopropylidene)diphenol) and many others. A total of 16 bisphenol analogues have been documented for industrial application. These chemicals share a common structure of two hydroxyphenol functionalities and are collectively referred to as bisphenol analogues (Kuroto-Niwa et al., 2005). BPF, BPS and BPAF are among the main substitutes of BPA in the manufacturing of polycarbonate plastics and epoxy resins. In the case of BPS and BPF, these substances are structural analogue to BPA (Figure 2), thus their effect in physiological systems may be similar. BPF has a broad range of applications such as lacquers, dental sealants, oral prosthetic devices and adhesives plastics (Cabaton et al., 2009). BPS is commonly used as an additive in dyes, epoxy glues and tanning agents, while BPAF is used in electronics plastics and optical fibres (Konno et al., 2004; Naderi et al., 2014). Estrogenic and antiandrogenic potencies of bisphenol analogues have been the subject of intense investigations. BPF, BPS, BPAF and BPB exhibit estrogenic potencies similar to or greater than that of BPA. Rosenmai et al. (2014) determined the effects of these analogues on estrogen and androgen receptor activities and revealed that most of them exhibited strong potencies within the same magnitude as that of BPA. BPS was less estrogenic and antiandrogenic, but the former study showed the largest effect on 17 $\alpha$ -hydroxyprogesterone. The inhibitory effect on the androgenic activity of 5 $\alpha$ -dihydrotestosterone in mouse fibroblast cell line were the highest in BPS, BPF and BPA (Kitamura et al., 2005). Audebert et al. (2011) reported similar ranges of cytotoxicity for BPA and BPF in human hepatoma cell line (HepG2). Cabaton et al. (2009) observed that BPF was effective on HepG2 cell DNA fragmentation, while concentrations of BPS ranging from 0.1 to 10  $\mu$ mol/L also induced significant DNA damage after 24 h exposure. In comparison with BPA, BPF and BPAF enhanced the formation for reactive oxygen species, which damages the lipid and proteins in human peripheral blood mononuclear cells (PBMCs) and definitely decreased the viability of PBMCs (Michalowicz et al., 2015). Rosenmai et al. (2014) used several assays to assess steroidogenic activity, as well as teratogenicity and metabolic effects. They found out that BPS and BPF had estrogen receptor binding, estrogenic activity and antiandrogenic activity similar to those of BPA, with BPS being the least potent. However, BPS and BPF exhibited the greatest steroidogenic (i.e., progesterone) activity, increasing levels of 17 $\alpha$ -hydroxyprogesterone and progesterone levels, whereas BPA did not. Zhang et al. (2011) suggest a direct inhibition of the CYP17 (cytochrome P450 17A1) lyase reaction, independent from estrogen receptor action. Thus, BPA analogues may have additional disruptive effects that have not been detected with BPA. Toxicological data on BPS, BPF, BPB etc. are scarce and experimental studies evaluated their effect are unclear. Therefore, it is necessary to bring novel and original data to help solve this deficiency.



**Figure 2.** Chemical structure of bisphenol A, bisphenol S and bisphenol F (Eladak et al., 2015)

There is an evidence that BPA and their analogues have adverse effect on animal health and it is also suspected of having negative effect on human health although available data are limited. In the present review, we would like to present results from human studies, where significant changes in reproductive processes in men and women were observed.

#### 4. Women reproductive health and BPA

There is accumulating evidence that fertility is decreasing among male and female. The reproductive health of female depends on maintaining coordinated responses of a network of endocrine signals that function primarily to ensure successful procreation but also have other wide-ranging influences on the female body. Consequences of any disrupting effects can be expected, therefore, not only to influence fertility, but to have wide repercussions for female health more generally (McLachlan et al., 2006). One of the most important considerations for endocrine disruption and female reproductive health is the timing of exposure. While exposure to EDs may be expected to affect adult life, there is increasing evidence that some adult female reproductive health problems may be programmed by exposures in the early embryo of fetus *in utero* (Jacob-Dickman and Lee, 2009). Sexual differentiation and congenital malformations of the developing fetus are extremely dependent on EDs action. Changes in hormone levels or the ration of hormones can disrupt sexual differentiation – clearly EDs that mimic important hormones like 17 $\beta$ -estradiol will perturb the levels that are required for normal development (Toppari and Skakkebaek, 1998). The placenta protects the developing embryo and fetus from hazardous substances, what could negatively affect sex-hormone mediated biochemistry. In terms of potential impact on the developing child EDs or estrogen mimics are the issue, because many of them have molecular structures very different from 17 $\beta$ -estradiol even though they still bind to and activate the estrogen receptor. The latter are likely to interfere with fetal development and therefore we should be aware of the implications of exposure during pregnancy (Jin and Audus, 2005).

Some EDs like BPA decreases the production of progesterone in placental cells. It can be explained by reduced levels of mitochondrial enzyme (CYP450sc) that convert cholesterol to pregnenolone or progesterone. BPA is also able to inhibit aromatase activity by interacting directly with the aromatase enzymatic complex (Nativelle-Serpentiny et al., 2003). Gould et al. (1998) found out that higher urinary BPA significantly correlated with lower serum of estradiol and oocyte yield. They also found that higher urinary BPA corresponded to reduced maturation of the oocytes, as measured by the number and

percentage of mature oocytes at metaphase II on the day of egg retrieval. There were also fewer normal fertilized oocytes in women with higher urinary BPA, measured by the number and percentage of oocytes with two pronuclei. Takeuchi and Tsutsumi (2002) tested healthy women and women with polycystic ovary syndrome (PCOS) for serum BPA and hormone concentrations. The PCOS women had significantly higher testosterone, estradiol, LH and androstenedione concentration than in healthy women, and the total amount of BPA was higher in PCOS women. The endometrial disorders in adult women have been also associated with BPA exposure, although the evidence in humans is not strong. Cobellis et al. (2009) tested women with and without endometriosis for total BPA exposure. Serum BPA was not detectable in any of the controls but was detected in 52.7% of the individuals with endometriosis, when the limit of quantification was 0,5  $\mu$ g/L. Itoh et al. (2007) also examined connection between urinary BPA and the severity of endometriosis. There was a trend for higher BPA correlation with more severe endometriosis. An accidental observation by Sugiura-Ogasawara et al. (2005) showed, that women with recurrent spontaneous abortion had significantly higher levels of serum BPA than healthy women from the same city in Japan. There are physiological and biochemical reason that might explain the observed effects. BPA increase progesterone receptor expression in the hypothalamus, which in turn alter hypothalamic mechanism and affects the onset of estrus and the receptivity of the uterus.

#### 5. Men reproductive health and BPA

The sexual differentiation and formation of the penis, scrotum and accessory sex gland during the fetal development is also extremely sensitive to EDs action. These formations are under the influence of steroid hormones secreted during the hormonal phase of testicular development. Especially, testosterone and dihydrotestosterone are two major hormones involved in the above process (Basrur, 2006). It has been reported that 20.8% of the males exposed to diethylstilbestrol (DES) *in utero* had epididymal cysts, 4.4% had hypospadias, 11.4% presented with cryptorchidism (Sultan, 2001). Among the factors responsible for the increase in male infertility, BPA have been studied extensively. It has been shown that BPA may affect many endpoints of male fertility. Several studies have focused on the effects of BPA, but the experimental data are rather controversial, and there is no general agreement about the effects of BPA on essential reproductive processes such as steroidogenesis and spermatogenesis, and sperm parameters (e.g., sperm mobility, viability, morphology) (Wetherill et al., 2007). According to the previous study performed on rodents, it was confirmed that exposure to BPA decrease free plasma testosterone and 17 $\beta$ -estradiol level and BPA had also negative effect on histomorphology of testis or sperm parameters. There were also alterations in daily sperm production, suppression in testosterone and follicle-stimulating hormone production, interruption of the hypothalamic-pituitary-testicular axis and progressive apoptosis in sperm, Leydig and Sertoli cells (Sakaue et al., 2001; Akingbemi et al., 2004; Li et al., 2009; Alves et al., 2013). Detrimental effects of BPA on the male reproductive system in experimental animal models have been confirmed by some studies conducted among groups of BPA exposed human males. Data from the study of Xiao et al. (2009), when man workers were exposed to high levels of BPA, showed that BPA causes erectile and ejaculatory problems, reduction of sexual desire and affects sperm morphology. Li et al. (2010) also declare the negative effects of BPA on men working in epoxy resins manufacturing companies in China. Participants took a general health survey but were not told that the effects of BPA were the targets of the study. Exposed workers had significantly



lower sexual functions (orgasmic function, sexual desire) than non-exposed men in the study. Decreased sexual function was related to BPA exposure in dose-dependent manner and higher urinary BPA concentration was confirmed. However, men who were exposed environmentally but not occupationally, showed a weak but significant negative correlation in a few parameters. It indicates, that BPA exposure could reduce male sexual function in the general population. In a cross-sectional study with 215 healthy men, it was investigated that urinary BPA concentrations are associated with a reduction in Leydig cell function, increased serum luteinizing hormone levels and decreased sperm count (Adoamnei et al., 2018). Meeker et al. (2010) tested sperm quality parameters of sub-fertile couples. When analyzing urine samples, there was a significant correlation with higher urinary BPA and lower sperm count, sperm morphology, and DNA damage. According to another prospective cohort study, Goldstone et al. (2015) investigated the relationship of urinary BPA concentrations and sperm parameters in 418 male partners of couples trying to become pregnant in Michigan and Texas. They found out that urinary BPA concentrations were associated with lower percentile of sperm DNA fragmentation and no association with semen parameters was observed. Using the FeTA system (Fetal Testis Assay) Eladak et al. (2015) confirmed that 1000 nmol/L BPA significantly reduced basal testosterone secretion by human testis. This method allows the precise study of the kinetics and duration of specific controlled concentrations of a given compound or mixture of compounds in a defined medium. They also evaluated the effect of BPA on LH-stimulated testosterone secretion. In the presence of 100 ng/mL LH, a concentration that induced the maximum steroidogenic response, the inhibitory effect of BPA in human testis was much less pronounced than in basal conditions. Indeed, only 10 000 nmol/L BPA significantly reduced testosterone secretion. In the next part of the study they found out that BPF and BPS reduced the basal testosterone production in cultured human testis and showed antiandrogenic effects already at 10 nmol/L.

## 6. Conclusion

Our review demonstrates that BPA and their analogues exhibit a range of toxic effects similar to those observed for BPA and that similar modes of action may be expected between BPA and other analogues. It is clear that BPA definitely affect reproductive processes in males and females with irreversible consequences for overall health. Some analogues exhibited toxic potencies similar to or even greater than that of BPA, raising safety concerns on their applications as BPA replacements. To date, toxicity studies remain remarkably limited in the determination of modes of action and quantitative toxic end points or benchmarks, both *in vitro* and *in vivo*, for a variety of analogues. Additional research is urgently needed to fill in knowledge gaps and deepen toxicity evaluations, given that the production and applications of bisphenol analogues are on the rise and that many of them have already been present in environmental compartments, foods and humans.

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## Declaration of interest

The authors declare no conflicts of interest.

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