Chapter 4

Interactions between Bisphenol S or Dibutyl Phthalates and Reproductive System

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Additional information is available at the end of the chapter

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Abstract

Endocrine disrupting chemicals (EDCs) adversely affect animals and human beings. This attracted the researchers in the previous decade to explore the possible association of these chemicals. However, among various studies, very limited data is available to explain the link between EDCs and reproductive tract outcome. One reason is that many potential EDCs and their probable mechanisms and underlying causes have not been studied so far. Bisphenol S (BPS) is used as an alternative of bisphenol A, after the worse effects of this bisphenol. Similarly, dibutyl phthalate (DBP) is the least studied of its group. Dibutyl phthalate is widely used in polyvinyl plastic products. The current chapter aims to explore the possibly association of these two chemicals with animals and humans.

Keywords: BPS, DBP, phthalates, reproductive system

1. Introduction

Endocrine disrupting chemicals (EDCs) are the exogenous agents that can disturb the synthesis, metabolism, and the action of endogenous hormones; also they affect the androgenic, antiandrogenic, and thyroid mechanism [1]. The "US Environmental Protection Agency" defined the endocrine disrupting chemicals as exogenous agents that affect the synthesis, transport, binding action, metabolism, and elimination of hormones required for homeostasis, development, and reproduction [2]. The idea of EDCs was formulated after their exposure studies and adverse effects on humans and wild animals [3]. The impact of these chemicals was examined on the embryonic and reproductive development of male and female reproductive systems [4, 5]. The exposure of EDCs showed long-term negative effect on animal development and

health [6]. Endocrine disrupting chemicals are one of the possible causes of reproductive problem.

Nowadays, plastics are used in most of the products, the harmful chemicals, bisphenols and phthalates, leach out into the environment. These chemicals attract the attention of regulatory agencies, scientific community, and general public due to its high production and uses [7].

2. Bisphenol S (BPS)

Due to the adverse effects of bisphenol A (BPA) on public health, certain alternative chemicals were replaced in consumer products. One such replacement, bisphenol S (BPS), is currently used in thermal receipts, consumer paper products, baby bottles, and personal care products, foodstuffs, and canned foods. BPS is chemically and structurally compassionate to bisphenol A. It is an organic compound with formula $C_{12}H_{10}O_4S$. It has two phenol functional groups on either side of sulfonyl group. It is commonly used in curing fast drying epoxy resin adhesives. Bisphenol S was made in 1896 and is presently used in consumer products. Bisphenol S is an analog of bisphenol A and it supersedes bisphenol A in variety of ways. Bisphenol S becomes endocrine disruptor in the existence of hydroxyl group on benzene ring. Bisphenol S also has endocrine disruptor properties. Bisphenol S is present in thermal receipts paper, plastics, and indoor dust. Scientific and public knowledge of negative consequences affiliated to bisphenol S disclosure have increased [8].

BPS is a more stable chemical compound with low biodegradability as compared to BPA [9]. This is alarming that these properties of BPS compared to BPA lead to higher burden on living organisms [10]. Due to this cause, BPS is measured as "regrettable substitution" of BPA. The esteem increases in BPS production and use in plastic industry will unfortunately spread this chemical to the level as for BPA [11]. BPS replaced BPA in almost every consumer goods, for example, clearing products, resins, and electroplating solvents [12, 13], in canned food stuff [14]. Increase consumption of BPS and its discharge in environment-noticed health hazard to human, aquatic life, and environmental risks [15].

The existence of BPS was determined in waste water, fluvial water, and indoor dust [4, 9, 16]. The humans are exposed to BPS through ingesting dust, recycled products, dietary exposures, and dermal contact [9]. Although BPS was not studied broadly, many studies indicate the estrogenic properties of this compound in genomic as well as membrane-associated estrogen signaling. To date, studies of BPS in mammals are limited, and there are very few studies investigating the effects of exposure on behavior [11]. The limited data is available dealing with the interaction of BPS with biological organisms. The studies indicate that BPS is capable to mimic the hormones and interact with its certain receptors including estrogen and androgens [17] and serum proteins [12]. The exposure of BPS changes the aromatase expression that is a major enzyme of the estrogen pathway [18]. In vivo studies demonstrate the effect of BPS, postnatal low and high dose exposure causes reproductive dysfunction including changes in gonads morphology and androgen level. BPS affects the reproductive and neuroendocrine pathway during embryonic development. The mechanism of action may involve the thyroid and estrogen receptors. This also changes the expression of genes involved in above pathways

[19]. The studies on cell cultures showed that BPS affects cells mutagenically, genotoxically, and cytotoxically [20, 21]. BPS exposure also disrupts the signaling pathway of apoptosis, so it may cause gametes cascades leading toward cell death and altered cell cycle [22, 23].

Consumer quest for bisphenol A products lead to the supersession of bisphenol A with other related compound including bisphenol S [12, 24]. Biomonitoring studies excavate that human manifestations are likely to distribute about 97% individual in US, have noticeable level of bisphenol S metabolites in urine [11]. The estimation from these urinary concentrations urge that daily exposure in the range of 0.3–2 ug/day, although these exposure will likely revolt as the displacement of bisphenol A in various consumer goods, also increase [25].

Like bisphenol A, human vulnerability to BPS seems to grow mostly by exposure through the skin absorption [26] and ingestion by plastic leaches [27]. There is also confirmation that bisphenol S vulnerability can affect body weight and neuro-behaviors in developmentally exposed male offspring [28].

The increase in urbanization and industrialization results in massive release of certain chemicals including bisphenols and phthalates into the surrounding and environment. These chemicals cause adverse effects on human beings, mainly reproductive system, endocrine disruption, and decline in life quality. The effect of potential hazards of BPS in human depends upon the exposure level. As its use is not regulated, it is difficult to mention the consumables that contain and leach this compound. It is often used as an alternative of BPA in "BPA free" products including plastic bottles and printing paper [11]. BPS is introduced in industry as safe substitute of BPA. However, little is available regarding the adverse effects of BPS on humans and mammals. Currently, few studies were carried out to study the role of BPS as endocrine disrupting chemical. Approximately, over and above "18 billion pounds" of phthalates are used every year worldwide [29]. Phthalates and its metabolites, after leaching from its product, were detected in environment [30], in saliva [31], and in urine [29] samples of human both children and adult. The children get exposure of DBP in mother's womb, breast feeding, and medical devices during neonatal care [31]. To date, the exposure of DBP is studied on fertility, development of female and male reproductive tract, sexual maturation, prenatal and postnatal effect, pregnancy, and tumor in animals and human beings.

3. Dibutyl phthalate (DBP)

The modern use of plasticizers has extensively increased the industrial and social well-being of the resident of both developing and under-developed countries. At the same time, they are very harmful for the living organisms, if taken inside the body through any source. Plasticizers or dispersants are the additive chemicals that are used to increase the plasticity or decrease the viscosity of a material. These substances alter the physical properties of certain products. These are available in different forms either liquids with low volatility or may be even solids. They make plastic products more flexible by decreasing the attraction between polymer chains. Among, more than 30,000 different substances have plasticizing properties. Of all, these plasticizers approximately 50 are commercially used to make various products [32].

Phthalates were used in 1930s for the first time to replace unpleasant odor camphor. Phthalate ester is colorless, odorless, nonvolatile, and potentially nontoxic plasticizers. Due to these properties, they are considered as consumer friendly plasticizers [33]. Phthalates are used mainly for manufacturing medical supplies, including blood storage bags and intravenous solution containers, food containers, food packaging materials, children's toys, curtain, bowls, raincoats, car interiors, floor tiles, food wraps, fabrics, and plastic products. Approximately, 3 million tons of phthalates are produced per annum around the globe. Dibutyl phthalate (DBP) is the most commonly used phthalate, fulfill about 40% of total phthalate use. Blood storage bags usually have a high content of 20–40% (DBP). The primary source of exposure to DBP is through contaminated food [34].

The diesters of similar phthalic acids constitute the phthalates, and these are commonly used plasticizers in polyvinyl chloride (PVC) plastics to make them flexible, durable, and soft [35]. The PVC is added in building materials, children's products, toys, clothing, intravenous fluid bags, infusion sets, blood bags, food packaging, and some medical devices. Humans are exposed to these phthalates mainly through foods as these are used in food processing, wrapping, and packing material [36]. The dibutyl phthalates are used as plasticizers in plastics, solvent in dyes, cosmetics, and other care products. DBP is also used in latex adhesives as a component [37]. Bisphenols and phthalates are known for weak estrogen properties and act as EDCs due to their capability to contest with steroid hormone binding to its receptors. The "National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction" broadly reported and reviewed the impact of phthalates on human health [38]. There are adequate evidences and studies on mice and rodent models showing that the exposure of DBP causes reproductive and development toxicities. Moreover, the genital tract disorder was observed in human infants after prenatal exposure of phthalates [39]. The profound effect of DBP exposure was observed on the development of male reproductive system during acute period of late gestation (sexual differentiation). The similar phenotypic variations of prenatal exposure of DBP was observed in male rats, comparable to human disorders including decrease sperm count, hypospadias, and cryptorchidism (Martino-Andrade and Chahoud [40]). Both low and high concentrations of phthalates showed antagonistic and synergistic activities, respectively [41].

Dibutyl phthalate (DBP) is an odorless oily liquid. It may be colorless or yellow to faint. The chemical formula of DBP is $C_{16}H_{22}O_{4,}$ with molecular weight of 278.35 g/mol. Dibutyl phthalate (DBP) is also known as di-n-butyl phthalate and is widely used as plasticizers that belong to the class of phthalate esters (PAEs). DBP is a plasticizer used in most plastics and present in water, air, soil, plants, and animals. Some adverse effects with long-term exposure are linked with this plasticizer. As a plasticizer, they are used in polyvinyl chloride (PVC); dibutyl phthalate is found in cloves. DBP was added to the California Proposition 65 (1986) list of suspected teratogens in November 2006. It is a suspected endocrine disruptor. In some nail polishes, DBP is also present as an active ingredient. DBP is soluble in alcohol, ether, and benzene. It can easily penetrate the soil and contaminate groundwater and nearby streams. It is combustible, though it may take some effort to ignite. It is used in paints and plastics and as a reaction media for chemical reactions. It has an excellent stability to light. It emits acrid smoke and fumes, when heated to decompose it [42] (**Figure 1**).

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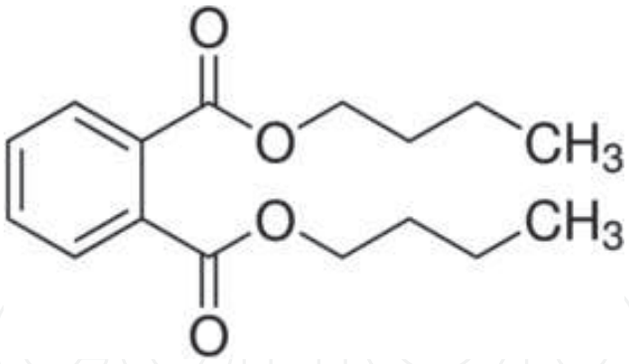

Figure 1. Chemical structure of dibutyl phthalate (DBP).

It does not break down in water but can break down in soil as a free chemical. The various stages of its release are: production, distribution, processing, use, incineration, and disposal. In the environment, high concentrations are mostly present in nearby production and processing sites of waste water and surface water nearby. It is also present in sediment, soil, and in aquatic and soil-dwelling organisms near to sources; its highest level is present in air around PVC-processing plants. Dibutyl phthalate is classified as Group D, not categorized as human carcinogenic agent by Environmental Protection Agency (EPA) [41].

DBPs are well-known endocrine-disrupting chemicals (EDCs) that have health risks to both animals and humans. Endocrine disrupting chemicals are exogenous substances that affect the endocrine system of the body and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. The occurrence of human disease increases by chronic exposure to DBP. It is banned in the United States, European Union, and many other countries; however, it is still present in our environment, as in water, its concentration is sufficient to affect development and reproduction in aquatic organisms. So, DBP as an endocrine-disrupting chemical also causes human health risks [42]. Studies revealed that the male reproductive system is mainly affected by exposure to DBP. It causes serious developmental disorders like spermatogenesis dysfunction, hypospadias, and cryptorchidism insufficient sperm motility [43]. The high dose of DBP has harmful effect on testis of mice. Several abnormalities regarding testis were observed like loss of spermatogenesis, abnormal level of serum hormones, and anomalous development of testis and epididymis [44]. The chronic exposure of DBP causes the reduction in weight of pubs and litter in both animals and humans [45]. During sexual development, even the short-term exposure to DBP can cause adverse permanent changes in the reproductive system of rats. DBP reduces the sperm count even for several months after the end of exposure to it. It reduces the male anogenital distance; decrease in the weight of both ventral prostrate and bulbocavernosus muscle was also clearly seen. The adverse changes in the mammary gland development were also noted clearly in the adulthood and puberty of rats [46].

Human exposure to DBP may take place, through its presence in the environment including workplace and consumer products. Workers are generally exposed through the air they inhale or through dermal contact. Plastic toys and baby equipment are the sources of children exposure to this chemical. A relatively low concentration of DBP is also determined in the

breast milk [47]. Humans are daily exposed to DBP through contaminated food, contaminated water, dermal contact, and by ingestion. In human, DBP decreases anogenital distance (AGD), affects pubertal development, disrupts sperm motility, and reduces sperm count. Continuous exposure of this plasticizer to humans decreases the number of sperms and suppresses spermatogenesis. It also reduces testosterone biosynthesis and disrupts the androgen:estrogen ratio in human embryos. DBPs have antiandrogenic-like properties and have a great role in hypospadias and cryptorchidism in humans [33].

The effect of DBP on sexual maturation was examined either through estrous cycle or vaginal opening. In animal models, the effect of low and high dose was observed in experimental trials. The highest dose used in these studies was 750 mg/kg/day, while the lowest dose was 0.5 mg/kg/day. Similarly, the duration of exposure was from postnatal day to twenty-first day, or the adult trial period from 10 to 45 days. Moreover, in humans, this study includes those people, who were directly exposed with the metabolites of phthalates [48]. Few previous studies on mice suggested that DBP had no effect on sexual maturity when exposure was given during gestation, weaning, or nursing period. However, some studies report delay in onset of vaginal opening, estrous cycle, and afterward in sexual maturation [49]. Few epidemiological studies also suggest that DBP exposure was not associated with sexual maturity [50]. In male offspring, the prenatal and postnatal exposures of phthalate were linked with reduced androgenic activity. Therefore, the level of phthalates in infants was associated with the exposure to mother. These results in hypospadias, decrease in anogenital distance, and endogenous hormones [51].

Studies confirmed the presence of dibutyl phthalate in the rat bile after oral administration, while in intestine, a fraction of dose was absorbed intact, indicating the nondegradable property of DBP [52].

The studies on the presence of phthalate esters in the blood of individuals who had ingested food that had been in contact with flexible plastics, suggested that levels of dibutyl phthalate observed in the blood were much higher than prior to eating food in the plastic packaging system. Results revealed that in blood, dibutyl levels were 0.35 ppm in comparison to an average value of 0.02 ppm before the use of plastic packaging system [43].

It is accumulated in viscera being rich in fat, like liver, kidney, and could overcome physiological barriers to penetrate testes. The accumulations of DBP exposed through dermal route as compared to the oral route and most of DBP was metabolized in 2 or 3 days [53].

DBP is metabolized along the same or parallel pathways for unsaturated fats indicated by the in vitro studies with pancreatic lipase. However, rats given DBP orally excreted the monobutyl ester as the principal metabolite in the urine with phthalic acid as the secondary metabolite. It is concluded that early life phthalate exposure may enhance the chance of allergic sensitization and atopic disorders [8].

Animal studies with mice exposed orally to dibutyl phthalate have suggested developmental effects, like reduced fetal weight, decreased number of viable litters, and birth defects (neural tube defects). In addition, oral animal studies reported the reproductive effects, like decreased spermatogenesis and testes weight. Structural degeneration in the epididymis

and deferens also caused by dibutyl phthalate administration studied in the mice exposed orally to this, parallel to dose evaluation and RSV can reverse these changes with its protective effects [54].

In the embryos of zebra fish, acetylcholinesterase activity was considerably inhibited. These results suggest that DBPs have the potential neurotoxicity in zebrafish embryos [55].

Dibutyl phthalate had been extensively used and its exposure in children has been thought to be one of the reasons causing a tendency of advanced pubertal timing in girls. As puberty starts from hypothalamic gonadotropin-releasing hormone, its release is controlled by several factors including neurotransmitter kisspeptin (Kiss 1) and its receptor G protein-coupled receptor (GPR54). So earlier pubertal timing in females and both neonatal and prepubertal periods are inducing by DBP and its exposure [56].

The cytokine secretion is also influenced by investigated phthalate monoester from monocytes/macrophages similar to that of the diesters. However, the effect of the monoester was different in T cells as compared to the diesters. The influence of the phthalates on the cytokine secretion did not seem to be a result of cell death. Thus, results indicate that phthalates influenced both human innate and adaptive immunity in vitro. Therefore, cell differentiation, regenerative and inflammatory processes are observed to be influenced by phthalates in animal in vitro studies [57].

The evaluation of phthalates exposure on pubertal development is rarely studied. Few previous studies support that high exposure of phthalates was associated with delay in puberty, although some controversies do exist [58]. In animal studies, decrease in mother and fetal weight and implantation losses was observed after exposing with DBP. Similarly, administration of high dose during gestation period badly affects the pregnancy and mother health [46]. Moreover, a study on female rat demonstrates that higher dose exposure make them unable to become pregnant. Inversely, at lower dose (50 mg/kg/day) exposure, the decrease in mother weight and increase in pregnancy loss were observed. However, some studies stated no effect of higher dose (500 mg/kg/day) on pregnancy, implantation, and serum progesterone level during gestation exposure of DBP [40, 59, 60]. The mode of action of DBP is poorly studied; but decreased in progesterone titer was measured in pregnant rats exposed with higher dose (1500 mg/kg/day) of DBP, however, no change was observed in estradiol level [59]. This suggests that DBP may affect the level of hormones required for pregnancy maintenance indirectly through circulation. A study on female rats suggests no effect of DBP on ovarian histology, ovary weight, number of follicles, serum luteinizing, and follicle stimulating hormone and mating behavior during lactation period exposure [60]. Thus, this concludes that female reproductive system is insensitive to the toxic effect of DBP. Although, certain animal experimental studies are lacking, but this is concluded that phthalates exposure is toxic to reproductive system. However, the adverse effects were observed at higher dose exposure as compared to lower dose.

DBP also affects kidneys of mice. The exposure to this chemical causes oxidative stress in renal fibroblast and tubular epithelial cells, which leads to the dysplasia of kidney and renal fibroblast [40]. Acute administration of DBP induces significant injuries in the kidneys and

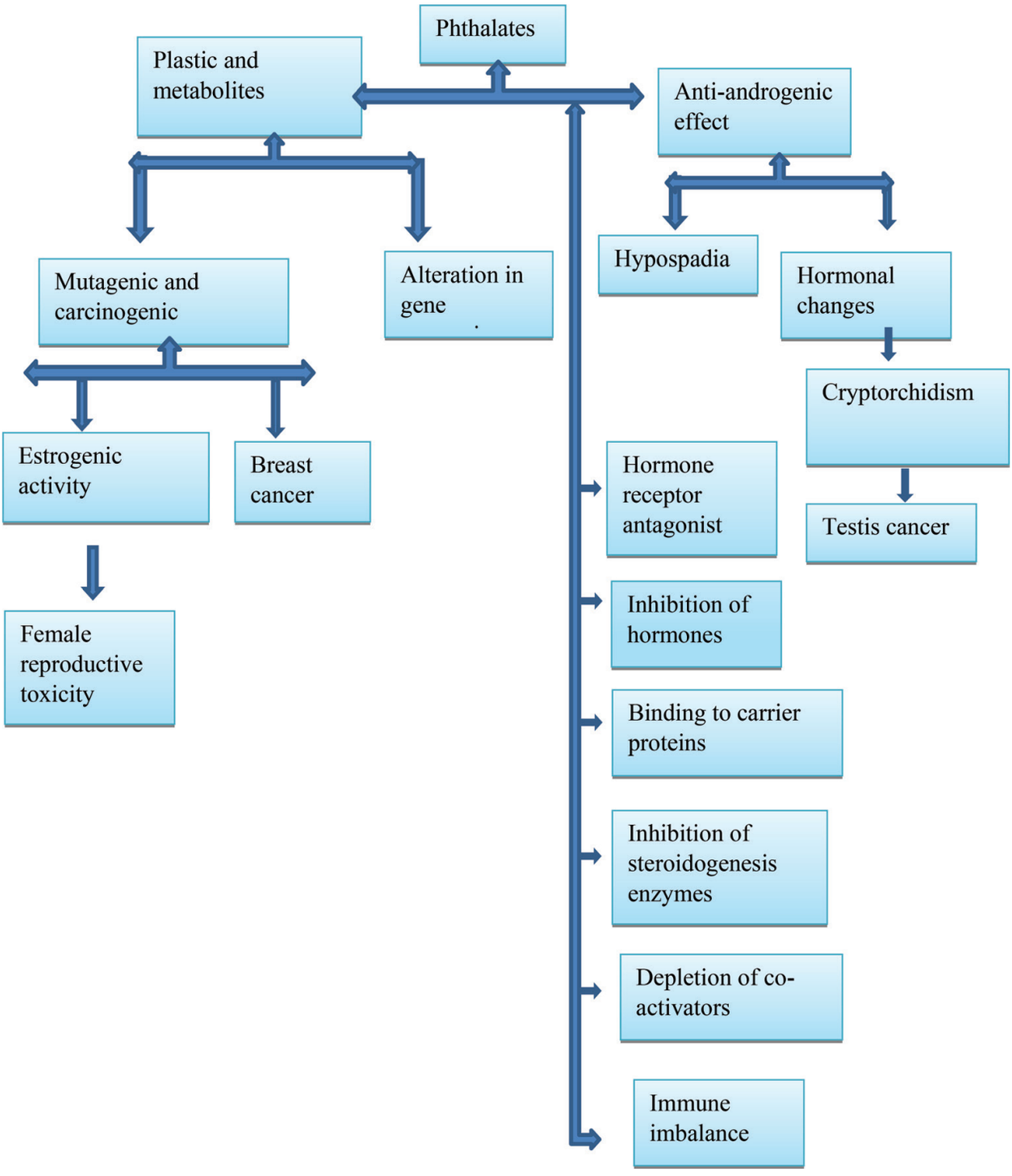

Figure 2. Schematic representation of phthalates effects on reproductive system.

liver of mice. The DBP alters the renal and hepatic cell structure by raising uric acid, blood urea level, lactate dehydrogenase, creatinine, etc. [61].

The prenatal exposure of DBP causes dysplasia in kidney of newborn offspring, while sever renal fibrosis in young adults. However, the mechanism of these disorders remains enigmatic.

Both androgen receptors and fibroblast growth factors (Fgf10) and their receptors (Fgfr2) recognized to be significant for renal development. The anti-androgenic properties of DBP played significant role in the pathological phenomena of prenatal exposure [62].

In a study of prenatal exposure on language development in boys and girls showed no notable effect on girls. However, in boys, this was significant for phthalates metabolites exposure [63].

A study on embryological development of zebrafish demonstrates that DBP causes proteomic changes leading toward the metabolic disorder and affects the networks of embryo development. Moreover, the concentration used in the study was higher than the actual in drinking water due to acute and chronic effects of DBP in experimental trials. This study concludes that DBP induces considerable changes in molecular mechanism of development and metabolism [64].

The effect of DBP was demonstrated on human prostate lymph node/adenocarcinoma epithelial cells (LNCap) to investigate the influence of eno-estrogen on prostate. The effect was also studied on cell viability along with 17β-estradiol. In the same study, the expression of genes involved in cell cycle was also studied. This study examined that the interaction of DBP with estrogen receptor was different from the estradiol. The exposure of DBP changes the gland physiology and ultimately causes the down regulation of cell cycle [65].

The mammary glands are influenced by hormones. The pre-pubertal and adult exposure of BPS was studied in female mice with low dose. Age- and dose-specific effects were associated with the mammary tissues when exposed with BPS and this effect was different from the other bisphenols [66].

The biological effect and mechanism of action of BPS was studied on cell models. The BPS binds with the estrogen receptors in a different way from BPA [67].

The alternative use of BPS was studied on zebrafish development. The study concludes that at concentration of 100 μg/L, showed same effects as were of BPA; so, BPS is also harmful for ecosystem and health and can be used with great care and limitation [68] (**Figure 2**).

4. Conclusion

From current review of literature, it is concluded that the increase use of plastic products enhances the phthalates in environment. The epidemiological studies of human as well experimental trials on animal models investigated the adverse effect of BPS and DBP at lower and higher doses. The reproductive system of male and female are at higher risk of exposure to these chemicals. In females, reduced size of mammary glands, degeneration of ovaries, immature follicles, and pubertal disorders were observed. While in males, decrease in sperm count, damage to sperm duct, and reduced testis was examined in various animal models.

5. Future directions and recommendations

The use of BPS as an alternative to BPA is not safe as it showed similar effect. This should be used with precaution and limitation. Similarly, the use of DBP should be restricted. There should be legislation on its use in various plastic products specially used in baby milk bottles, toys, dermal, and personal products. Many large scale studies are needed to investigate its adverse effect.

Conflict of interest

The author does not have any conflict of interest.

Abbreviations

AGD	anogenital distance
BPA	bisphenol A
BPS	bisphenol S
DBP	dibutyl phthalate
EDCs	endocrine disrupting chemicals
EPA	Environmental Protection Agency
Fgf	fibroblast growth factors
GPR	G protein-coupled receptor
Kiss 1	kisspeptin
LNCap	lymph node carcinoma epithelial cells
PAEs	phthalate esters
PVC	polyvinyl chloride

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