

REVIEW

Endocrine disruptors and male reproductive health: mechanisms, epigenetics, and clinical perspectives

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Abstract

Male infertility, a pressing public health issue, is increasingly linked to exposure to endocrine-disrupting chemicals (EDCs), such as phthalates, bisphenol A (BPA), organochlorines, pesticides, as well as natural EDCs such as phytoestrogens. This review synthesizes mechanistic and translational evidence on how EDCs impair male reproductive function through multifaceted pathways. EDCs disrupt the hypothalamic-pituitary-gonadal (HPG) axis, induce cytotoxic effects in Leydig and Sertoli cells, and impair steroidogenesis and spermatogenesis, leading to clinically significant reductions in sperm concentration, motility, and morphology. Emerging data highlight transgenerational effects via epigenetic modifications, including altered DNA methylation and microRNA expression, which may perpetuate infertility across generations. We critically evaluate epidemiological and experimental studies, revealing consistent associations between EDC exposure and adverse reproductive outcomes, such as cryptorchidism, testicular cancer, and idiopathic infertility. Notably, prenatal and perinatal exposure windows exhibit heightened vulnerability, with lifelong consequences. Despite progress, key gaps persist in understanding low-dose mixture effects, interindividual susceptibility, and the interplay between EDCs and lifestyle factors (*e.g.*, oxidative stress, psychosocial stressors). Clinically, this review underscores the need for enhanced biomonitoring to quantify real-world EDC exposures and their interactions, mechanistic research elucidating dose-response relationships and non-monotonic effects, and evidence-based policies to regulate EDCs in consumer products, agriculture, and healthcare. We propose a translational framework integrating high-throughput toxicology, epigenetic biomarkers, and clinical interventions to mitigate risks. Addressing these challenges is urgent to safeguard male reproductive health amid rising global infertility rates. Future research should also explicitly consider the role of natural endocrine-disrupting compounds, particularly phytoestrogens, in shaping male reproductive outcomes.

Keywords

Endocrine disruptors; Male infertility; Spermatogenesis; Epigenetic transgenerational inheritance; Environmental toxicology; Clinical policy; Natural endocrine disrupting compounds

Disruptores endocrinos y salud reproductiva masculina: mecanismos, epigenética y perspectivas clínicas

Resumen

La infertilidad masculina, un problema creciente de salud pública, se asocia cada vez más con la exposición a disruptores endocrinos (EDCs), incluyendo ftalatos, bisfenol A (BPA), compuestos organoclorados, pesticidas, así como disruptores endocrinos naturales como los fitoestrógenos. Esta revisión sintetiza evidencia mecanística y traslacional sobre cómo los EDCs afectan la función reproductiva masculina a través de múltiples vías interrelacionadas. Los EDCs alteran el eje hipotálamo-hipófiso-gonadal (HPG), inducen efectos citotóxicos en células de Leydig y Sertoli, y afectan la esteroidogénesis y la espermatogénesis, lo que se traduce en reducciones clínicamente significativas en la concentración, motilidad y morfología espermática. Evidencia emergente destaca efectos transgeneracionales mediados por modificaciones epigenéticas, incluyendo alteraciones en la metilación del ADN y la expresión de microARN, que podrían perpetuar la infertilidad a lo largo de generaciones. Evaluamos críticamente los estudios epidemiológicos y experimentales, los cuales revelan asociaciones consistentes entre la exposición a EDCs y resultados reproductivos adversos, como criptorquidia, cáncer testicular e infertilidad idiopática. Las ventanas de exposición prenatal y perinatal representan períodos de especial vulnerabilidad, con consecuencias a largo plazo sobre la salud reproductiva. A pesar de los avances, persisten importantes lagunas en la comprensión de los efectos de mezclas a bajas dosis, la susceptibilidad individual y la interacción entre EDCs y factores de estilo de vida, como el estrés oxidativo y los factores psicosociales. Desde el punto de vista clínico, esta revisión subraya la necesidad de mejorar la biomonitorización para cuantificar exposiciones reales, profundizar en los mecanismos dosis-respuesta y en los efectos no monotónicos, y fortalecer las políticas regulatorias basadas en evidencia. Se propone un marco traslacional que integre toxicología de alto rendimiento, biomarcadores epigenéticos e intervenciones clínicas para mitigar riesgos. Abordar estos desafíos es fundamental para proteger la salud reproductiva masculina ante el aumento global de la infertilidad. Futuras investigaciones deberán considerar de manera explícita el papel de los disruptores endocrinos naturales, particularmente los fitoestrógenos, en los resultados reproductivos masculinos.

Palabras Clave

Disruptores endocrinos; Infertilidad masculina; Epigenética; Calidad espermática; Exposición ambiental; Fitoestrógenos; Disruptores endocrinos naturales

1. Introduction

Endocrine disrupting chemicals (EDCs) have emerged as pervasive environmental contaminants with well documented potential to interfere with hormonal signaling across multiple biological systems. These substances include synthetic and natural compounds such as bisphenols (*e.g.*, bisphenol A), phthalates, pesticides (*e.g.*, organophosphates, organochlorines, glyphosate, atrazine), toxic non essential metals (*e.g.*, cadmium, lead, mercury, arsenic), and polychlorinated biphenyls (PCBs), which may disrupt endocrine homeostasis through diverse and interconnected molecular mechanisms [1–5]. Their widespread presence in air, water, food, plastics, personal care products, and agricultural applications facilitates chronic human exposure, frequently occurring as complex low dose mixtures with bioaccumulative potential [6, 7]. These exposures have been associated with a broad spectrum of adverse health outcomes, including metabolic dysfunctions, hormone dependent cancers, and reproductive disorders [8, 9]. Among these, male reproductive health represents a particularly sensitive endpoint, with epidemiological evidence indicating that male infertility affects approximately 7% of men worldwide and contributes to nearly half of all infertility cases, alongside reported global declines in sperm quality parameters over recent decades [10–13].

At the mechanistic level, EDCs have been shown to interfere with male reproductive physiology through multiple, often overlapping pathways, highlighting their systemic im-

pact across multiple biological levels (Fig. 1). Disruption of steroidogenesis occurs through the inhibition of key enzymes, such as steroidogenic acute regulatory protein and cytochrome P450 family members, resulting in reduced testosterone synthesis. In parallel, EDC-induced oxidative stress promotes excessive generation of reactive oxygen species (ROS), leading to lipid peroxidation, DNA damage, and impaired sperm function. Mitochondrial dysfunction further contributes to these effects by compromising cellular energy metabolism and activating apoptotic pathways in germ cells. Additionally, EDCs may alter gene expression within the seminiferous epithelium and disrupt the integrity of the blood-testis barrier, thereby impairing spermatogenesis. Dysregulation of the Hypothalamic-Pituitary-Gonadal axis (HPG) axis, including altered gonadotropin signaling, represents another key mechanism contributing to endocrine imbalance. In addition, increasing evidence suggests that epigenetic mechanisms, such as aberrant DNA methylation, histone modifications, and microRNA regulation, may contribute to persistent and potentially transgenerational effects. However, despite strong experimental support, the translation of these mechanisms into consistent human outcomes remains heterogeneous and, in some cases, uncertain, highlighting limitations in causal inference and the need for cautious interpretation.

Given the chemical diversity of EDCs and the complexity of their biological actions, there is a need for integrative and critically informed syntheses that move beyond descriptive summaries. Unlike previous reviews, the present work adopts

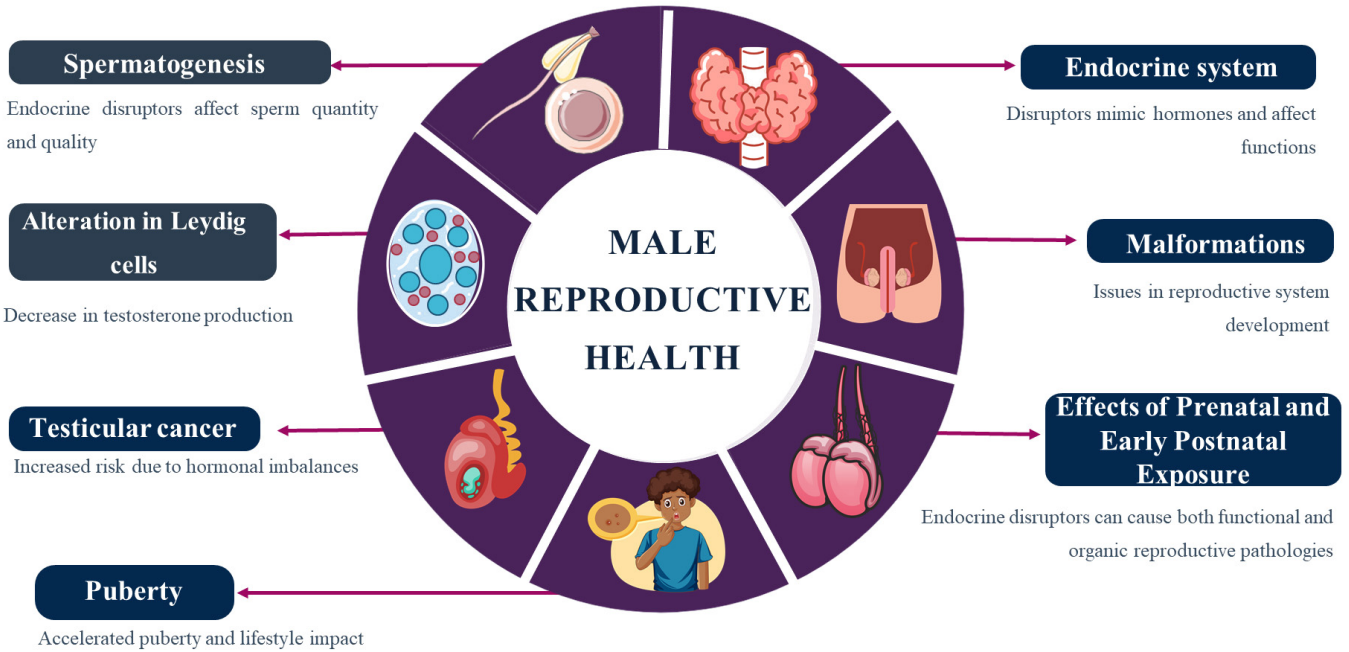


FIGURE 1. Endocrine disruptors and critical periods of exposure on male reproductive health.

a translational perspective that integrates adverse outcome pathways, mechanistic toxicology, and emerging epigenetic evidence within a unified conceptual framework linking environmental exposure to clinical reproductive outcomes. This narrative review aims to elucidate principal molecular mechanisms by which selected EDCs may impair male reproductive physiology, critically evaluate evidence supporting epigenetic and transgenerational effects, and identify persistent gaps in risk assessment and regulatory frameworks that limit effective clinical and public health responses. Evidence was prioritized based on reproducibility, biological plausibility, consistency across independent studies, and relevance to real world exposure scenarios, while conflicting or limited findings are explicitly discussed in the context of their implications for human reproductive risk.

While a substantial body of evidence supports the biological plausibility of EDC-induced reproductive toxicity, the strength and consistency of human evidence remain variable and, in some cases, inconclusive.

2. Review

2.1 Methodology and literature search strategy

A non-systematic critical narrative review was conducted to offer a comprehensive and impartial synthesis of the impacts of EDCs on male reproductive health. The literature review used PubMed/MEDLINE, Scopus, and Web of Science databases, focusing on publications from 2020 to 2025. Earlier, important studies were also included to help build a mechanistic framework. The search strategy used a combination of Medical Subject Headings (MeSH) terms and keywords. These included “Endocrine Disruptors”, “Male Infertility”, “Spermatogenesis”, “Epigenetics”, “Bisphenol A”, and “Phthalates”. The inclusion criteria were defined by three key fac-

tors: (1) the requirement for peer-reviewed original research and meta-analyses; (2) the necessity for studies that clarified molecular or epigenetic mechanisms; and (3) the inclusion of epidemiological cohorts that presented clear biomonitoring data. Bisphenol A (BPA) and Phthalates (Di(2-ethylhexyl) phthalate (DEHP), Dibutyl phthalate (DBP)) were selected as reference compounds because they are commonly found in human biomonitoring studies and have established non-monotonic dose-response relationships. This approach allowed for the integration of different types of evidence, from molecular signaling observed in lab settings to clinical findings related to reproduction.

2.2 Overview of endocrine disruptors

These compounds interfere with hormonal balance by altering synthesis, metabolism, receptor binding, or signal transduction [14]. They enter the human body via inhalation, dermal absorption, ingestion, or placental transfer [15], and their impact depends on exposure route and intensity, with higher infertility rates observed in exposed populations [16]. Major groups include bisphenols, phthalates, pesticides, dioxins, polybrominated diphenyl ethers (PBDEs), phytoestrogens, and toxic non-essential metals, which can mimic or antagonize endogenous hormones and disrupt receptor-mediated signaling [15].

BPA, detected in 90% of the U.S. population, is widely used in plastics and food containers, and heating increases its leaching [15, 17]. BPA and its analogs disrupt the HPG axis, impair steroidogenesis and Leydig cell function, and reduce sperm quality through oxidative stress and mitochondrial dysfunction [18, 19]. Phthalates and related endocrine disruptors induce ROS generation, decrease testosterone levels, and impair sperm motility and DNA integrity [20, 21]. Dioxins are associated with impaired spermatogenesis and testicular dysgenesis [22], whereas PBDEs may interfere with thyroid hormone signaling pathways relevant to male infertility

[23]. BPA-induced testicular immune dysfunction has also been linked to suppressed steroidogenesis [24]. In addition, several endocrine-disrupting compounds, including phytoestrogens and other environmental contaminants, may alter hormonal balance and adversely affect male reproductive health [25].

2.3 Endocrine disruptors and their impact on male reproductive function

EDCs impair male reproductive function through diverse molecular mechanisms. Regulatory agencies have recognized their impact: The European Chemicals Agency (ECHA) classifies phthalates (DEHP, DBP) and BPA as Substances of Very High Concern (SVHC), while the U.S. Environmental Protection Agency (EPA) monitors them under its Endocrine Disruptor Screening Program (EDSP). The molecular mechanisms described in the following paragraphs derive predominantly from experimental models (*in vitro* and animal studies). At the molecular level, EDCs exert agonist or antagonist effects on estrogen receptor alpha/beta ($ER\alpha/\beta$), androgen receptor (AR), and aryl hydrocarbon receptor (AhR), disrupting endocrine signaling cascades and steroidogenesis-related pathways in Leydig cells [26–28]. They inhibit steroidogenic enzymes (*e.g.*, Steroidogenic Acute Regulatory Protein (StAR), Cytochrome P450 Family 11 Subfamily A Member 1 (CYP11A1)), impair mitochondrial function, increase apoptosis in germ and Sertoli cells, and dysregulate junctional proteins necessary for spermatogenesis. These changes manifest as reduced sperm count, poor motility, DNA fragmentation, and reproductive tract abnormalities [26–28].

The estrogenic pathway appears particularly susceptible to disruption, with consequences including testicular dysgenesis, prostate alterations, and increased cancer risk [29–32]. Moreover, many idiopathic infertility cases show consistent associations with chronic EDC exposure [29–32].

Timing of exposure is critical. Fetal and neonatal exposure windows are particularly vulnerable, with long-term effects on genital development and reproductive capacity [33–35]. Disruption of lipid metabolism in sperm and altered epigenetic programming (*e.g.*, DNA methylation, histone modification) further contribute to long-lasting reproductive dysfunction [31, 32]. An emerging area of research examines the interaction between EDC exposure and psychosocial and lifestyle factors in male reproductive outcomes. In this context, chronic stressors have been associated with activation of the (Hypothalamic–Pituitary–Adrenal) HPA axis and increased cortisol, which may contribute to hormonal alterations linked to EDCs. Additionally, lifestyle factors, such as obesity, sedentary behavior, alcohol consumption, and tobacco use, may exacerbate oxidative stress and inflammation, with potential implications for sperm quality [29–32].

A critical yet insufficiently integrated aspect of EDC research is their lipid solubility and consequent accumulation in adipose tissue, which challenges conventional exposure assessment paradigms [6, 7]. Lipophilic EDCs, such as organochlorines, dioxins, and certain bisphenols, preferentially partition into fat depots, where they may persist for prolonged periods and be intermittently released

during lipolysis, including states of weight loss or metabolic stress [14]. This reservoir-like behavior sustains chronic internal exposure independent of ongoing environmental contact, thereby complicating dose-response interpretation and potentially contributing to the non-monotonic effects characteristic of EDCs. Moreover, the endocrine and inflammatory activity of adipose tissue itself may amplify these effects, introducing a biologically plausible, but poorly quantified, interaction between metabolic status and reproductive toxicity, particularly at the level of the HPG axis [26]. Despite its mechanistic relevance, this dimension remains underrepresented in human studies and is rarely incorporated into epidemiological or toxicokinetic models, limiting its translation into risk assessment frameworks.

Bisphenols, particularly BPA, exert multifaceted toxicity on testicular cells, targeting both Sertoli and Leydig populations. In Sertoli cells, BPA induces apoptotic signaling cascades, disrupts tight junction integrity, and impairs mitochondrial function, leading to calcium overload and oxidative stress [36–39]. These alterations compromise the blood-testis barrier and the nutritive microenvironment required for germ cell survival. Concurrently, Leydig cells experience suppressed steroidogenic output due to downregulation of key enzymes and mitochondrial dysfunction, resulting in reduced intratesticular testosterone—a critical regulator of spermatogenesis [36–39].

Rodent models reveal that BPA activates pro-apoptotic proteins, such as caspase-3, -7, -9, and Bax, while concurrently downregulating anti-apoptotic B-cell lymphoma 2 (Bcl-2) expression [39]. BPA also perturbs autophagic flux via Protein Kinase B (Akt)/Mechanistic Target of Rapamycin (mTOR) dysregulation and induces ferroptosis through lipid peroxidation mechanisms, reflecting broader disruption of cellular homeostasis [39]. While these findings provide mechanistic clarity, the extent to which these pathways operate similarly in human testicular physiology remains under investigation.

2.4 Epidemiological evidence on the link between endocrine disruptors and male infertility

2.4.1 Prevalence of male reproductive disorders associated with endocrine disruptors

Animal studies consistently demonstrate that EDCs disrupt multiple domains of male reproductive function. While these findings derive predominantly from experimental paradigms, human epidemiological data provide direct translational support. For example, diethylstilbestrol exposure impairs erectile tissue contractility in mice, mirroring erectile dysfunction (ED) [34]. Consistently, a U.S. cohort of 555 men reported a 33% increased risk of ED among individuals with the highest urinary levels of organophosphate metabolites [35]. Given that ED may contribute to up to 5% of male infertility cases, this association holds clinical significance [40]. Meta-analyses confirm that prenatal and postnatal EDC exposures elevate risks for male reproductive anomalies, including testicular germ cell tumors, cryptorchidism, and hypospadias [41]. The concept of testicular dysgenesis syndrome (TDS), proposed

by Skakkebaek *et al.* [42], integrates these conditions as potentially linked developmental disorders with environmental origins, while BPA has been associated with increased cryptorchidism risk through disruption of androgen signaling during fetal development [43, 44]. Additionally, bisphenols and alkylphenols have been associated with reduced anogenital distance and structural testicular alterations [45, 46], indicating that EDCs affect male reproductive health across the lifespan.

2.4.2 Global trends in male infertility and its association with endocrine disruptors

Male infertility affects over 30 million men globally and contributes to approximately 50% of all couple-level infertility [47–50]. Though multifactorial in origin, environmental exposures are emerging as central contributors. A 52% decline in sperm concentration has been documented between 1973 and 2011 among men in Western countries [51], a trend unlikely to be explained by genetics alone.

This decline correlates with increased exposure to phthalate metabolites, such as Mono(2-carboxymethylhexyl) phthalate (MCMHP), Mono(2-ethylhexyl) phthalate (MEHHP), Monobenzyl phthalate (MBZP), and Monoisononyl phthalate (MNP), which exhibit dose-dependent associations with reduced sperm concentration, total sperm count, motility and morphological integrity, including enlarged sperm head size [52]. These consistent temporal and geographic trends highlight EDCs as modifiable environmental risk factors in the ongoing deterioration of male reproductive capacity.

2.5 Specific endocrine disruptors and their relationship with male infertility

BPA is a ubiquitous synthetic phenol present in plastics, thermal papers, and food containers. *In vivo*, BPA binds both nuclear (ER α /ER β) and membrane-bound (G Protein-Coupled Estrogen Receptor (GPER), Estrogen-Related Receptor gamma (ERR γ)) estrogen receptors, triggering Mitogen-Activated Protein Kinase (MAPK) cascade activation (Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2), p38 Mitogen-Activated Protein Kinase (p38), c-Jun N-terminal Kinase (JNK)) and downregulation of tight junction proteins within the seminiferous epithelium [53–55]. Epigenetic transgenerational effects have been reported, including histone hyperacetylation and DNA methylation changes that impair embryonic development and long-term testicular function [55, 56].

Phthalates—including DEHP and DBP—exhibit potent anti-androgenic properties. They inhibit testosterone biosynthesis, reduce AR expression, and disrupt Sertoli cell energy metabolism. Clinical studies in infertile men show that Mono(2-ethylhexyl) phthalate (MEHP) and related metabolites correlate with reduced miRNA106a expression and increased mtDNA damage in sperm, reflecting impaired mitochondrial integrity and functional capacity [57–60].

Pesticides, such as dichlorodiphenyltrichloroethane (DDT) and organochlorines, persist in the environment and disrupt hormonal balance through alterations in steroidogenesis and oxidative stress pathways [61–63]. Heavy metals such as cadmium, lead, arsenic, and mercury also interfere with the

HPG axis. Cadmium induces apoptosis in Sertoli and Leydig cells, lead reduces sperm motility, and mercury promotes DNA fragmentation in spermatozoa, effects largely associated with oxidative stress (Fig. 2) [64, 65].

2.6 Cellular and molecular mechanisms involved in the effects of endocrine disruptors on fertility

2.6.1 Interference with hormonal receptors and disruption of intracellular signaling

EDCs act through multiple converging mechanisms, primarily by binding to nuclear hormone receptors or interfering with intracellular signaling pathways. Bisphenols A, F and S (BPA, BPF, BPS) mimic 17 β -estradiol, functioning as ER agonists, while concurrently antagonizing AR signaling. These dual effects alter gene transcription, reduce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, and inhibit the steroidogenic acute regulatory protein (StAR), leading to deficient testosterone synthesis in Leydig cells (Fig. 3) [64].

Phthalates, such as DEHP and Diisononyl Phthalate (DiNP), inhibit AR expression and impair aromatase activity, further compromising the androgen-to-estrogen balance critical for spermatogenesis. These compounds also disrupt Sertoli cell architecture and Leydig cell differentiation, as evidenced by malformed seminiferous tubules and Leydig cell vacuolization in animal studies. Correlational human data consistently demonstrate reduced sperm quality in men with elevated urinary phthalate metabolites (Fig. 3) [64].

Pesticides, including chlorpyrifos and dioxins, impair testicular function by suppressing the Cyclic Adenosine Monophosphate (cAMP)/Protein Kinase A (PKA) signaling cascade in Leydig cells. This results in downregulation of steroidogenic enzymes—StAR, CYP11A1, and Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- and Steroid Delta-Isomerase 1 (HSD3B1)—thereby limiting testosterone production [61, 66–69]. Moreover, inhibition of LH-mediated Luteinizing Hormone/Choriogonadotropin Receptor (LHCGR) activation compromises both steroidogenesis and cellular differentiation, exacerbating male reproductive dysfunction (Fig. 3).

2.6.2 Oxidative stress, sperm DNA damage, and apoptosis

EDCs, such as BPA, phthalates, and certain pesticides, compromise male fertility through the induction of oxidative stress and apoptosis. These compounds increase the generation of ROS while impairing the activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx), leading to lipid peroxidation and damage to the sperm plasma membrane [70–72]. BPA further amplifies oxidative stress via activation of the Toll-Like Receptor 4 (TLR4)/Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway, which increases pro-inflammatory cytokines, notably Tumor Necrosis Factor alpha (TNF- α), aggravating cellular dysfunction [70–72].

Experimental models demonstrate that chlorpyrifos, a common organophosphate pesticide, induces DNA fragmentation and mitochondrial dysfunction in rat testes

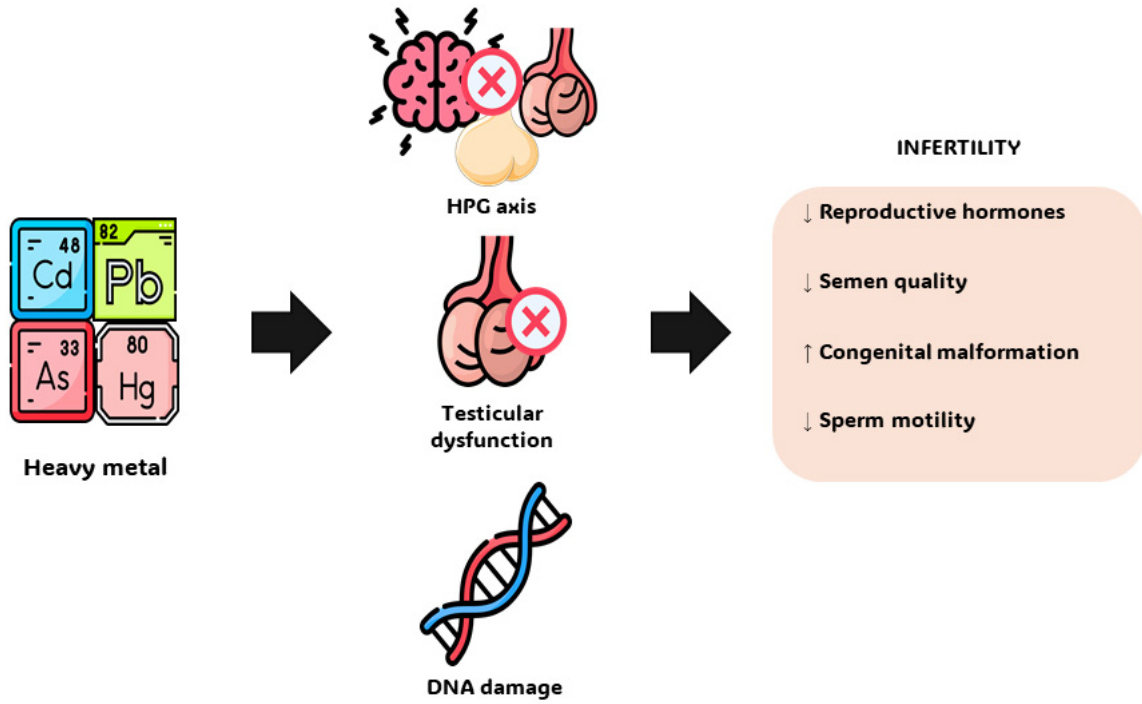


FIGURE 2. Relationship between heavy metals and male infertility. DNA: Deoxyribonucleic acid; HPG axis: hypothalamic-pituitary-gonadal axis.

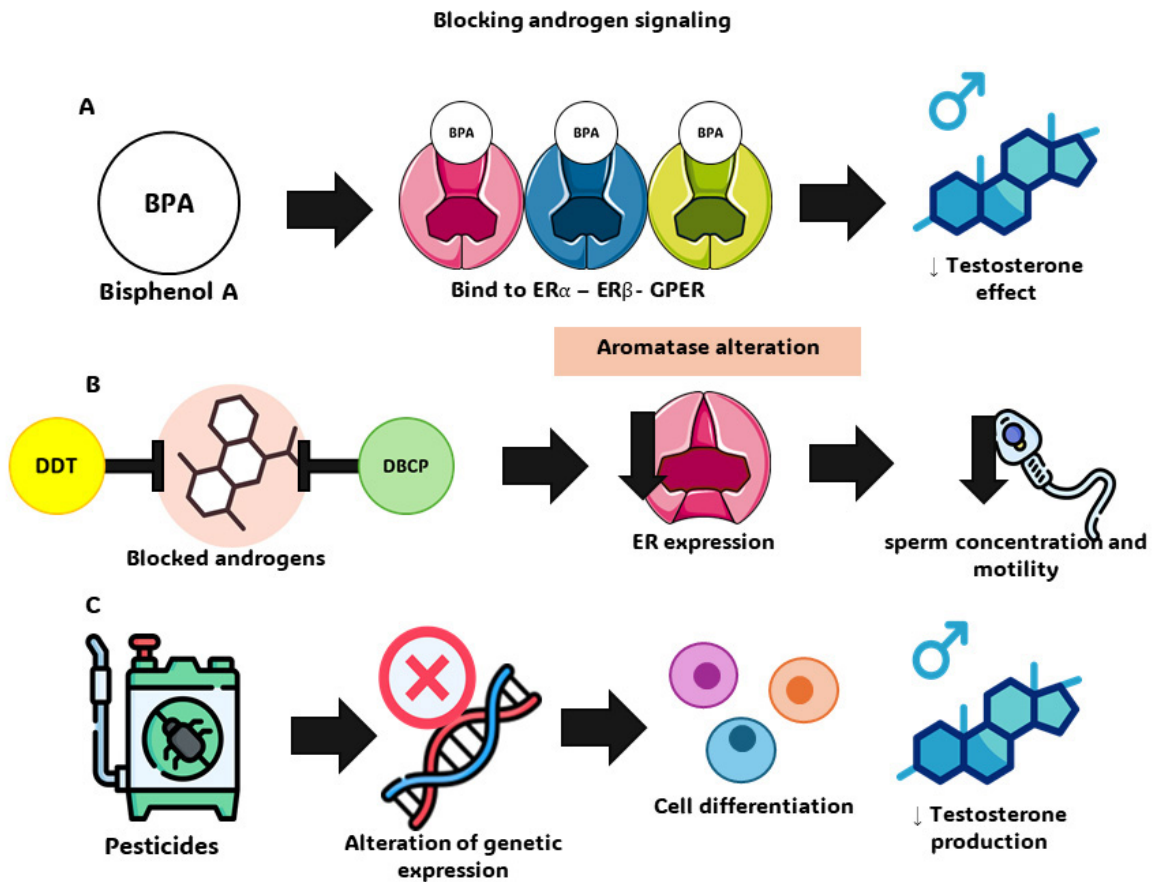


FIGURE 3. Action of endocrine disruptors on nuclear and membrane receptors. (A) Bisphenol A. (B) Phthalates. (C) Pesticides. ER: Estrogen receptor; GPER: G Protein-Coupled Estrogen Receptor; DDT: dichlorodiphenyltrichloroethane; DBCP: dibromochloropropane.

through ROS-mediated mechanisms and endoplasmic reticulum (ER) stress—evidenced by upregulation of C/EBP Homologous Protein (CHOP) and caspase-3. Similarly, BPA initiates germ cell apoptosis through caspase-9 activation, driven by ER stress markers, such as Glucose-Regulated Protein 78 (GRP78) and Protein Kinase RNA-like Endoplasmic Reticulum Kinase (PERK), and enhanced lipid peroxidation [70–72]. Other EDCs, including dioxins and Per- and Polyfluoroalkyl Substances (PFAS), exacerbate these processes by suppressing anti-apoptotic Bcl-2 and compromising the blood-testis barrier, facilitating toxicant penetration and amplifying spermatogenic damage. These disruptions culminate in mitochondrial failure, DNA damage, and decreased sperm viability and motility—hallmarks of compromised male reproductive potential (Fig. 4) [66–68, 73].

2.6.3 Epigenetic changes and transgenerational effects

EDCs also exert long-lasting effects through epigenetic modifications in the male germline, thereby propagating reproductive dysfunction across generations. The concept that environmental exposures can reprogram the epigenome of gametes and embryos, ultimately shaping reproductive capacity across the life course and even across generations, is supported by a substantial body of foundational literature [74–77].

Animal studies reveal that BPA and phthalates induce hypomethylation of critical genes involved in testicular development and endocrine regulation, such as Estrogen Receptor

1 (*Esr1*) and H19, while dioxins promote hypomethylation of androgen-regulating gene promoters [78–80]. These DNA methylation aberrations can persist across F2 and F3 generations, as demonstrated in vinclozolin exposure models, which lead to sustained downregulation of spermatogenesis-related genes [76].

In addition to DNA methylation, BPA and glyphosate have been shown to alter histone acetylation patterns—particularly decreasing acetylation of histones H3 and H4—resulting in chromatin condensation defects that impair spermatogenesis [78, 79]. Oxidative stress has emerged as a key mediator linking environmental exposures to epigenetic instability in germ cells, with ROS-induced DNA damage directly impairing global sperm DNA methylation [81, 82].

Furthermore, organophosphates and phthalates disrupt the expression of sperm-specific microRNAs, including miR-34c and miR-202, which are essential for germ cell differentiation and maturation (Fig. 5) [78–80, 83]. Early-life and in utero exposures appear particularly critical, as demonstrated by studies showing that maternal exposure to BPA induces persistent DNA hypomethylation in offspring, an effect that can be partially mitigated by maternal methyl-donor supplementation [84, 85].

While experimental studies provide compelling evidence for epigenetic inheritance following EDC exposure, several limitations must be acknowledged. Most transgenerational data derive from animal models using controlled exposure paradigms that may not fully recapitulate the complexity of human expo-

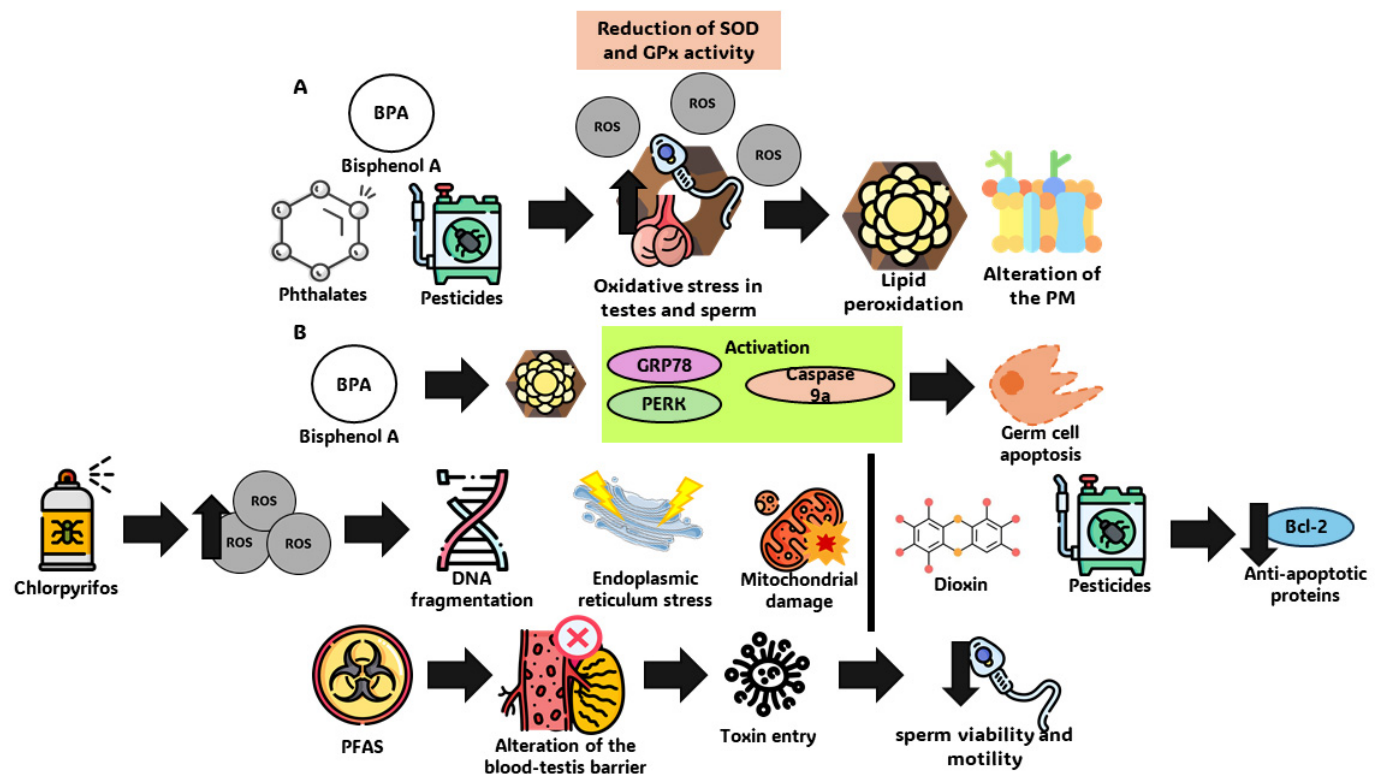


FIGURE 4. Oxidative stress, sperm DNA damage, and apoptosis. (A) Generation of reactive oxygen species (ROS). (B) DNA fragmentation and mitochondrial damage. SOD: Superoxide Dismutase; GPx: Glutathione Peroxidase; PM: Plasma Membrane; GRP78: Glucose-Regulated Protein 78; PERK: Protein Kinase RNA-like Endoplasmic Reticulum Kinase; Bcl-2: B-cell Lymphoma 2; PFAS: Per- and Polyfluoroalkyl Substances.

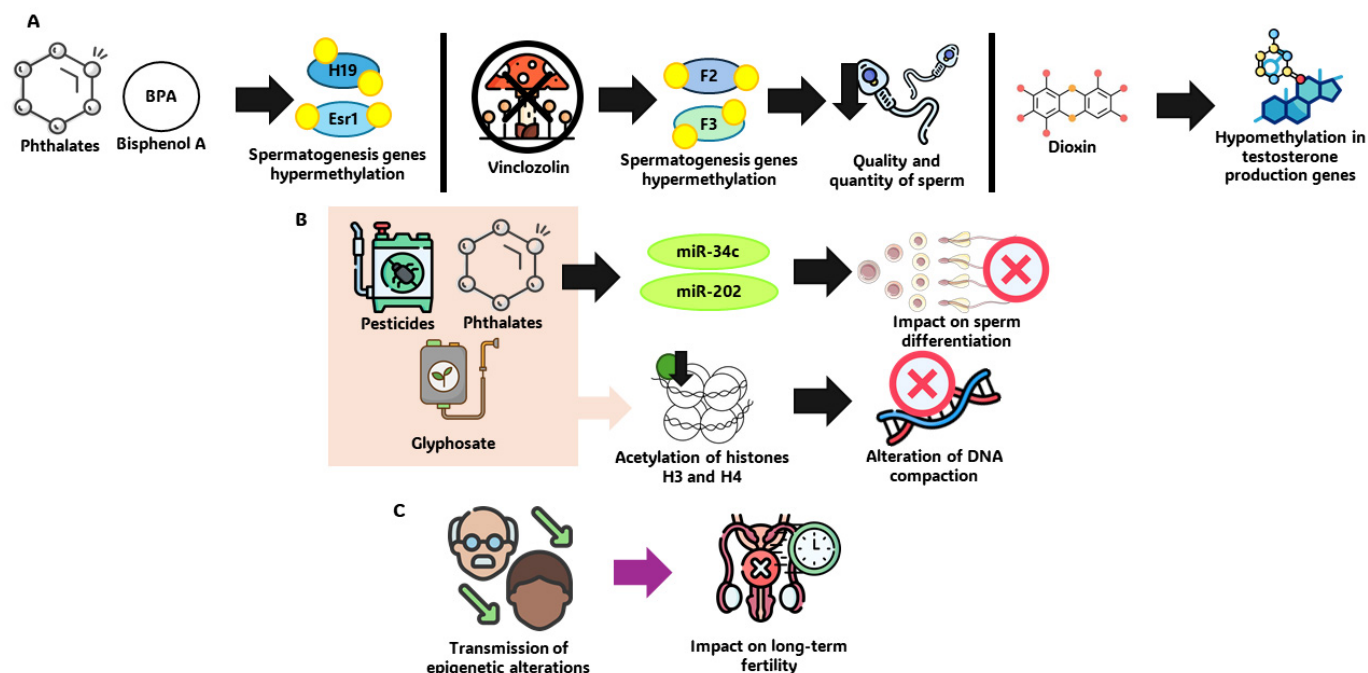


FIGURE 5. Epigenetic changes and transgenerational effects. (A) Alterations in DNA methylation. (B) Modifications in histones and microRNAs. (C) Hereditary effects. DNA: Deoxyribonucleic acid; miR: Micro ribonucleic acid; Esr1: Estrogen Receptor 1.

sure scenarios, including mixed chemical exposures, variable timing, and interindividual susceptibility [75]. Moreover, the causal linkage between specific epigenetic marks and clinically manifest infertility phenotypes in humans remains incompletely established. Consequently, current evidence supports strong biological plausibility, rather than definitive causality, underscoring the need for longitudinal human studies integrating epigenomic profiling with reproductive outcomes.

It is critical to differentiate between intergenerational and true transgenerational epigenetic inheritance. Exposure of a pregnant female involves direct contact with the F1 fetus and the F2 germ cells; thus, phenotypic changes in these generations are considered intergenerational. In contrast, true transgenerational inheritance is defined by the persistence of epigenetic marks in the F3 generation and beyond, which were never directly exposed. While vinclozolin and BPA models provide compelling evidence in rodents, the current evidence in humans supports strong biological plausibility, rather than definitive clinical causality [74–76].

2.6.4 Adverse outcome pathways and male infertility

Adverse Outcome Pathways (AOPs) describe the progression from molecular disruptions induced by EDCs to adverse reproductive outcomes. In experimental models, BPA interacts with estrogen receptors and antagonizes androgen receptors, altering steroidogenic enzyme expression, increasing oxidative stress, and promoting germ cell apoptosis, processes that may contribute to impaired sperm quality [64, 77–80]. Phthalates such as DEHP and DBP have been associated with disruption of androgen signaling, reduced testosterone biosynthesis, and altered spermatogenesis, while other EDCs, including dioxins, pesticides, and heavy metals such as cadmium, arsenic, and

lead, are linked to pathways involving mitochondrial dysfunction, epigenetic alterations, and blood-testis barrier disruption. These mechanisms support the application of AOP frameworks in integrating toxicological evidence, although their translation to human reproductive outcomes remains heterogeneous [52, 81–83] (Table 1, Ref. [3, 65, 70, 72, 78–80]).

2.6.5 Dose relevance, non-monotonicity, and translational limitations

A critical challenge in interpreting the reproductive toxicity of EDCs lies in the discrepancy between experimental exposure levels and real-world human conditions. Many *in vitro* and *in vivo* studies employ concentrations that exceed those detected in biomonitoring studies, limiting direct toxicological extrapolation. At the same time, EDCs exhibit non-monotonic dose-response relationships, whereby low doses within environmentally relevant ranges may induce biological effects not predicted by traditional high-dose paradigms. For instance, BPA and certain phthalates exert endocrine and epigenetic effects at nanomolar to micromolar concentrations overlapping with levels reported in human serum and urine [17, 53, 54]. Population data indicate urinary BPA concentrations of 1–10 ng/mL and DEHP metabolites such as MEHP in the range of 20–200 ng/mL [17, 57–60], levels that have been associated with altered sperm parameters and molecular changes, suggesting potential biological relevance under typical exposure conditions [52, 84–86].

However, not all mechanisms identified in experimental systems are necessarily operative in humans. High-dose models may overrepresent pathways such as severe oxidative stress, apoptosis, or mitochondrial dysfunction, which may not fully reflect responses at lower exposure levels. In parallel, epidemiological evidence remains heterogeneous, with some studies

TABLE 1. Summary of EDC classes, mechanisms of male reproductive toxicity, and key supporting studies.

EDC Class	Key Compounds	Mechanisms of Male Reproductive Toxicity	Representative Studies
Bisphenols	BPA, BPS, BPAF	<ul style="list-style-type: none"> - Binds ERα/ERβ, antagonizes AR - Increases ROS and inflammatory cytokines via TLR4/NF-κB - Induces germ cell apoptosis and DNA fragmentation - Alters epigenetic marks (e.g., Esr1 methylation, miRNA dysregulation) 	Castellini <i>et al.</i> [70], 2020; Uwamahoro <i>et al.</i> [72], 2024; Lü <i>et al.</i> [80], 2024
Phthalates	DEHP, DBP, BBzP	<ul style="list-style-type: none"> - Inhibits androgen biosynthesis - Damages Sertoli cell function and tight junctions - Alters histone acetylation and DNA methylation - Disrupts miR-34c and miR-202 expression 	Presunto <i>et al.</i> [78], 2023; Montjean <i>et al.</i> [79], 2024
Pesticides	DDT, DBCP, Chlorpyrifos	<ul style="list-style-type: none"> - Triggers oxidative stress and mitochondrial dysfunction - Upregulates caspase-3, CHOP (ER stress) - Alters steroidogenesis and blood-testis barrier integrity 	Uwamahoro <i>et al.</i> [72], 2024
Heavy Metals	Cd, Hg, Pb	<ul style="list-style-type: none"> - Accumulates in testes; disrupts HPG axis - Reduces testosterone and LH - Induces oxidative stress and germ cell apoptosis 	Manouchehri <i>et al.</i> [65], 2022
Dioxins & PCBs	TCDD, PCB-153	<ul style="list-style-type: none"> - Binds AhR receptor - Causes DNA hypomethylation and apoptosis - Alters Leydig cell steroidogenesis 	Presunto <i>et al.</i> [78], 2023; Castellini <i>et al.</i> [70], 2020
Perfluoroalkyl Substances (PFAS)	PFOS, PFOA	<ul style="list-style-type: none"> - Disrupts blood-testis barrier - Increases lipid peroxidation - Bioaccumulates and induces transgenerational effects 	Maxwell DL <i>et al.</i> [3], 2024

EDC: endocrine-disrupting chemical; BPA: Bisphenol A; PCBs: Polychlorinated Biphenyls; BPS: Bisphenol S; PFAS: Per- and Polyfluoroalkyl Substances; BPAF: Bisphenol A Fluorinated; DEHP: Di(2-ethylhexyl) phthalate; DBP: Dibutyl phthalate; BBzP: Benzyl Butyl Phthalate; DDT: Dichlorodiphenyltrichloroethane; DBCP: 1,2-Dibromo-3-chloropropane; TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin; PCB-153: 2,2',4,4',5,5'-Hexachlorobiphenyl; PFOS: Perfluorooctane Sulfonate; PFOA: Perfluorooctanoic Acid; ER: endoplasmic reticulum; AR: androgen; ROS: reactive oxygen species; TLR4: Toll-Like Receptor 4; NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells; Esr1: Estrogen Receptor 1; CHOP: C/EBP Homologous Protein; HPG: hypothalamic-pituitary-gonadal; LH: luteinizing hormone; AhR: aryl hydrocarbon.

reporting associations between EDC exposure and impaired semen quality, while others show inconsistent findings. A recent systematic review and meta-analysis reported no uniform association between EDC exposure and male fertility outcomes [86]. This variability is largely explained by methodological limitations, including exposure misclassification, reliance on single time-point measurements, and incomplete adjustment for confounders such as diet, lifestyle, and co-exposure to other endocrine-active compounds, including dietary phytoestrogens [68, 86].

The interpretation of EDC-related reproductive risk is further complicated by real-world exposure scenarios. Individuals are exposed to complex chemical mixtures with potential additive or interactive effects, which are not adequately captured by conventional toxicological or epidemiological approaches. In addition, male infertility is a multifactorial condition influenced by environmental, behavioral, and biological factors, including obesity, smoking, alcohol use, heat exposure, psychosocial stress, dietary patterns, and genetic susceptibility. These overlapping influences limit causal inference and may contribute to inconsistencies across studies. Consequently, although mechanistic evidence supports the biological plausibility of EDC-induced reproductive toxicity, translation to human outcomes remains variable, underscoring

the need for integrative approaches incorporating longitudinal biomonitoring, human-relevant exposure models, and mixture-based risk assessment frameworks [8, 26].

2.6.6 Multifactorial nature of male infertility and confounding factors

Importantly, male infertility is a multifactorial condition influenced by a wide range of environmental, lifestyle, and biological factors. Variables such as obesity, smoking, alcohol consumption, heat exposure, psychosocial stress, dietary patterns, and genetic susceptibility have been independently associated with impaired semen quality and reproductive outcomes [63, 65, 67]. In addition, occupational and environmental exposures unrelated to endocrine-disrupting chemicals may further contribute to reproductive dysfunction [16, 63]. Disentangling the relative contribution of EDC exposure from these factors remains a major challenge in human studies and may partially explain the inconsistency observed across epidemiological findings. Moreover, interactions between these variables and EDC exposure may result in additive or synergistic effects, further complicating causal inference and risk attribution in real-world scenarios [67, 68].

2.7 Impact of endocrine disruptors on public health

2.7.1 Broader public health risks of EDC exposure

Beyond infertility, EDC exposure is increasingly associated with systemic endocrine disruption affecting thyroid function, metabolism, and oncogenesis. BPA and phthalates exhibit dose-dependent thyroid-disrupting activity, altering circulating levels of T3 and T4, and perturbing thyroxine-binding globulin levels [87]. These hormonal imbalances may affect male reproductive function both directly and indirectly.

Moreover, exposure to EDCs such as Perfluorooctane Sulfonate (PFOS) and phthalates contributes to testicular carcinogenesis through oxidative DNA damage. Mechanistically, ROS-induced genomic instability leads to mutations during germ cell proliferation, predisposing to tumor development [88]. These findings highlight the multifaceted threat of EDCs to endocrine homeostasis and underscore the urgency of addressing their broader health impacts.

2.7.2 Regulatory challenges and the role of public policy

Although regulations such as the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) framework have designated several EDCs—*e.g.*, DEHP, DBP—as Substances of Very High Concern (SVHC), critical gaps persist in global chemical governance. Current risk assessments often fail to account for low-dose and non-monotonic dose-response effects characteristic of EDCs. For example, DEHP causes testicular toxicity in rats at doses as low as 3.7 mg/kg/day, well below established safety thresholds [89–91].

Regulatory disparities between countries perpetuate exposure risks, especially in regions lacking harmonized standards. Bisphenol A Fluorinated (BPAF), a persistent BPA analog, remains widely used in certain markets, despite its long half-life and proven bioaccumulation [83]. The lack of comprehensive global policies creates a disconnect between scientific evidence and regulatory action, enabling continued use of hazardous EDCs. This reinforces the need for precautionary regulation that prioritizes public health even in the face of incomplete mechanistic data [89–91].

2.8 Approaches to mitigate exposure to endocrine disruptors

2.8.1 Exposure reduction strategies

Reducing EDC exposure requires comprehensive strategies encompassing personal behavior, environmental interventions, and public education. At the individual level, substituting plastic food containers with glass or stainless steel and avoiding canned and processed foods significantly lowers BPA and phthalate intake. Households can reduce indoor contamination through ventilation, regular wet cleaning, and limiting the use of phthalate-containing products and materials [92, 93]. Agricultural mitigation strategies, including improved pesticide management and sustainable agricultural practices, may reduce environmental contamination and pesticide-associated

reproductive risks while supporting agricultural productivity [94]. At the population level, eliminating BPA and phthalates from medical equipment and food packaging has proven effective. Educational campaigns to raise awareness and drive behavior change are essential components of exposure reduction [95, 96].

2.8.2 Regulatory and policy-based interventions

Several countries have implemented regulatory measures to reduce EDC exposure, particularly in vulnerable populations. In North America, the U.S. banned the use of DEHP, BBzP, and DBP in children's products, while Canada eliminated BPA from baby bottles [97, 98]. The EU enforces a 0.1% weight limit for these compounds in childcare products through its REACH regulation [99].

Despite these advances, regulatory fragmentation remains a key obstacle. Differences in pesticide maximum contaminant levels (MCLs) for drinking water reflect unresolved debates about dose thresholds and health risks [99]. Moreover, many EDCs in food contact materials and cosmetics remain unregulated. To close these gaps, a coordinated global approach based on biomonitoring data, precautionary risk assessment, and consistent regulatory frameworks is imperative for effective EDC exposure control [98, 99].

2.9 Clinical recommendations for reproductive medicine practitioners

The translational implications of the evidence reviewed herein extend directly to clinical practice. Reproductive medicine practitioners including andrologists, urologists, and reproductive endocrinologists are increasingly positioned to identify EDC-related contributors to male infertility and to implement evidence-based preventive strategies [31]. The following recommendations are proposed based on the mechanistic, epidemiological, and toxicological evidence synthesized in this review.

2.9.1 Environmental exposure history

Routine andrological evaluation of infertile men should incorporate a structured environmental and occupational exposure history. Clinicians should inquire about: (i) occupational contact with pesticides, solvents, plastics, or industrial chemicals; (ii) dietary habits, including frequency of canned or packaged food consumption and use of plastic containers for food storage or heating; and (iii) habitual use of personal care products containing phthalates, parabens, or synthetic fragrances. This exposure assessment is particularly relevant in cases of idiopathic infertility or unexplained poor semen parameters, where EDC-related mechanisms may constitute an underrecognized etiology [67].

2.9.2 Biomonitoring in clinical practice

Where available, urinary biomonitoring of key EDC metabolites including BPA, MEHP and related phthalate metabolites, and urinary or blood levels of heavy metals (cadmium, lead, arsenic) should be considered in men presenting with unexplained oligozoospermia, asthenozoospermia, or elevated

sperm DNA fragmentation. Although biomonitoring is not yet standard of care in most clinical settings, emerging evidence supports its utility in stratifying EDC-related reproductive risk and guiding targeted counseling [57–60].

2.9.3 Preventive counseling and exposure reduction

Reducing EDC exposure requires comprehensive strategies encompassing personal behavior, environmental interventions, and public education. At the individual level, substituting plastic food containers with glass or stainless steel and avoiding canned and processed foods may reduce BPA and phthalate exposure. Households can reduce indoor contamination through ventilation, regular wet cleaning, and minimizing the use of phthalate-containing products and materials [93]. Lifestyle and behavioral interventions aimed at reducing contact with endocrine-disrupting compounds have shown potential to decrease overall exposure levels [96]. Agricultural mitigation strategies, including the adoption of Good Agricultural Practices (GAPs), may help reduce pesticide residues [95]. Educational campaigns and policy-based interventions are essential components of exposure reduction strategies [96, 97].

2.9.4 Periconceptual counseling

Given the vulnerability of prenatal and perinatal exposure windows and their potential long-term impact on male reproductive capacity, preventive counseling should be initiated prior to conception and extended to both partners. Male patients planning fatherhood should be informed of the potential effects of preconceptional EDC exposure on sperm epigenetic integrity and early embryonic development. These recommendations are consistent with current guidance in reproductive medicine and support the integration of environmental health considerations into routine andrological care [31, 67, 84].

3. Conclusion

This review integrates mechanistic, epigenetic, and translational evidence to examine the role of endocrine-disrupting chemicals in male reproductive health, linking molecular pathways with clinically relevant outcomes. While experimental data support the biological plausibility of EDC-induced reproductive toxicity, human evidence remains heterogeneous and, in some cases, inconclusive, largely due to variability in exposure assessment, study design, and confounding factors. These limitations underscore the need for cautious interpretation and more robust research frameworks. Future studies should prioritize longitudinal human data, improved exposure characterization, and mixture-based approaches to better define the contribution of EDCs to male infertility within real-world contexts, thereby strengthening the evidence base for risk assessment and clinical translation.

AVAILABILITY OF DATA AND MATERIALS

No original datasets were generated or analyzed. All cited data are available in the referenced publications.

AUTHOR CONTRIBUTIONS

MJCZ—Manuscript drafting; Critical revision of the manuscript; Technical or administrative support. JPVLC, JCRS, JFM, JCA, LCU and JQA—Manuscript drafting. JPI—Conception and design of the work; Data collection; Manuscript drafting; Critical revision of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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