



Bisphenol A and male infertility – a mini-review of mechanisms of endocrine disruption and reproductive toxicity

Bisfenol A a niepłodność męska: miniprzegląd mechanizmów zaburzeń hormonalnych i przedstawienie toksycznego wpływu bisfenolu A na układ rozrodczy

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■ Abstract

Introduction and Objective. Bisphenol A (BPA) is a widely used industrial chemical found in plastics, food containers, and thermal receipts. As an endocrine-disrupting compound, BPA poses a potential threat to male reproductive health. The aim of this review is to examine the mechanisms by which BPA may impair male fertility, and to present current evidence linking BPA exposure to hormonal imbalance and reduced sperm quality.

Brief description of the state of knowledge. BPA exerts both estrogenic and anti-androgenic activity by binding to estrogen and androgen receptors, interfering with the hypothalamic-pituitary-gonadal axis, and inhibiting testosterone production. It also induces oxidative stress and mitochondrial dysfunction in sperm cells, impairing motility, viability, and DNA integrity. Animal studies have consistently demonstrated these effects, while human studies suggest a correlation between urinary BPA levels and reduced sperm quality. Analogues, such as BPS and BPF, developed as substitutes, show similar endocrine-disrupting potential.

Summary. BPA undermines male fertility by interfering with hormones, inducing oxidative stress, and interfering with sperm mitochondria and membranes. Alternatives like BPS and BPF have been proposed, but there are indications that

they, too, pose similar reproductive risks. It is necessary to minimize exposure to BPA and analogues while exploring safer options. Further research, particularly large-scale human studies, is needed to clarify BPA's long-term effects on fertility.

■ Key words

Bisphenol A, male infertility, reproductive toxicity, Endocrine-Disrupting Chemicals

■ Streszczenie

Wprowadzenie i cel pracy. Bisfenol A (BPA) jest związkiem chemicznym szeroko stosowanym w produkcji tworzyw sztucznych, opakowań spożywczych oraz papieru termicznego. W ostatnich latach coraz więcej badań wskazuje na potencjalne działanie BPA jako dysruptora hormonalnego, co może przyczyniać się do obniżenia jakości nasienia. Celem niniejszego przeglądu jest analiza mechanizmów działania BPA oraz ocena jego wpływu na parametry płodności u mężczyzn. **Opis stanu wiedzy.** Bisfenol A wykazuje zdolność do łączenia się z receptorami estrogenowymi i androgenowymi, co prowadzi do zaburzeń homeostazy hormonalnej. Dodatkowo BPA wpływa na oś podwzgórze–przysadka–jądra, hamując syntezę testosteronu. Wykazano również, że związek ten indukuje stres oksydacyjny oraz uszkodzenia mitochondrialne w plemnikach, co skutkuje obniżeniem ich ruchliwości, żywotności oraz integralności materiału genetycznego. Większość dostępnych danych pochodzi z modeli doświadczalnych na zwierzętach,

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jednak dostępne wyniki badań epidemiologicznych u ludzi wskazują na korelację pomiędzy stężeniem BPA w moczu a pogorszeniem jakości nasienia. Substytuty BPA, takie jak BPS i BPF, wykazują podobne właściwości względem układu hormonalnego.

Podsumowanie. Bisfenol A (BPA) wywiera niekorzystny wpływ na płodność mężczyzn poprzez zaburzenia hormonalne, indukcję stresu oksydacyjnego oraz uszkodzenia mitochondriów i błon komórkowych plemników. Choć wprowadzono alternatywne związki, takie jak BPS i BPF, dane wskazują,

że one również mogą wykazywać podobne działanie toksyczne wobec układu rozrodczego. Z tego względu konieczne jest ograniczenie ekspozycji na BPA i jego analogi oraz równoczesne poszukiwanie ich bezpieczniejszych alternatyw. Niezbędne są dalsze badania, szczególnie na dużych grupach ludzi, po to by pełniej zrozumieć skutki działania BPA na płodność.

Słowa kluczowe

niepłodność męska, dysruptory endokrynne, Bisfenol A, związki toksyczne dla płodności

INTRODUCTION

Bisphenol A (BPA) is a synthetic phenol, a widely employed industrial chemical used in manufacturing various plastics and resins. Numerous human studies have highlighted its strong potential to disrupt hormonal homeostasis, directly affecting the development and functioning of the reproductive system in both men and women [1]. BPA, primarily used in products that come into direct contact with food, poses potential risks to human health. These products include packaging materials, kitchenware, and internal coatings of metal containers, such as epoxy resin linings, which enable direct contact [2, 3]. Other prominent sources of BPA exposure include airborne dust, dental composites, medical devices, thermal paper, and consumer products aimed at children and infants, such as toys and baby bottles [4, 5]. While BPA is not naturally occurring, its prevalence results from substantial production, consumption, and environmental release [2]. According to ChemAnalyst's BPA market analysis, the global BPA market was approximately 5,600,000 tonnes in 2022 and is projected to grow at a CAGR of 3.51% until 2032, potentially reaching 8,000,000 tonnes by that year [6]. As a result, BPA is regularly detected in human biological samples, including urine, blood, amniotic fluid, and breast milk, indicating widespread and chronic human exposure.

BPA is increasingly recognized as a harmful endocrine-disrupting chemical (EDC). Due to its structural similarity to estrogen, BPA can disrupt regular hormonal activity by binding to hormone receptors or influencing gene expression [7, 8]. Although much research has focused on BPA's effects on female reproductive health, recent studies have also highlighted its negative influence on male fertility. In particular, BPA exposure in men has been linked to hormonal imbalances and lower sperm counts [9]. This is especially concerning in the light of global data showing a long-term decline in sperm quality, raising important public health questions [10].

OBJECTIVE

The aim of the study is to examine how BPA exposure might affect men's infertility. By analyzing scientific research and current literature it aims to understand the mechanisms underlying the relationship between BPA and male fertility.

MATERIALS AND METHOD

A mini-review of the current literature was conducted using the PubMed and Google Scholar databases, using the key word 'BPA' in combination with such terms as 'reproductive', 'men's infertility', 'spermatogenesis', 'exposure', 'safety', 'oxidative stress', 'testosterone', and 'urine'. Thirty-seven original and review articles were included in the analysis.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Chemical structure and utilization. BPA is a crystalline chemical compound (formula $C_{15}H_{16}O_2$) and a structure made of two hydroxyphenyl groups, which give it a mild phenolic odour [1]. BPA is widely used as a stabilizer in the production of polycarbonate plastics, which are known for their strength, durability, and thermal stability, making them valuable in safety equipment, medical devices, water bottles, and food containers [2]. BPA is also a key component in epoxy resins used for protective coatings, commonly lining metal cans to prevent corrosion and extend shelf life [3]. This widespread use poses a contamination risk, as BPA can leach into food and drinks, especially when cans are sterilized at high temperatures [7]. BPA can also be found in thermal paper and water supply pipes [4, 5] (Fig. 1).

Exposure, biotransformation and elimination. In humans, the primary route of BPA exposure is through food and drink consumption, with additional exposure occurring via inhalation, ingestion, and skin contact, especially among occupationally exposed groups, such as cashiers [5]. BPA has been detected in blood, urine, amniotic fluid, follicular fluid, and umbilical cord blood [11]. As illustrated in Figure 1, BPA is metabolized to BPA-glucuronide in the liver and excreted in urine, which explains its frequent detection in urine, blood,

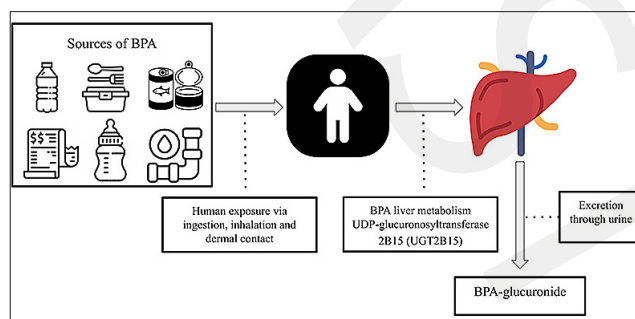


Figure 1. Sources of BPA and liver metabolism according to the literature [1, 2, 3, 13]

and breast milk [12]. Although BPA is rapidly metabolized and eliminated from the human body, continuous daily exposure to BPA leads to its frequent detection in biological samples, including urine, blood, and amniotic fluid [13–15].

Safe dosage. BPA safety is increasingly questioned due to evidence of its endocrine and immunotoxic effects. In 2015, the tolerable daily intake (TDI) was 4 µg/kg body weight/day, but in 2023, EFSA reduced this to 0.2 ng/kg/day due to concerns about immune system disruption [14]. Regulatory responses include the European Union and the USA banning BPA in baby bottles [16, 17], and Canada classifying it as toxic [18]. Despite efforts, such as reducing the specific migration limit in food contact materials, biomonitoring data from HBM4EU found BPA in 92% of adults across 11 European countries – levels often exceeding safety thresholds [13, 19].

Mechanisms of endocrine disruption. The estrogenic activity of BPA has been well documented in *in vitro* and *in vivo* studies, particularly in rodent and zebrafish models, showing it can alter estrogen receptor signalling and disrupt the endocrine system at environmental doses [8, 20]. BPA structure consists of two hydroxyphenyl rings, which mimic natural estrogen, allowing it to bind to ERα and ERβ and influence gene expression related to cell proliferation and apoptosis [20]. BPA can also activate non-classical receptors, such as the membrane-bound G protein-coupled receptor GPR30, leading to rapid cellular responses and affecting reproductive and metabolic processes [21]. This enables it to activate or block normal hormonal signals, resulting in changes in gene expression that impact cell growth, development, and reproductive function.

Although BPA is primarily known for its estrogenic activity, numerous studies have also demonstrated its anti-androgenic effects. These may occur through several mechanisms: (1) the ability of BPA to bind to the androgen receptor (AR) ligand-binding domain, (2) interference with the release of heat shock protein 90 (Hsp90), which binds unliganded AR in the cytoplasm and prevents its activation, and (3) inhibition of AR nuclear translocation by disrupting the dihydrotestosterone (DHT)-induced signalling pathway [22, 23].

Another critical target of bisphenol A (BPA) is the hypothalamic-pituitary-gonadal (HPG) axis – the hormonal system that regulates reproductive functions. BPA may interfere with the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus which, in turn, affects the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland. LH plays a key role in stimulating testosterone production in Leydig cells, while FSH is essential for proper sperm development. Moreover, testosterone itself is crucial for maintaining spermatogenesis, as it supports the maturation of germ cells and the function of Sertoli cells within the seminiferous tubules [24–26].

Impact on sperm parameters. Another concerning effect of BPA exposure is its negative impact on sperm count and overall semen quality. Research using animal and *in vitro* models has demonstrated that chronic low-level exposure to BPA deranges gonadotropin secretion, shows estrogenic and anti-androgenic properties, and suppresses spermatogenesis by arresting it at various stages of development [27]. BPA also induces mitochondrial dysfunction and oxidative stress,

causing apoptosis of spermatogenic cells and an overall reduction in sperm concentration [28]. The sperm plasma membrane, rich in polyunsaturated fatty acids (PUFAs), is highly susceptible to oxidative damage. Although BPA is not itself an oxidizer, it leads to cellular changes, usually manifested by lipid peroxidation (LPO) and the production of free radicals, which cause oxidative stress. This process compromises membrane integrity and fluidity, ultimately reducing sperm motility and viability. Additionally, BPA-induced oxidative stress has been shown to cause mitochondrial and DNA damage in sperm cells [29].

Despite these lines of evidence, very little is known about the role of BPA as a reproductive toxicant in humans. A few human studies supported these findings, for instance, a Polish study in 2018 of 315 men who were visiting infertility clinics, found that increased urinary BPA levels were associated with increased proportions of immature sperm and reduced motility [30]. A 2014, a Danish study of healthy young men screened for military service also found a clear negative association between urinary BPA levels and sperm motility [31]. A cross-sectional study from China among men attending an infertility clinic found that higher urinary levels of bisphenol A and its analogues were significantly associated with poorer semen quality – including reduced sperm concentration, motility, and morphology [32].

Collectively, these studies highlight the potential for environmental BPA exposure to adversely affect male reproductive health. Nonetheless, large-scale human studies are needed to elucidate further the precise relationship between BPA exposure and male fertility.

Figure 2 summarizes the multifaceted mechanisms through which BPA disrupts male reproduction, including impaired GnRH secretion, oxidative stress-induced mitochondrial dysfunction, estrogen receptor activation, and androgen receptor antagonism.

Alternatives to BPA. Although BPA is widely known for its endocrine disruptor properties, its structural analogues, e.g. Bisphenol S (BPS), bisphenol F (BPF), and Bisphenol AF (BPAF), have been developed as substitutes in several consumer products. However, based on the findings of recent studies, substitutes do not necessarily present a safer option, as they also exhibit comparable endocrine-disrupting activity [24]. For instance, BPS and BPF have been reported to interfere with hormonal mechanisms [23]; similarly, BPF has been shown to interfere with steroidogenesis and reproduction [33], and has also exhibited greater estrogenic activity than BPA. BPAF is documented to cause oxidative stress-induced mitochondrial dysfunction and apoptosis in human granulosa cells, which are crucial for female reproductive health [34].

Protective effects of natural compounds against BPA toxicity. Promisingly, natural compounds like cyanidin-3-glucoside (C3G), found in dark-coloured fruits and vegetables, have shown the potential to mitigate BPA-induced damage.

In 2023, research from China revealed that C3G and its metabolite protocatechuic acid (PCA) can protect testicular function by alleviating oxidative stress, Leydig cell apoptosis, and cell cycle arrest. Moreover, these compounds share key binding sites on the estrogen receptor with BPA, suggesting they may competitively inhibit BPA's endocrine-disrupting activity and help normalize hormone levels [35, 36].

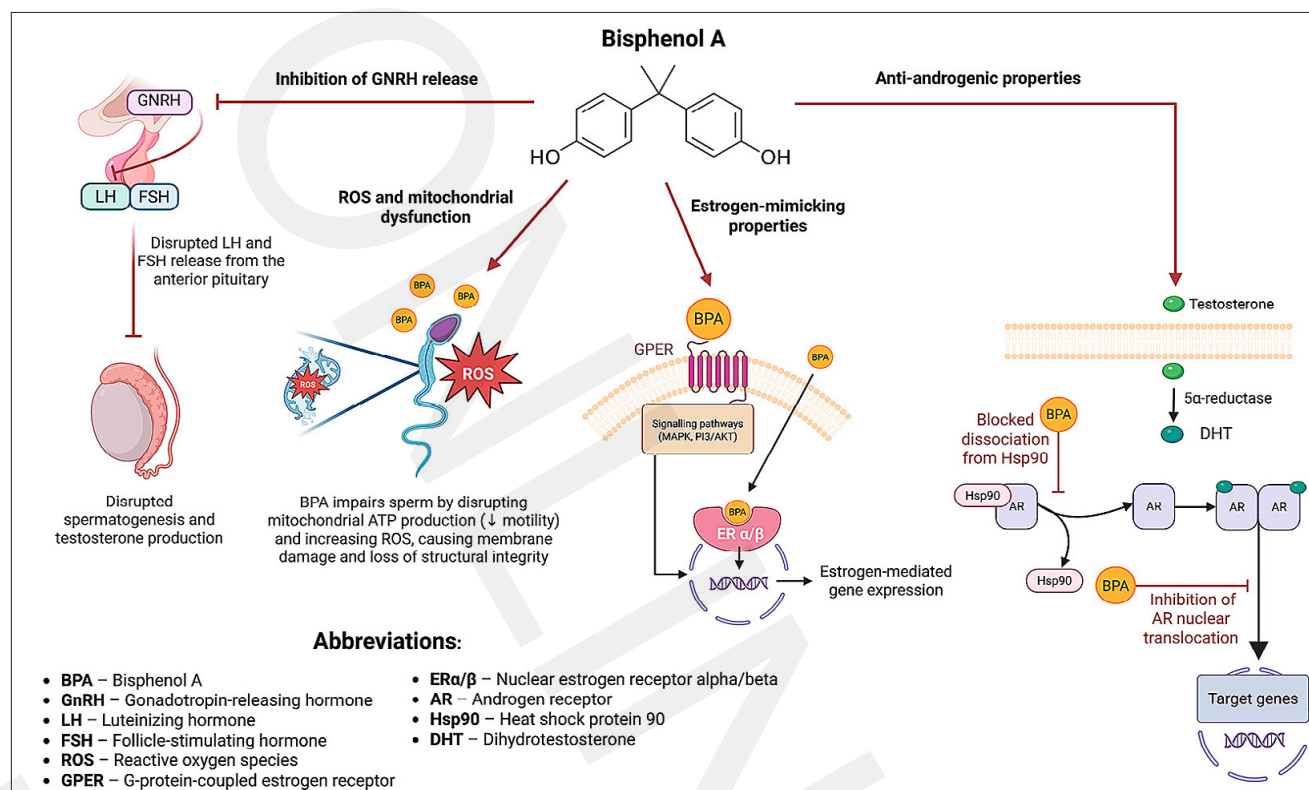


Figure 2. Mechanisms of BPA-Induced Endocrine Disruption in Male Reproduction. Created in <https://BioRender.com>, based on references [8, 9, 19, 20, 21, 22, 24]

Protective measures and alternatives. In parallel with exploring protective compounds, reducing BPA exposure remains critical. Substituting polycarbonate (PC) plastics with safer materials, such as PET, HDPE, BPA-free containers, or lightweight glass, is strongly recommended. Exposure risks increase significantly when PC plastics are subjected to heat through boiling, microwaving, or filling with hot liquids, practices that should be avoided [4]. Thorough rinsing after washing with detergents, particularly alkaline, is essential to minimize residual BPA. Bottled water should not be stored in direct sunlight or outdoors, as this can accelerate the leaching of BPA [16, 36]. Manufacturers should provide clear labelling regarding cleaning methods, usage duration, and BPA content, and conduct thorough testing to monitor BPA release under varying conditions. Consumers must also be proactive: discard ageing bottles, watch for changes in colour or odour, and replace containers regularly. Public awareness of health hazards caused by BPA, particularly for infants, is vital [37].

Limitations of the study. Although the reviewed studies provide compelling evidence linking BPA to impaired male fertility, several limitations must be acknowledged. Many studies are based on animal models or *in vitro* data, which may not fully reflect the complexity of human reproductive physiology. Human studies often vary in design, sample size, BPA exposure measurement, and control for confounding factors, making it difficult to draw firm conclusions or establish causality.

In addition to these limitations within the literature, this review itself has certain constraints. The analysis was narrative and not conducted as a systematic review or meta-analysis. The selection of studies was limited to those published in English and accessible through selected databases, which may have introduced selection bias.

Despite these limitations, the review provides an integrative overview of current findings, emphasizing both molecular mechanisms and human evidence, and offers a perspective on the potential impact of BPA on male fertility.

CONCLUSIONS

BPA poses a serious risk to male fertility through hormonal disruption, oxidative stress, and cellular damage. While BPA analogues, such as BPS and BPF, are used as alternatives, emerging evidence suggests they are similarly hazardous. Minimizing exposure through informed consumer behaviour, stricter regulations, and the adoption of inert or biodegradable alternatives is crucial. Ongoing research must focus on establishing safe thresholds and developing non-toxic materials to safeguard reproductive health. As infertility becomes a growing concern globally and BPA remains pervasive, collaborative action in scientific research, regulatory measures, and public education is critical in addressing its impact on reproductive health.

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