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Study on the Toxic effects of Di-N-Butyl Phthalate on Male reproductive system: A review

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Abstract

Di-n-butyl phthalate (DBP) is a plasticizer in plastics, cosmetics, and many consumer products. People and the environment are regularly exposed to it. It is a significant chemical pollutant due to its widespread use and its ability to stay in the environment. This study aims to show the harmful effects of DBP on the male reproductive system. Several studies identify DBP as an endocrine disruptor. It can reduce hormone production, especially testosterone, and disrupt normal fertility processes. Exposure to DBP is also connected to poor sperm quality, testicular damage, oxidative stress, and developmental disorders. For assessing the hazards to eco-system and human health and for emphasizing the need of controlled use and more research we have to understand the toxic effects of DBP.

Key words : Di-n-butyl phthalate (DBP), male reproductive toxicity, endocrine disruption, testicular dysgenesis, sperm abnormalities, reproductive health.

A frequently-used phthalate ester is di-n-butyl phthalate (DBP), which constitutes largely one of the plasticizers to enhance strength, flexibility and durability of some types of plastics, particularly polyvinyl chloride (PVC) products[36]. In addition to plastics, DBP is commonly found in adhesives, surface coatings, cosmetics and personal care products, printing inks and medical devices and a wide range of industrial formulations[1,5]. It is an oily liquid that is colourless to pale yellow in appearance and produced by esterification reaction of phthalic anhydride and n-butanol[20,31]. DBP is widely distributed in the environment such as soil, water, air and food because of its widespread production and use[29]. The primary biologically active metabolite of DBP is monobutyl phthalate

(MBP), which undergoes rapid hydrolysis upon release into biological systems or into the environment. A comprehensive evaluation of DBP toxicity is warranted, as it is commonly used in industry, has a ubiquitous environmental presence, and has well-documented male reproductive toxicity in animal experiments, human biomonitoring studies, and in vitro systems have been reported[37,38]. DBP can easily transfer from plastic products into the environment during manufacturing, use, and disposal processes due to its weak binding to polymer matrices[36]. However, the release rate of DBP in environment usually surpasses the ability for natural breakdown, even though there are studies suggesting bacterial biodegradation of DBP both aerobically and anaerobically[39].

DBP's adverse effects on male fertility have been extensively reported. Experimental studies have reported that DBP disrupts androgen synthesis, suppresses testosterone production, and alters the function of sertoli and leydig cells as well as affecting spermatogenesis[18,28]. Testicular dysgenesis, cryptorchidism, hypospadias, reproductive tract malformations and long-term fertility impairment have all been associated with exposure at critical windows during development (pregnancy and puberty)[22,26].

The goal of this review is to briefly look at and include recent experimental and epidemiological findings about how di-n-butyl phthalate affects the male reproductive system. It will focus on its mechanisms of action, the relationship between the level of toxicity, the dose, and the stage of development, and human and environmental health impacts.

Using databases including PubMed, Scopus, Web of Science, Science Direct, and Google Scholar, the review covers both experimental and non-experimental studies published between 1998 and 2025.

1. Mode of Action of DBP :

DBP causes its harmful effects mainly by disrupting hormones. It especially affects androgen production and signaling. Even at the lowest DBP concentration (1 nM), the levels of the steroidogenic regulator StAR and the steroidogenic enzyme cytochrome P450 family 11 subfamily A member 1 (CYP11A1) were reduced, indicating upstream actions in the testosterone production pathway. It showed a significant decrease in blood testosterone and testicular levels of the enzymes 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase, along with an increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH)[3,28]. DBP also down-regulates genes critical for male reproductive development, including insulin-like peptide 3 (INSL3), a hormone essential for the formation of the gubernacular ligament, and CYP11A, leading to cryptorchidism and other developmental abnormalities[11]. Additionally, DBP induces DNA damage, increases apoptosis, and decreases proliferation, all of which are dependent on the PTEN/AKT pathway and including mitogen-activated protein kinase kinase 1/2 (MEK1/2), Bcl-2, Bax, and Ras related dexamethasone induced 1 (RASD1), were examined in order to investigate the causes[19,21]. Oxidative stress induction further amplifies cellular damage and disrupts reproductive processes[27,40].

2. Histological Alterations Induced by DBP:

DBP exposure during fetal development induces prenatal testicular dysgenesis syndrome outcomes (infertility, cryptorchidism), markers of dysgenesis in the prenatal testis (abnormal leydig cell aggregation, multinucleated gonocytes (MNGs)), and disorders that may result from these indicators in adulthood was assessed[17,22]. In addition to causing histological changes in the epididymal tubules and seminiferous epithelium, the DBP has reduced testosterone levels[32]. The testicular histopathology showed that the disorientation of spermatogenic cells reduced the diameter. The mean diameter of the seminiferous tubules decreased significantly when compared to the control and combined DBP and curcumin groups[28,33]. The reproductive toxicity potential of DBP was highlighted by structural abnormalities in the testis, such as vascular congestion, leydig cell hyperplasia, and severe congestion in tunica albuginea combined with both sertoli cell and leydig cell damage[34]. Studies in birds and fish further confirm DBP-induced disorganization may interfere with spermatogenesis and disturb the blood-testis barrier, highlighting cross-species susceptibility[25,35].

3. Adult and Infant Exposure :

The toxic effects of DBP are strongly age and stage-dependent. Fetal and neonatal exposure, particularly during the masculinization programming window, results in irreversible structural abnormalities such as testicular dysgenesis, malformed reproductive organs and germ cell loss[6,17]. In contrast, adult exposure primarily disrupts spermatogenesis, fertility and hormone balance, with some degree of reversibility following cessation of exposure[15,40]. Infant and fetal testes are significantly more sensitive to DBP; reduced cellular proliferation, rather than increased apoptosis, leads to DBP-induced abnormal fetal seminiferous tubule development and contributes to testicular dysgenesis[14,16]. DBP exhibits a 'strong male-biased reproductive toxicity'. In males, it severely disturbs spermatogenesis, testicular development, steroidogenesis, and fertility across species[13].

4. Biochemical and Hormonal Changes:

DBP exposure leads to pronounced "biochemical and hormonal disturbances". A consistent finding across studies is a significant reduction in serum and intra testicular testosterone levels, often accompanied by compensatory alterations in LH and FSH levels[2,28]. Steroidogenic enzyme activities are markedly reduced, impairing testosterone production[15]. Proteomic and molecular analyses reveal altered expression of leydig cell markers (CYP11A1), sertoli cell markers (vimentin, SOX9) and germ cell markers (DAZL), indicating widespread cellular dysfunction within the testis[3,4]. DBP also induces epigenetic modifications, such as PTEN promoter demethylation, which suppresses the AKT pathway and further compromises spermatogenesis[19]. Changes in sperm RNA profiles in individuals exposed to the chemical imply that the molecular effects persist for several generations beyond a single spermatogenic cycle[9].

5. Role of Oxidative Stress :

Oxidative stress is a central mechanism

underlying DBP-induced reproductive toxicity. Elevated levels of lipid peroxidation markers like malondialdehyde (MDA) have been recorded in several studies, which lead to a strong inhibition of glutathione, glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) activities by the two doses. Seminiferous tubule atrophy and seminiferous epithelial cell disintegration were the main pathological features observed[27,40]. Elevated markers of oxidative stress are also evidence of oxidative injury to cellular macromolecules[15]. Oxidative stress results in DNA damage, germ cell apoptosis, and mitochondrial dysfunction that eventually lead to reduced sperm quality and fertility[9]. The slight antioxidant effects with ginger and curcumin along with the combined group validate the role of oxidative mechanisms in DBP toxicity[30,33].

6. Experimental and Case-Based Evidence:

Experimental data on male reproductive tract malformations demonstrate that exposure to DBP during pregnancy and lactation leads to serious reproductive problems. These include hypospadias, decreased anogenital distance, and permanent testicular dysgenesis[22,26]. In the influence of preconception exposure to Di(2-ethylhexyl) phthalate (DEHP), DBP, and a combination of both on sperm quality, fertilization capacity, and early embryonic development and affects reproductive function, leading to reduced sperm count, motility and viability[24,28]. Combined exposure to DBP with other toxicants such as DEHP, benzo(a)pyrene, or nanoplastics results in producing more severe reproductive impairment than individual exposures and contain additive or synergistic toxicity[11,12]. Multigenerational studies reveal that paternal DBP exposure adversely affects sexual sperm quality, sperm head abnormalities, sexual maturation, and sex ratio in the F1 generation, with detectable genotoxic effects in subsequent generations[7,8].

7. Effect of DBP on Other Reproductive Organs :

Beyond the testes, DBP significantly affects the development of an androgen-dependent accessory reproductive organ. Developmental exposure results in under-development or complete agenesis of the epididymis, vas deferens abnormalities, and reduced relative organ weights of the bilateral prostate and seminal vesicles[23,26]. These organs depend on adequate androgen levels for normal differentiation and function, making them particularly exposed to DBP-induced testosterone suppression. Epididymal dysfunction compromises sperm maturation and motility, further reducing fertility[32]. Several studies have shown that DBP exposure led to extensive loss of germ cells and testicular atrophy. In some cases, the epididymis was completely absent or very poorly developed, the rats had hypospadias, and there was a reduction in anogenital distance; all these features point to the fact that the masculinization of the external genitalia was disrupted[10,26]. The harm to these organs progressively worsens as the exposure to DBP increases. This increased level of toxicity is not only affecting male reproductive organs but also leading to the development of liver injuries. Other environmental toxins may be involved in liver damage as well, which means that the overall toxicity might be even higher in situations where metabolic conditions are compromised[23].

Table-1. Toxicity of Di-n-butyl Phthalate

Sr. No.	Doses and Duration	Parameters	Inference	Reference
1.	0, 250, 500, 750 mg/ kg/day DBP (oral); 10 pregnant CD rats; assessed to Postnatal Day 20.	Maternal and developmental reproductive assessment.	AGD decreased in males at 500 and 750 mg/kg.Severe testicular atrophy and germ cell loss: epididymis absent/ underdeveloped in 9%, 50%, 71% at 250, 500, 750 mg/kg respectively. Hypospadias: 3%, 21%, 43% at respective doses.Ectopic/missing testes: 3%, 6%, 29% at respective doses.Effects similar to anti-androgen flutamide.	Mylchreest *et al.,*[26]
2.	Dose–response study; pregnant rats exposed during critical male reproductive window (gestational exposure)	Androgen-dependent developmental and reproductive toxicity assessment.	DBP/DEHP did not bind androgen receptors;DBP caused ↓ fetal Testosterone, ↓ leydig cell number, hypospadias, vas deferens/ epididymal abnormalities; persistent nipples; ↓ AGD;Leydig cell adenomas at 100 days.	Foster *et al*.,[10]
3.	72 male F344 rats (8 groups); TAA 200 mg/kg/week; DBP 500, 123, 31, 25 mg/ kg/day (23 doses); 4-week DBP exposure starting 1 week post-TAA	Toxicological and reproductive assessment.	Liver damage increased DBP reproductive toxicity; ↓ sperm count and motility; ↓reproductive organ weights; ↑ sperm abnormalities; severe testicular damage high DBP.	Mitsuhashi *et al*.,[23]
4.	Pregnant Sprague–Dawley rats; DBP 500 mg/kg, DEHP 500 mg/kg, and DBP+ DEHP (500+500 mg/ kg); GD 14–18	Developmental and reproductive toxicity assessment.	DBP + DEHP caused >50% increase in malformations (*e.g.*, epididymal agenesis); cumulative ↓ in organ weights, fetal testosterone, INSL3 and CYP11A expression; dose-additive mechanism.	Howdeshell *et al*.,[11]
5.	Pregnant rats; 0, 4, 20, 100, 500 mg/kg/ day; gestational exposure	Testicular dysgenesis and reproductive analysis.	Adult effects only at 500 mg/kg; fetal endpoints more sensitive: altered Testosterone, ↑ LC aggregation, ↑ MNGs at 100 mg/kg; trend at 20 mg/kg.	Mahood *et al.,*[22]
6.	Pregnant Sprague–Dawley rats; DBP 30, 50, 100 mg/kg/day;	Fetal and early postnatal testicular	High doses ↓ somatic cell growth; no change in apoptosis; ↓ testis volume; ↑ multinucleated gonocytes; Post-birth	Kim *et al*.,[16]

	mid-gestation exposure	development assessment.	recovery by post nateral day.	
7.	40 adult Sprague–Dawley rats; 0, 100, 250, 500 mg/kg/day; 2-week exposure	Sperm quality and and oxidative stress analysis.	Dose-dependent toxicity; ↓ sperm parameters at ≥ 250 mg/kg; ↑ MDA; ↓ GSH, GPx, SOD; Histological degeneration at 500 mg/kg.	Zhou *et al.,*[40]
8.	Prepubertal male rats (3 weeks old); daily DBP; 7-day exposure	Endocrine and cellular response analysis.	DBP caused spermatogenic apoptosis; acute dose ↓ Testosterone and LH in 3 hr; apoptosis peaked at 6 hr; estrogen receptor blocker reduced apoptosis.	Alam *et al.,*[2]
9.	Pubertal male Sprague–Dawley rats; 0.1, 1, 10, 100, 500 mg/kg/day; 30-day exposure	Physiological, histological, and molecular markers analysis.	High doses: severe testicular/epididymal damage and hormonal disruption; Low doses: altered leydig/sertoli cell function and differential protein expression.	Bao *et al.,*[4]
10.	Male mice; DBP 500 or 2000 mg/kg; 8-week exposure; mated with untreated females	Offspring developmental and reproductive assessment.	No effect on fertility; F1 litters had growth retardation, altered sex ratio, delayed female puberty; ↑ sperm head abnormalities (2000 mg/kg). F2 fertility normal.	Dobrzynska *et al.*,[8]
11.	Pregnant rats; DBP 500 mg/kg/day (oral); from e13.5	Germ-cell development analysis.	DBP reduced fetal GC number by 60%, prolonged proliferation, altered OCT4 and DMRT1, caused late gestation GC aggregation, and delayed radial migration.	Jobling *et al.,*[14]
12.	Albino rats; DBP 500 mg/kg in maize oil; daily gavage	Histological and hormonal analysis.	Marked seminiferous tubule atrophy, apoptosis, exfoliation, abnormal spermatocyte regeneration; testosterone significantly decreased.	Salama *et al.*,[33]
13.	Male Sprague–Dawley rats (4 groups); DBP 250 mg/kg/day; BaP 5 mg/kg/day; 90-day exposure	Reproductive and molecular analysis.	DBP and BaP reduced seminiferous tubule area; BaP and DBP combine elevated stillbirths; combined exposure caused most severe impairment of meiosis.	Huang *et al.,*[12]
14.	Male rabbits (*Oryctolagus cuniculus*; n=24, 6/group); DBP 0, 250, 500, 750 mg/kg/day via gavage; 4-week exposure	Hormonal, histological, and sperm analysis.	DBP dose-dependently reduced sperm parameters, testosterone, hematological indices; caused histopathological testicular damage.	Rihani *et al.*,[32]
15.	40 Wistar rats; DBP 500, 1,000, 1,500 mg/	Histological and oxidative stress	Dose-related degeneration of germinal, leydig, sertoli cells; oxidative stress	Nair [27]

	kg/day (oral); 7-day exposure	biomarkers analysis.	increased; antioxidant defenses decreased.	
16.	Rats with human fetal testis xenografts; exposure from e13.5 to e17.5/e21.5	Germ-cell development analysis.	DBP caused germ cell loss, MNG induction, germ cell aggregation in both species; sertoli cell microfilament changes indicated.	Van Den Driesche *et al.*,[38]
17.	Pregnant rats; DBP 750 mg/kg/day; exposure windows—FW (e13.5–20.5), MPW (e15.5–18.5), LW (e19.5–20.5)	Analysis of testicular developmental abnormalities.	MPW exposure caused most severe dysgenesis, ectopic sertoli and germ cells, disrupted cords; LW exposure showed no dysgenesis.	Lara *et al.*,[17]
18.	Adult male rats; DBP 100 & 500 mg/kg	Reproductive performance and histological analysis.	Significant reduction in fertility; sperm abnormalities; decreased sperm parameters; Reduced testosterone; increased LH/FSH; histological degeneration.	Nelli and Pamanji[28]
19.	Pregnant rats; DBP by gavage; GD 12.5–21.5 exposure	Histopathology, testicular morphology and molecular markers analysis.	DBP led to ↓AGD, testicular damage, ↑ seminiferous tubule cell death; Altered RASD1, MEK1/2, and Bcl-2/Bax ratio.	Ma *et al.*,[21]
20.	Male mice (4.5 weeks); DBP at 1/16 or 1/4 LD_{50} by gavage every 3 days for 8 weeks	Developmental toxicity assessment.	DBP caused germ-cell toxicity, poor sperm quality, fetal skeletal defects, ↑ postnatal mortality, altered sex ratio (better survival of females), and ↑ DNA damage in F1 males, F2 effects mild.	Dobrzynska *et al.*,[7]
21.	20 male rabbits; DBP 520 mg/kg BW; DBP 520 mg/kg + ginger 400 mg/kg	Testis/prostate weights, sperm, hormonal, and histological analysis.	DBP ↓ testis and prostate weight, ↓ testosterone, ↓ sperm count/motility, ↑ MDA;Caused clear testicular histological damage. Ginger partially restored these changes.	Oda *et al.*,[30]
22.	Human males with Inflammatory Bowel Disease, subjected to a cross-over design between high and background DBP.	Sperm molecular analysis.	High DBP altered repetitive elements, activating DNA damage and oxidative stress pathways; Small RNAs minimally affected.	Estill *et al.*,[9]
23.	In vitro and in vivo models.	Epigenetic regulation and sperm analysis	DBP induces germ cell toxicity and reduces sperm quality by increasing PTEN expression through demethylation, which inhibits the AKT pathway.	Li *et al.*,[19]

24.	*Pseudetroplus maculatus*; DBP 0.2 mg/L; exposure for 1, 3, 4, 7, 15 days	Hormonal, biochemical, sperm and histological analysis.	DBP ↑ estradiol and cortisol, ↓ testosterone, FSH, LH, TSH; ↑ sperm count, motility, viability; testicular histology disrupted.	Sruthi *et al.,*[35]
25.	Adult male mice; DBP 10 or 100 mg/kg/day (oral); 5-week exposure	Testicular cell markers, hormonal analysis.	DBP ↓ testicular testosterone, ↑ LH receptor, oxidative stress marker, steroidogenic enzymes, leydig, sertoli, and germ cell markers.	Kallsten *et al.*,[15]
26.	Adult male C57BL/6J mice; DBP, DEHP, or DBP+DEHP 2.5 mg/ kg/day via osmotic pump. 40-day exposure	Sperm analysis, biochemical and developmental effects.	Preconception DBP, DEHP, and combined exposure impaired sperm function, reduced fertilization, and hindered embryo development.	Mohanty *et al.,*[24]
27.	Adult Japanese quail; DBP 50, 200, 400 mg/ kg/day (oral); 30-day exposure	Histological analysis.	Dose-dependent disruption of sertoli cell cytoplasm, mitochondria, and BTB junctions; potential interference with spermatogenesis.	Molele *et al.,*[25]
28.	Male Swiss albino mice; DBP 900 mg/kg bw, PSNP 0.2 mg/ml; 60-day exposure	Sperm parameters, antioxidant enzyme activity, histological analysis.	Both DBP and PSNP individually and in combination decreased sperm quality, altered testis structure, and reduced antioxidant activity; combination s howed more severe effects.	Sharma *et al.,*[34]
29.	In vitro; DBP 1 nM–100 µM on leydig, sertoli, and germ cells; 7-day exposure	Germ cell markers and hormonal analysis.	DBP reduced leydig cell number, testosterone, and minor effect on sertoli junction proteins.	Almamoun *et al.*,[3]

↑- Increase; ↓- Decrease; AGD- anogenital distance; TAA- thioacetamide; GD- gestation days; e- embryonic day; FL- full window; MPW-masculinization programming window; LW- late window; BaP- benzo(a) pyrene; PSNP- polystyrene nanoplastic.

Thus, it can be concluded that DBP, one of the most frequently used chemicals in industry, is a major cause for concern due to its hazardous effects on the male reproductive system. Studies found that DBP disrupts endocrine function by inhibiting testosterone synthesis and altering hormonal balance. Such disorders lead to damage to testicular structure, impaired spermatogenesis as well as altered sperm parameters, which eventually result in male infertility. Toxicity is closely linked to increased oxidative stress, damage at the cellular level, and changes in reproductive organs.

The effects of exposure vary with age; the prenatal and early stages of development are the critical windows during which exposure leads to permanent reproductive abnormalities. In contrast, exposure in adulthood mainly leads to functional and hormonal problems. Therefore, it is important to reduce DBP exposure through regulations and ongoing research to protect male reproductive health and prevent long-term adverse effects.

Conflict of Interest

None.

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