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Review Article

Plasticisers: A Potential Reproductive-toxicant for Humans

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A B S T R A C T

The advancement in science and technology has led to the discovery and formulations of various cheaper alternatives to our day to day commodities. Plastic is one of them. Plasticisers include a group of chemicals that increase the flexibility of plastics so that they can be moulded into the forms of our use. The plasticisers have led to a number of health hazards when they leach out into the environment. This review is going to be a comparative discussion, on the effects of different plasticisers on human health, and the main focus on plasticiser-induced reproductive toxicity. This study revealed that there are anomalies in the male reproductive system like cryptorchidism, hypospadias acrosomal dysgenesis, prostate cancer, and testicular cancer. Reduced fertility, deterioration in sperm quality, drop in testosterone synthesis, and reduced anogenital distance reveal the feminising effects of phthalates. Mono phthalates are the metabolites of these chemicals and cause similar effects. Bisphenol A (BPA) also has similar endocrine-disrupting potential. DNA damage has been recorded in sperms along with disruption in the secretion of the follicle-stimulating hormone and plasma and intratesticular testosterone. Both spermatogenesis and spermiogenesis were highly affected due to exposure to these chemicals. Females exposed to plasticisers show oocyte incompetence, increased possibility of miscarriage, polycystic ovarian syndrome, and disrupted secretion of oestrogen and progesterone leading to ovulatory cycles. Abnormalities in oogenesis occur during the meiotic phases.

Keywords: Plasticiser, Bisphenol A, Phthalates, Reproductive Toxicity

Introduction

Plasticisers are additives added to a polymer which induce plasticity and increase the workability of a material. Plastics contain plasticisers that are most commonly phthalate (diesters derivatives of phthalic acid) esters with a wide application in polyvinyl chloride (PVC). Most of the plasticisers (almost 90%) are used in PVC and are responsible for their improved flexibility and durability. The major uses are in the production of films and cables, in order to lower their cold flex temperature.[1] On the basis of the cost-performance assessment, ester plasticisers are selected. There is a wide variety of ester chemistries which are in production including sebacates,[2] adipates,[3] terephthalates,[4] dibenzoates,[5] gluterates,[6] phthalates,[7] azelates,[8] and other speciality blends. It has an extensive array of performance benefits on several elastomer applications like wall-coverings, tubing

and hose products, belts, print rolls, flooring, wire and cable, and seals and gaskets. Both high and low polarity esters are utilised in various elastomers such as nitrile, polychloroprene, ethylene propylene diene monomer (EPDM), chlorinated polyethylene, and epichlorohydrin. The interaction between plasticiser and elastomer is ruled through various factors including solubility parameter, molecular weight, and chemical structure. Additionally, plasticiser plays an important role in rubber manufacturing as it acts as a softener, extender, and lubricant of the rubber.[9,10] According to studies, such chemicals mainly act as endocrine disruptors and affect the reproductive system of animals.[11] There are numerous literature and research articles concerning the effects of a particular or a few plasticisers on any metabolic pathway of the reproductive physiology of animals like fishes, reptiles, amphibians and mammals like rodents and also primates including human beings.[10] This review article aims at putting forward the effects of plasticisers on the human reproductive system. It provides a better understanding of the harmful effects of the daily use of plastic goods, thereby creating awareness. It paves way for research to mitigate the adverse effects and also to discover new alternatives.

Various Exposure Routes of Plasticisers

Animals are exposed to plasticisers, which can easily abrade and migrate because of their loose binding to the polymer matrix. Phthalates can evaporate from PVC (off-gassing) as they are not chemically bonded to PVC. The rate of BPA leaching from polycarbonate products increases with repeated use like washing, exposure to heat, and contact with acidic or basic substances.[12-17] BPA is found to be absorbed and metabolised, though in a very lower amount, in the human skin.[18,19] Reports of the United States show that BPA intake in adults and toddlers is happening majorly via foodstuff and by inhaling indoor dust containing BPA.[20] Phthalates that are inhaled or come with dermal contact are hydrolysed in the pulmonary tract, skin, liver, and kidney. Phthalate esters like DEHP, a major component in polyvinyl chloride (PVC) plastics, have extensive uses in the production of medical tubing and blood storage bags.[21-23] The presence of DEHP and its metabolites in the urine of premature babies in a neonatal care unit on intravenous infusions, indicates DEHP releasing from those medical devices.[24,25] Phthalates that are released into the environment deposited in the soil or through crops enter into the food chain. Occupational exposure can happen through skin contact as well as inhalation of vapours and dust. Although phthalates are synthesised in closed systems, employees may be exposed during filtration or tanker loading and unloading. These compounds have been found in cord blood, breast milk, and cow's milk and recently in cologne and aftershave. If a process runs at a higher temperature, more amount of phthalates incorporate into the final product.[24,26-28] Orally ingested phthalate diesters can be hydrolysed by pancreatic lipases in the wall of the small intestine, and not by gut flora. Usually, phthalates are absorbed in their corresponding monoester forms or are further metabolised and are lastly eliminated as a soluble glucouronide conjugated form through urine.[24,26,27,29,30] Correlation studies have found that parental BPA and phthalate exposure can alter sex hormone profile in cord blood and can cause decreased stretched penile length and anogenital index like health defects in male newborns.[31]

Effect on Reproductive System

Bisphenol A (BPA)

BPA, a xenoestrogenic chemical, is a high production volume plastic monomer and plasticiser that is used to make polycarbonate (PC) plastic and is utilised in numerous consumer products, such as polycarbonate bottles, dental sealants, and thermal receipts.[32-35] Body fluids of the majority of children and adults are found to be contaminated with BPA.[25,27,36] BPA exposure at the embryonic level can disrupt lipid metabolism which might alter early cell fate differentiation.[37] It is a hepatotoxic anti-androgen and stimulates prolactin release, impairs aromatase expression and alters thyroid hormone action. Like the other phthalates, BPA is also rapidly metabolised into inactive metabolites and excreted in urine.

Effects/ Impact on Males

BPA exposure in male mice has been linked to genitourinary malformations, DNA damage in spermatozoa, reduced epididymal weight, decreased sperm quality and count, increased prostate weight, and epigenetic changes in offspring.[2,38,39] BPA affects testicular Leydig cells and lowers intratesticular and plasma testosterone (T), resulting in decreased spermatogenesis in males. It has been reported that BPA plays an important role in sexual differentiation by inhibiting aromatase, an enzyme which converts testosterone to estradiol. BPA, in a very low dose, has considerable effects in laboratory animals and such has also been noticed in the blood and tissue of human beings.[25,36,38] Being estrogenic, pubertal mice orally receiving BPA show a reduction in Leydig cell numbers and plasma T levels. Low dose foetal exposure resulted in larger prostate size in adulthood as compared to controls. Prostatic intraepithelial neoplasia lesions and tumours are common in BPA exposed rats and human males revealing perturbed homeostasis-increased proliferation and apoptosis.[25,34,40] In human males, an inverse relation has been established between BPA and Follicular stimulating hormone (FSH).[25,27] An epidemiological study has proved a correlation between the occurrence of epigenetic modification in human sperm and BPA exposure which leads to the alteration of semen quality and thus infertility may arise.[41,42,43] BPA exposure is correlated with elevated serum estrogen and increased risk of sexual dysfunction in males.[44]

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Impact on Females

BPA treatments in swine ovarian granulosa cells show a significant decrease in estradiol and progesterone production. BPA can decrease estradiol metabolism.[10,26] In an in vitro analysis, BPA treated human granulosa cells have shown a significant decrease in estradiol and progesterone biosynthesis as well as a significant decrease in the mRNA expressions associated with steroid hormone synthesis.[45] This additive induces progressive proliferative lesion in the oviduct and causes leiomyoma, adenomyosis, atypical hyperplasia in the murine model, and other such complications of the uterus.[46] BPA exposure leads to complete loss of the impairment implantation sites by decreasing migration and inhibiting apoptosis of ovine trophectoderm cells at the time of early pregnancy.[26,47] BPA is found to cause necrosis and apoptosis and is shown to elicit immune responses in human placental trophoblast cells which play a major role in supplying nutrients and gas to the foetus. Changes in placental cell number, changing their proliferation rate, and alteration in genomic pathways are observed with BPA exposure as well and these all have severe effects on foetal metabolism and foetal metabolic disorders may arise.[48,49] It affects foetal growth and there is a possibility of it being carcinogenic, gradually leading to the precursors of breast cancer. Breast cancer cell migration becomes induced with BPA induction by activating the expressions of a few genes related to epithelial-mesenchymal transition.[10,25,46,50] In the case of foetuses with mothers having been exposed to larger doses of BPA, alterations in growth parameters of the mammary gland anlagen have been reported. In the mammary epithelium, a reduction in cell size, delays in lumen formation, as well as an increased ductal area have been noticed. In the stroma fat pad, advanced maturation and fibrous collagen altered localisation have been found. BPA exposed females have higher testosterone levels thereby resulting in polycystic ovarian syndrome.[16,25,46] A high concentration of BPA generates oxidative stress in the ovary which targets the biomacromolecules and causes damage to the follicular cells.[51] DBP shows estrogenic activity in estrogen-responsive human breast cancer cells and also increases the incidence of post-implantation loss.[28,52-54] Postmenopausal women are more susceptible to BPA toxicity because of their lower estrogen levels and the estrogen receptor occupancy; BPA exposure can cause oxidative stress and inflammation to them.[55]

Phthalates

Phthalates are di-esters of 1,2-benzenedicarboxylic acid and are divided into two groups depending on the number of carbon atoms in the backbone: low molecular weight (LMW - implying 3 to 6 C-atoms in the backbone) and high molecular weight (HMW - implying more than 6 C-atoms in the backbone). Humans get exposed to HMW phthalates majorly through the food chain, and studies monitoring urine samples of humans for LMW phthalates have indicated their concomitant exposures. Different types of phthalates are presented in Table 1. Studies done on animals have revealed that their hormone concentration can vary as per their exposure to phthalate, which in turn, may adversely impact their reproductive physiology as well as the growth of estrogen-sensitive target tissues.[22,23,28,56,57] These endocrine-disrupting chemicals (EDCs) sometimes mimic the actions of sex steroids as well as thyroid hormones, and sometimes they inhibit their action by inhibiting the expression of different genes involved in steroid or thyroid hormones biosynthesis.[24,28,30,38,42,58] "Phthalate syndrome" is referred to the condition that affects the reproductive system of not only rodents but also human beings.[24,30,38,42]

Table 1.Different Phthalates and their Uses

Phthalates	Uses
Bis [2-ethylhexyl] phthalate (DEHP)	Medical devices and construction materials[59]
Bis [2-propylheptyl] phthalate (DPHP)	Roofing material, wires and cables[60]
Diisononyl phthalate (DINP)	Flooring materials, building materials, shoes, garden hoses, and toys[61]
Di-n-butyl phthalate (DnBP, DBP)	Food wraps, cellulose plastics, adhesives, cosmetics, perfumes, sunscreens, shampoos, and insect repellents[62]
Butyl benzyl phthalate (BBzP)	Traffic cones, vinyl tiles, artificial leather, food conveyor belts, and plastic foams[63]
Diisodecyl phthalate (DIDP)	Cables, wire insulation, pool liners car undercoating, carpets, and shoes[64]
Dioctyl phthalate (DOP or DnOP)	Covers of notebooks, carpets, flooring materials, and high explosives. It was the most frequently used plasticiser along with DEHP[65]
Diisooctyl phthalate (DIOP)	Rubbers, polyvinyl chloride, cellulose plastics, polyvinyl acetate, and polyurethane[66]
Diethyl phthalate (DEP)	Found in cosmetics[67]
Diisobutyl phthalate (DIBP)	Used as a plasticiser in PVC[68]
Di-n-hexyl phthalate (DHP)	Automobile parts, flooring materials, and tool handles[69]

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Impact on Males

Phthalate esters like DEHP, DBP, BBP, and DINP are anti-androgenic. They interfere with testosterone biosynthesis and inhibit the production of protein insulin-like factor 3 (Insl 3) from the foetal testicular Leydig cells when exposed during foetal and postnatal life.[28,57] This is required for normal testicular descent. Xenograft studies have shown that these phthalates can cause androgen-independent toxicity, and can inhibit androgen synthesis in males.[70] A potential association has been found between antenatal exposure of DEHP, DINP and their metabolites with testicular volume, total plasma testosterone level, and a positive association has been found with serum FSH level in men.[71] DEHP causes Leydig cell hyperplasia and also affects systemic physiology. Prolonged exposures to this agent cause rise in gonadotropin luteinizing hormone (LH) and with this serum, sex hormone concentration is also increased (testosterone and 17-estradiol by > 50%). In short term exposure, androgen biosynthesis is synthesised in Leydig cells by high-serum LH levels, but long term exposure may induce Leydig cell proliferation along with premature reduction of steroidogenic capacity.[21,23,28,57] DEHP exposure increases the estrogen/ testosterone ratio in men; it indicates the higher aromatase activity in males with DEHP exposure.[33] DEHP administration during the gestational period may induce several negative effects such as an increase in plasma T levels (as Leydig cell numbers increase). Higher doses of DEHP decrease plasma T levels due to impaired steroidogenic activity and increase germ cell apoptosis.[10,24,41,42] It decreases FSH which impairs fertility and results in defective elongated spermatids and Sertoli cells. High LH, Prolactin and T cause precocious puberty.[41] Severe pubertal gynaecomastia has been recorded in individuals exposed to this additive. In human males, it is associated with low sperm count, distorted sperm morphology and reduced fertility. DEHP-treated dams also had haemorrhagic testes, decreased weight of prostates, reduced anogenital distance and incidence of nipple retention.[10,24,41,42] A severely atrophic testis is formed with degenerated seminiferous epithelium. Sertoli cell dysfunction in early life may cause spermatogenic failure later, and DEHP exposed prepubertal males and adult males with atrophic testes show alteration in serum inhibin B. Effects on the epididymis resulting in foetal Leydig cell dysfunction can lead to reduced testosterone that can also secondarily cause testicular atrophy.[10,24,41] It is indirectly estrogenic due to elevation in estradiol level caused by an increase in aromatase gene expression in Leydig cells.[21,41]

Dialkyl phthalates including DBP are anti-androgenic and most of the time, they metabolise to the monoesters by enzymes present in many tissues. Intrauterine, lactational and prepubertal exposure to DBP reduces fertility in rabbits that has been correlated with the human male reproductive system. In the human male population, it is found to cause a decrease in sperm count, a delay in spermatogenesis and other malformations like cryptochordism.[12,13,17,52,72-74] It reduces foetal testicular testosterone. In high doses, it results in the degeneration of seminiferous tubules. DBP exposure reduces litter size, number of litters per pair, number of fertile pairs, live pups, and also weight of litters.[17,52-54,57,74] Reduction in the weight of foetus along with malformations in cleft palate, fused sternebrae and reduced anogenital distance (feminisation effects) are observed in male foetuses. Studies in human males have revealed an increased incidence of the undescended or ectopic testis, testicular atrophy, hypospadias, increase in the number of areolas and nipples at birth and adulthood, per cent areolas and nipples at birth, delayed preputial separation, and epididymal atrophy or agenesis.[17,28,56] In rats, there are incidences of reduced gestational index and reduced gestational length.[17,28,52,53] All types of di-alkyl phthalates exposure at postnatal week cause alveolar atrophy or vacuolar deterioration of alveolar cells in the mammary gland of male pups.

DINP is considered a weak reproductive toxicant since it has caused only an increase in nipple retention due to in utero exposure.[24,74] The deformities in the reproductive system include flaccid, fluid-filled testes, atrophic and small testes, scrotal fluid-filled testis without spermatids, and unilateral epididymal agenesis with hypo spermatogenesis. A reduction in the concentration of the androgen receptor testosterone complex is the background of such deformities.

Diphenyl phthalate (DPP) is a LMW phthalate and has been established as an anti-androgenic compound, which interferes with cellular immunity. Being of lipophilic nature, it easily leaches out from the packing materials used for storing milk and dairy products and inhibits foetal testicular testosterone production.[38]

In human males, BBP affects the reproductive system by reducing the weight of testes and epididymis followed by a reduction in body weight gain, and fluctuation in food consumption. BBP exposure at a lower level during lactation and in utero condition in rats increases testicular degeneration and daily sperm production in male offspring.[10,24,28,38] At the highest dose, plasma T is decreased.

Monophthalates can cross placenta. MBuP-exposed males exhibited cryptorchidism with unilateral/ bilateral undescended testes. Majority (87%) of these were located in the abdominal cavity, and the rest (13%) were present at the external inguinal ring.[52]

Monoethylhexylphthalate (MEHP) is the main metabolite of DEHP and acts as an anti-oestrogenic at low doses. DEHP is metabolised into MEHP by various enzymes in the

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kidneys, liver, pancreas, lungs, and plasma. At high doses, MEHP has estrogenic effects that have been reported in rats and are extremely significant in human males.[42,72,74-76] It leads to preterm births. Abnormalities of the male reproductive system like cryptorchidism, hypospadias, and decreased sperm count, frequently called 'testicular dysgenesis syndrome', have been studied in both rats and human beings.[13,14,23,77] It causes pubertal gynaecomastia. In a report based on Massachusetts (USA) infertility clinic study done on 295 men, an indicative inverse association has been found between MEHP and testosterone and also a positive relation between inhibin B and urinary MBP has been established. From this study, an inverse relationship between urinary MBzP and FSH has also been recorded.[27] There is an inverse association of free T4 (Tetra-iodothyronine) and total T3 (Tri-iodothyronine) with MEHP, while thyroid-stimulating hormone (TSH) shows no such relation. A major metabolite of DBP, monobutyl phthalate (MBP) can cause damage to the male reproductive function by altering steroid biosynthesis on exposure. On the other hand, at lower doses, it induces increased steroidogenesis in vitro and in vivo.[24,28,73,74] It causes disrupted descent of testis. Along with a reduction in the weight of prostates, epididymis, testes, penis, and an increase in pituitary weight in human males, decreased levator muscle weight was also observed in the treated rats and rabbits.

Impact on Females

It has been reported that chronic occupational exposure to high levels of phthalates in female factory workers is associated with reduced rates of pregnancy and an elevated frequency of miscarriage.[16,30] A relation between a rise in the cases of early pregnancy loss and high levels of MEHP with reduced gestational time and other complications like endometriosis, eclampsia, breast cancers, impaired oocyte competence, uterine fibroids, ovarian dysfunction or menstrual cycling along with premature breast development has been reported in studies done on human females.[14,16,25,30,54] It decreases HCG-stimulated steroid formation along with premature thelarche (due to anti-androgenicity of phthalates). In girls exposed to phthalates, various disorders have been reported in ovulation and lactation.[25,34,40] Sexual precocity is significant.[25,41] In primary cultures of rat granulosa cells [GCs], MEHP is found to inhibit the stimulation of adenylate cyclase and progesterone synthesis by FSH. A significant decrease is observed in the DHEA level by such treatment. An insignificant amount of pregnenolone indicates that when 3b-HSD [3b-hydroxysteroid dehydrogenase] was blocked; CYP17a changed the complete compound into DHEA.[21,78]

On gavaging rats with a high dose of DEHP, anovulation, absence of the LH surge, suppression of estradiol levels, onset of polycystic ovaries, and increased oestrous cycles have indicated ovaries as a target organ of DEHP toxicity.[10,16,21,39] Primary cultures of granulosa cells isolated from these rats exhibit attenuation in progesterone secretion in response to stimulation by LH and FSH, and a lower degree of endogenous cholesterol transport into mitochondria as well.[24,78] Similarly, in the case of DBP exposed individuals, a significant reduction in maternal body weight gain is found.[24,52] However, DEHP, is probably the only phthalate which directly affects the granulosa cells and lowers estradiol levels probably by reducing aromatase expression, while other phthalates such as DBP enhance the degradation rate of estradiol through upregulation of liver-metabolising enzymes. Extremely high exposures have resulted in decreased pregnancy rates.[25,76,78] Female newborns exposed to such phthalates are significantly heavier than controls.[16] A significant delay in the timing of vaginal opening has been observed in a few cases.[56] DEHP results in the induction and/ or potentiation of an intrauterine inflammatory response.[74] A study done on the human granulosa cell line has shown that DBP upregulates aromatase gene expression and thus increases the serum estradiol level.[79]

Butyl benzyl phthalate (BBP) is considerably more mitogenic with respect to other phthalates and affects two estrogen-responsive human breast cancer cell lines, MCF-7 and ZR-75.[58,80] In females, there is an adverse impact on food consumption, body weight gain, and reproductive indices. Production of the follicle-stimulating hormone was increased in a dose-dependent manner, whereas in the case of Luteinising hormone, it was increased at the lowest dose and at the two highest doses of BBP.[80] It resulted in spontaneous abortion and a reduction in litter size.[54]

Conclusion

Plasticiser, a reproductive-toxicant, is a relatively new discovery and its potential effects on human beings have still not been entirely addressed. Many of these have been suspected of causing side effects at dosages significantly lower than those predicted by traditional toxicology or those mandated by current risk assessment and management standards. Additives used in plastics have varying effects at different doses that are often results of improper use. Although the association between these endocrine disrupters and specific diseases has not been established, there is sufficient evidence to associate these disrupters with plasticisers in the human population. Although taxonomically distant, structural similarities between hormones and their receptors in various species, are valuable indicators of the deleterious effects of such chemicals in wildlife and their potentially comparable adverse health risks in humans. Phthalate esters are environmental contaminants that are present everywhere and show low toxicity in general. At higher doses, they adversely affect the male and female

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reproductive systems while mainly targeting the testis and ovary. In males, the effects of perinatal exposure are of main concern. Studies have shown that certain phthalates cause intense irreversible changes in the developing male reproductive system. Several pieces of literature have shown the detrimental effects of a few phthalates like DEHP and DBP while the same cannot be ascertained in the case of less well-known phthalates including DiBP and DPP. Changes in behaviour patterns like lack of sexual desire have also been noticed in individuals exposed to these chemicals. This is mainly due to the lack of synthesised androgens. Besides all alkylphenols, bisphenol A is an endocrine-disrupting chemical as well, which shows more pronounced effects in females. Effects of BPA in males are anti-androgenic that are quite similar to the ones of phthalates. In females, this xenoestrogen is a major cause of oviduct lesions, breast and ovarian cancers, and endometriosis. However, their actual adverse impact is still not clear due to issues like problems in animal to human extrapolation, uncertainties in the epidemiological database, and the lack of awareness regarding low-dose effects on human health.

There must be adequate research and investigation of the effects of phthalates in non-human primates models during pre and early postnatal periods. This might help in determining the harmful effects on the human population from a closer view. Mechanistic research should be carried on to find the relevance of the modes of action of plasticisers in human beings. Studies should take into account the importance of the reported low dose variations in the expression or activity of steroidogenic enzymes on animals who were under study and were exposed to certain phthalates. Moreover, larger human populations should be involved in epidemiological studies to observe and estimate accurate doses and effects of these chemicals. In order to avoid further damage to the metabolism of infants who have been exposed to phthalates, follow-up studies should be conducted. Possible cumulative effects of various active phthalates have to be investigated. In other words, more knowledge, awareness and immediate actions must be taken to prevent and overcome the deadly health hazards inflicted by plasticisers. Therefore alternatives to plasticisers must be formulated to prevent extensive damage to wildlife and human populations.

Conflict of Interest: None

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