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Environmental Endocrine Disruptors: Effects on the human male reproductive system

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Abstract

Incidences of altered development and neoplasia of male reproductive organs have increased during the last 50 years, as shown by epidemiological data. These data are associated with the increased presence of environmental chemicals, specifically “endocrine disruptors,” that interfere with normal hormonal action. Much research has gone into testing the effects of specific endocrine disrupting chemicals (EDCs) on the development of male reproductive organs and endocrine-related cancers in both *in vitro* and *in vivo* models. Efforts have been made to bridge the accruing laboratory findings with the epidemiological data to draw conclusions regarding the relationship between EDCs, altered development and carcinogenesis. The ability of EDCs to predispose target fetal and adult tissues to neoplastic transformation is best explained under the framework of the tissue organization field theory of carcinogenesis (TOFT), which posits that carcinogenesis is development gone awry. Here, we focus on the available evidence, from both empirical and epidemiological studies, regarding the effects of EDCs on male reproductive development and carcinogenesis of endocrine target tissues. We also critique current research methodology utilized in the investigation of EDCs effects and outline what could possibly be done to address these obstacles moving forward.

Keywords

endocrine disruption; developmental origins of adult disease; carcinogenesis; male reproduction; prostate cancer; testicular cancer; male breast cancer; tissue organization field theory

1.0.0 Introduction

Between 1950 and 2000, the incidence of several conditions deleteriously affecting male sexual organs increased annually. Epidemiological studies showed that, in most areas of the industrialized world, incidence rates of prostate and testicular cancer [1], maldescended

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testes and anatomical malformations of the male genitalia increased [2], while sperm quality steadily declined [3]. In the past 25 years, explanations have been offered to justify these trends and better interpret the scientific data collected in this field. For instance, Sharpe and Skakkebaek proposed the "estrogen hypothesis," wherein exposure to increased levels of estrogen *in utero* was responsible for these changes drawing connections between altered development and diseases of adulthood [4]. Others suggested a connection between the increased presence of environmental chemicals which affected pregnant women and, directly or indirectly, their conceptus during early development [5].

Normal development and maintenance of the prostate gland and testes are heavily dependent on the regulation of both locally acting and circulating hormones; the same is true for postnatal development and maintenance of the mammary gland (MG). Knowledge regarding the complex development of these organs as well as the nature of their interactions with endocrine disrupting chemicals (EDCs) has increased substantially. These findings suggest that EDCs have the potential to alter cell and tissue behavior over both short- and long-time frames. Importantly, it has been proposed that exposure to EDCs during a man's lifetime, i.e. from fetus to adult, is responsible for an increased predisposition toward developing endocrine-related cancers later in life. This "EDC hypothesis" was derived from the broader perspective originally offered at the 1991 Wingspread Conference, where biologists met to discuss the implications of EDCs in the environment, their effects on wildlife, and their impact on the future of human health [5, 6]. In this review, we discuss the current literature regarding the roles of EDCs in sexual development and carcinogenesis in men, how the two may be linked, and attempt to address some of the contradictions and controversies in the field.

2.0.0 What is an EDC?

In the Statement of Principles released by The Endocrine Society, an EDC is defined as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action [7]."

2.1.0 How do EDCs exert their effects?

While the biological function of an EDC is disruption of normal hormonal action, the processes by which this is achieved vary widely. Hormones interact with their specific receptors, mostly nuclear, and exert their effects on cells by activating or repressing target genes [8]. Similarly, EDCs interact with hormone receptors specific for the hormones that they mimic. For example, estrogen-mimics like bisphenol A (BPA) and diethylstilbestrol (DES) act by exerting their effects mainly through the estrogen receptor (ER) alpha, while BPA can also exert its action through ER-beta [9]. EDCs can also exert their effects through different nuclear receptors such as members of the peroxisome-proliferator activated receptor (PPAR) family present in reproductive tissues [10]. Following phthalate exposure, adult mice have shown developmental effects attributed to direct activation of PPARs, especially PPAR-alpha and PPAR-gamma [11].

Of note, EDCs are not strictly "specific" in their binding to hormonal receptors, as several EDCs have been found to have multiple hormonal activities.

Dichlorodiphenyltrichloroethane (DDT), for example, is categorized as an estrogen agonist, while one of its metabolites is an anti-androgen [12]. BPA, which has estrogenic activity, is also a thyroid hormone antagonist and has been shown to bind prostatic androgen receptors in men afflicted by castration-resistant prostate tumors [7, 13, 14]. Estrogens from exogenous sources bind the nuclear ER, cell membrane ERs, estrogen-binding protein GPR30, and plasma carrier proteins, albeit with a lower binding affinity than the endogenous estrogens [15–17]. Additionally, chemical structural analysis of a candidate EDC is an insufficient predictor of its potential hormone receptor targets [18]. It is also important to note that given the dynamic physiology of exposed organisms, these chemicals affect their perceived “primary target,” which in turn can secrete other hormones or factors that act on “secondary target tissues” and so on. Xenoestrogens exert their activity in additive and synergistic manners when present in low doses [15]; the effects of EDCs do not have a linear relationship with the dose of exposure, a topic that is discussed in the next section.

EDCs also interfere with hormone synthesis and metabolism either directly or indirectly [5]. Thiophosphates inhibit p450 enzymes that are involved in the metabolism of estrone and testosterone in the liver [19, 20]. EDCs can also affect hormone receptor expression, e.g. perinatal exposure to BPA showed dysregulation of steroid receptors and co-regulators in the rat testes, and interestingly, this latter phenotype was passed down for generations [21]. *In utero* exposure to diethylhexyl phthalate (DEHP) resulted in decreased mineralocorticoid receptor mRNA and protein expression in adult interstitial Leydig cells of Sprague-Dawley rats [22].

Besides directly interfering with hormonal pathways, EDCs can affect the epigenetic landscape of cells in target tissues. For example, exposure to BPA [23], cadmium [24], vinclozolin [25] and DEHP [26] altered DNA methylation patterns in both prostate and testicular cells. Histone methylation patterns can also be affected, as seen in testes exposed to vinclozolin and dibutyl-phthalate (DBP) [27]. EDCs directly or indirectly affect gene expression profiles and transcriptomes on a large scale. For instance, *in utero* exposure to vinclozolin altered the expression of 576 genes in embryonic rat testes [28]. Also, the testes of CD-1 mice exposed to mono(2-ethylhexyl) phthalate (MEHP), and zearalenone, a fungicide, showed distinct gene expression signatures [29]. Given that epigenetic patterns can be heritable, it is not surprising that the effects of EDCs on transcriptomes, DNA methylation patterns and histone modifications have been observed in successive generations [21, 30, 31].

The evidence that EDCs alter development is further supported by findings that EDCs can affect small non-coding RNAs that are implicated in development. In particular, microRNAs (miR) are involved in proper differentiation of primordial germ cells (PGCs) and have been shown to be dysregulated in testicular germ cell tumors [32]. Alterations in miR expression have been observed in mouse Sertoli cells that were exposed to nonyl-phenol [33]. Other EDCs, such as BPA and DDT have also been linked to altered miR expression in estrogen-responsive human breast cancer MCF-7 cells and in placental cell lines, respectively [32].

Epithelial-stromal interactions are necessary for development of the MG [34] and the prostate [35]; disruption of these interactions have been well characterized in these tissues during tumorigenesis [35–38]. While effects of EDCs are mostly manifested in the epithelial compartment of target tissues, EDCs can also exert their effects through the stromal compartment. For example, prenatal exposure to BPA alters the differentiation pattern of periductal stromal cells in the rat ventral prostate [39]. *In utero* exposure to BPA accelerates fat pad maturation and increases the density of collagen fibers around epithelial structures during embryonic development of the mouse MG with a concomitant delayed lumen formation in the epithelium [40]. Transcriptomal analyses of BPA-exposed embryonic mammary epithelium and periductal stroma showed alterations in apoptosis genes in the former and focal adhesion and adipogenesis genes in the latter [41]. In the adult mouse MG, *in utero* exposure to BPA altered the DNA synthesis rate in stromal cells [42]. Similarly, inhibition of the prostatic epithelial bud during embryonic development in mice by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is mediated through the mesenchyme rather than the epithelium [43]. TCDD also exerts its inhibitory effects on pregnancy-associated MG development in mice by acting on both the stroma and the epithelium [44]. DES exposed hamster seminal vesicles showed altered stromal cell organization and epithelial dysplasia in both neonates and adults [45], and perinatal BPA exposure altered the prostatic stroma [39].

Epithelial morphogenesis requires changes in cell shape, a phenomenon that involves biomechanical forces [46]. The role of biomechanical cues in tissue development is only recently being explored in different tissue systems such as the developing lung [47, 48], heart [49], kidney [48] and the MG [48, 50]. Hormones can also provide biomechanical cues; for example, estrogen has been shown to affect the biomechanical properties of cells isolated from the cornea [51], endothelium [52] and the anterior cruciate ligament [53]. In addition, treatment of estrogen-responsive human breast cancer T47D cells in collagen type I matrix with mammogenic hormones (estradiol, progesterone and prolactin) resulted in differential collagen organization patterns around epithelial structures [54, 55]. Although the hypothesis that EDCs change the biomechanical properties of target tissues has yet to be tested, there is evidence that EDCs affect structural protein expression in the extracellular environment. For example, BPA has been shown to affect collagen fiber organization around epithelial structures [40], as well as expression of tenascin and filamin b proteins in the periductal stroma [41] in the embryonic mouse MG. Neonatal hamster seminal vesicles exposed to DES showed altered expression of E-cadherin and beta-catenin proteins [45]. Malignant transformation of normal tissue is associated with changes in biomechanical properties as seen in the MG [56–58] and the prostate gland [59, 60].

Together, these findings highlight both the short- and long-term effects of EDCs on tissues. While the phenotypes of affected tissues might be different, it is clear that EDCs act in a systemic manner, a conclusion also supported by reports that EDCs can trigger inflammatory responses in several target tissues [61].

The effects of embryonic and fetal exposure to EDCs are best understood from the perspective of ecological developmental biology (Eco-Devo), because this discipline studies the environmental determination of phenotypes, a phenomenon known since the late 19th century [62]. Eco-devo also further supports the Barker hypothesis whereby some adult

diseases have fetal origins [21]. The timing of exposure to EDCs can influence the severity of consequential effects; those effects observed after fetal exposure occur at significantly lower doses than those reported to produce effects in adults (example in section 5.4).

2.2.0 EDCs in development and cancer

The activity and long-term effects of individual EDCs have been studied in the context of endocrine action, especially during early development. Thus, it becomes difficult for an EDC to fit the classical definition of a carcinogen under the current *zeitgeist*. Under the tenets of the currently prevailing theory of carcinogenesis, namely the Somatic Mutation Theory (SMT), carcinogenesis is a two-step process that occurs within a single normal cell, which, after accumulating somatic mutations, proliferates uncontrollably, and gives rise to a tumor [63]. As discussed above, beyond their cell-specific effects, EDCs can have tissue-centered effects. While some EDCs can generate mutations, most are not mutagenic *per se* [21]. However, evidence points to correlations between EDC exposure and the development of cancers in endocrine target tissues [64]. Therefore, on the one hand, empirical evidence requires an alternative theory of carcinogenesis to comprehensibly explain the available data, while, on the other, the same evidence demands attention on how to evaluate a chemical's toxicity and carcinogenicity by regulatory agencies.

The connection between EDCs and tumorigenesis is better understood under two alternative key premises. They are 1) proliferation and motility is the default state of all cells, and 2) carcinogenesis is a tissue-based process [64]. These are the premises adopted by the Tissue Organization Field Theory (TOFT) of carcinogenesis. More explicitly, TOFT posits that the morphogenetic tissue units are the target of carcinogens, and that carcinogenesis occurs when the reciprocal communication between the stroma and the epithelium of those morphogenetic units is disrupted [65].

The case of DES, administered to pregnant mothers *en masse* beginning in the 1940s to prevent miscarriage [66], is a prime example that explains how an EDC effectively acts as a carcinogen under the premises of TOFT. Young women who had been exposed to DES *in utero* developed a rare cancer, namely, clear cell carcinoma of the vagina. Later, this same exposure resulted in increased incidence of breast cancer at the age of prevalence [66, 67]. Rodents exposed to DES *in utero* showed abnormal development of the female reproductive tract in adulthood [64]. Experimental data suggests that exposure to DES, as well as other synthetic estrogens altered the reciprocal stromal-epithelial interactions needed for proper development, thus increasing the tissues' proclivity towards a neoplastic state as posited by TOFT [41, 64].

These findings, along with emerging epidemiological and experimental data, lend to the conclusion that cancer is "development gone awry" [17, 64, 68]. The xenoestrogen BPA represents a more recent model of how an EDC can cause cancer - BPA affects MG development in female rats exposed to it *in utero* and perinatally in a number of ways such as by accelerating fat pad maturation, changing the stromal composition, inducing ductal elongation, inhibiting lumen formation and altering the pattern of gene expression of both stroma and epithelium during fetal development. The exposed MG exhibits increased sensitivity to estrogen and progesterone, and thus continues to develop abnormally in

response to normal levels of ovarian hormones. All these changes, when taken in the context of hormonal action during puberty, disrupt the MG environment. As a result, an increased incidence of preneoplastic conditions in the MG is observed when sexual maturity is reached [17, 64].

Human and animal studies, as well as *in vitro* experiments, have shown that sex hormones have differential effects on target tissues; in the same tissue, a hormone may act to induce cell proliferation at low concentrations, and inhibit it at higher concentrations (shut-off) – a phenomenon that was termed the direct negative hypothesis of control of cell proliferation [69]. Both estrogen and testosterone induce the proliferation of their respective target cells *in vitro* at low concentrations and inhibit it at higher doses and therefore support the above-referred hypothesis [70, 71]. Interestingly, the androgen-induced shut-off is mediated by the *APRIN* gene, that is only expressed at high doses of androgens and not at the low doses, both *in vitro* and *in vivo* [72]. Similar observations were made *in vivo* in the rat prostate [73] and, in the case of estrogens, the uterus [74], and the mouse MG [75]. These findings support the biphasic pattern of androgen therapy that favors intermittent androgen suppression approaches for prostate cancer (PC) treatment in clinical settings [76–78]. EDCs exhibit a similar dose response in reproductive tissues; male CF-1 mice exposed to DES or estradiol *in utero* showed an inverted-U-dose-response relationship with their prostate weight in adulthood [79]. Similarly, female CD-1 mice exposed *in utero* to either DES or methoxychlor (organochlorine pesticide), followed up by an estradiol challenge in adulthood, showed increased uterine weight at lower doses of DES or methoxychlor compared to those exposed to higher doses of both EDCs [80], thus confirming the non-monotonic dose response (NMDR) of EDCs.

These findings illuminate two seemingly conflicting aspects regarding EDCs' effects, namely, 1) receptor affinity to many EDCs is much lower than those of endogenous hormones and 2) mid-to-high doses of EDCs do not always result in obvious effects nor are dose-effect relationships always consistent throughout life stages. Over the past decade, increasing evidence has accumulated supporting the deleterious "low-dose" effects of chemicals, such as BPA [41, 81, 82]. The NMDR nature of EDCs is a direct result of the dual activity of hormones under normal conditions. Out of 148 papers describing NMDR-like chemical action across a wide-range of doses, 82 examples of moderate-to-high plausibility of non-monotony have been identified [83]. Explanations for NMDR include: differential activation of discrete receptors at varying concentrations, receptor desensitization, receptor dimerization incompatibility, dose-dependent differential gene expression, and cell-specific negative feedback regulation [83, 84]. These factors must be considered in both tissue-dependent and developmental contexts when investigating the action of candidate EDCs.

3.0.0 EDCs in Prostatic Development and Cancer

The prostate gland relies on circulating hormones for normal developmental morphogenesis and functionality in men during the reproductive years and beyond. Reciprocal interactions between the urogenital sinus epithelium and its associated mesenchyme regulate prostatic differentiation and morphogenesis; however, the presence of exogenous hormones or

reductions of systemic hormone levels disrupt this sensitive balance [85]. In the former circumstance, an increased risk of PC has been documented; that is, chronic exposure of humans or rodents to high levels of estrogen leads to increased risk of PC [86, 87]. In contrast, castration in early life results in dramatic decreases in the levels of circulating androgens, prostate size and, consequently, PC [88].

3.1.0 Prostate gland development

The prostate gland develops from endodermal origins while the seminal vesicles are derived from the mesonephric ducts and are of mesodermal origin [89]. Prostatic development and function are highly dependent on androgen receptor activity. Loss of the androgen receptor (AR) in rodents or in humans leads to failure of the prostate to develop [90, 91]. Conversely, exposure of female urogenital sinus tissues *ex vivo* to androgens leads to the formation of prostatic buds [92]. Androgenic steroids trigger both the initiation of prostate development from the urogenital sinus and the masculinization of the Wolffian ducts to form the epididymis, seminal vesicles, and vas deferens [93]. Unlike the multi-lobular rodent prostate, the human prostate is a single, dense organ divided into three distinct zones, each defined histologically based on its ductal organization. Androgen dependent expansion of both stromal and epithelial compartments of the prostate occurs throughout sexual maturation with the gland growing from 1 g at birth to 20 g following puberty [94]. The expression of 5-alpha reductase by the prostatic mesenchyme is necessary for local conversion of androgens to testosterone, which, together with local conversion of androgens to estrogen by aromatase, play important roles in cell proliferation and morphogenesis [95].

The prostatic stroma expresses ER-alpha while prostate epithelial cells express ER-beta [96]. Expression of the ERs varies throughout life and their function in adult tissue is not fully understood. ER-alpha is expressed homogenously in the prostatic stroma where it seems to be indirectly responsible for the hyperplasia and squamous metaplasia reported in the epithelium following estrogenic exposure [97]. Complete loss of ER-alpha activity does not result in gross changes in prostate development or function in rodents. In rodents, ER-beta expression is low at birth and gradually increases until puberty, while in the human urogenital sinus, it is maintained during morphogenesis and cellular differentiation before drastically decreasing in early puberty. This low-level expression continues throughout men’s reproductive life but may increase in response to androgenic activities associated with benign prostatic hyperplasia (BPH) and PC [98]. Excessive *in utero* exposure to estrogens may be responsible for the estrogenization of the prostate leading to permanent alterations of hormone receptor expression and function [99]. African-American men have a two-fold higher risk of developing PC and higher levels of circulating estradiol compared to Caucasian Americans [100]. In addition to heredity and lifestyle differences, exposure to elevated levels of maternal estrogen in the womb may be a major factor in these men’s higher incidence of PC [101].

3.2.0 Prostate Cancer

In 2012, PC resulted in the death of an estimated 307,500 men worldwide, making it the fifth most common cancer-type mortality in men [1]. Following an increased incidence of PC in the three previous decades, the number of patients with PC has stabilized, a pattern

primarily associated with early detection [102]. The prostatic zones differ in their respective cancer susceptibility; the inner zone is the most common site of BPH while the outer zone is the most likely site of PCs. Differences in developmental patterns between the prostate and adjacent accessory glands may be responsible for the profound differences in their cancer susceptibility, as only about 50 cases of seminal vesicle adenocarcinoma have been reported [103]. Most prostate tumors are dependent on circulating androgens for growth and, accordingly, early interventions are aimed at lowering serum androgen levels [104]. Despite initial reductions seen in tumor size following castration or androgen-attenuating interventions, advanced PC continues to be dependent on androgens through increased AR and/or 5-alpha reductase expression [104]. In some patients, anti-androgen treatments may later act as AR agonists in advanced cancers [105]. Later in life, the aromatization of testosterone to estradiol by peripheral adipose tissue, coupled with decreasing testosterone synthesis, is believed to be, at least partially, responsible for the increased occurrence (~50%) of BHP and PC in men by the age of 60 [106].

3.3.0 Effects of EDCs on Prostate Development and Cancer in Humans

Driscoll and Taylor (1980) performed a histological analysis of tissues derived from infant autopsies and found that all infant boys in the study exposed to DES *in utero* presented prostatic utricles and dilated ducts with squamous metaplasia while low exposure-risk controls appeared normal [107]. Recently, it was found that young men with histopathologically verified PC had higher serum levels of BPA than healthy controls. In fact, BPA levels were a more relevant indicator of PC than prostate-specific antigen, which was shown to be a less reliable marker [108].

On the experimental front, administration of genistein, a phytoestrogen commonly present in soy-based foods, dietary supplements and infant formulas, to athymic mice implanted with human prostate PC3-M cells reduced metaplasia by 96% [109]. While this may suggest that some estrogens directly attenuate prostatic hyperplasia and metastasis, it is equally possible that genistein triggers a negative feedback response through the pituitary gland resulting in reduced androgen synthesis. Finally, using prostate epithelial cells from healthy donors, Prins et al. found that BPA increased the expression of genes associated with self-renewal and maintenance of non-differentiated phenotypes [110]. These cells were grown under the mouse kidney capsule and the resulting epithelial structures were exposed to an estrogen/testosterone mix. The exposed, grafted tissues developed neoplasia, implying that the prostate epithelial cells were targets of BPA.

Polychlorinated biphenyls (PCBs) are highly lipid-soluble compounds that leach continually into ecosystems from waste, despite not having been commercially manufactured since the late 1970s [111]. Occupational and environmental studies have provided strong evidence for an association between lifetime exposure to PCBs and the prevalence of PC [112, 113]. Teenage boys born with high levels of PCBs in their cord blood where shown to have significantly lower levels of both luteinizing hormone and testosterone, indicating an interaction of PCBs with the hypothalamic-pituitary-gonadal axis [114]. Various pesticides have been shown to induce endocrine disruption and exposure to them has been found to correlate with increased risk of PC [6]. Organochlorine pesticides have a half-life of up to

several years, accumulate in adipose tissue and exposure may result in continuous endocrine disturbances that increase PC risk through both direct exposure or indirectly through maternal transfer through the placenta [115]. Pesticide applicators who came in contact with organophosphates fonofos, malathion, terbufos or the organochlorine Aldrin showed an increased risk of aggressive PC [116].

3.4.0 Effects of EDCs on Prostate Gland in rodents

High serum levels of estrogen have been implicated in an increased risk of PC in humans; however, rodents required increased levels of both androgens and estrogen to promote PC formation [117]. Early life exposure of neonatal rats to BPA enhances the prostate's susceptibility to estrogen-induced hyperplasia [118]. Similarly, Sprague-Dawley rats exposed to low-dose BPA (25 ug/kg/day) *in utero* showed a dramatic increase in hyperplastic lesions in the ventral prostate at PND180 [119]. Epigenomic analysis of the rat prostates exposed to environmentally relevant doses of BPA revealed alteration in the methylation status of several genes associated with preneoplastic lesions [118].

In rats exposed to mixtures of anti-androgens or a mixture of 13 well-characterized endocrine disruptors, the ventral prostate epithelium was hypertrophic and displayed cribriform patterns in late adulthood despite a normal prostate weight observed at PND55 [120]. The anti-androgenic EDC vinclozolin caused atrophy of the prostate in adult rats while low-dose exposure during gestation resulted in irreversible decreases in prostate size [121]. Metabolites of methoxychlor have both estrogenic and anti-androgenic properties. Administration of methoxyclor to pregnant mice led to male offspring with permanently enlarged prostates [81]. In the same study, male mice exposed to high levels of estrogen or DES *in utero* presented with smaller prostates than controls. Despite these findings, methoxyclor's effects in developing and adult humans have been given limited additional attention as an EDC. Complex mixtures of PCBs were reported as *bona fide* rodent carcinogens and were shown to demonstrate both estrogenic and anti-androgenic activity *in vitro* [122]. Following exposure to PCBs, male rodents showed reduced ventral prostate weight, possibly resulting from their dual action on sex hormone receptors in the prostate [123]. Aroclor-1254, a mixture of 60 PCBs believed to be relevant in the evaluation of environmental exposures in humans, altered the expression of gap-junction proteins [124], ultimately disrupting cell-cell communication [125].

4.0.0 EDCs in Testicular Development and Cancer

Testes are the site of male gametogenesis and where most of the production of testosterone, the principal androgen in males, takes place. In turn, testicular development and function require proper hormonal control and, therefore, are sensitive to disruption by exogenous hormones [85]. The most common risk factor for testicular cancer (TC) is improper testicular development [126], further strengthening the notion that cancers represent "development gone awry", a notion that is implicit in the TOFT, and made explicit in a later publication [127]. In addition, by interfering with normal testicular development, EDCs may increase the risk of neoplastic development.

4.1.0 Testicular Development

Early in human development, the male and female gonads are sexually naive. The *SRY* gene on the Y chromosome, responsible for testicular organogenesis and the formation of testicular cords from pools of germ cells, is inactive before the 7th week of gestation [128]. Sertoli cells produce anti-Müllerian hormone responsible for suppressing the formation of the uterus and associated structures from mesonephric ducts. Once the testicular capsule, the tunica albuginea, is formed, the connection between the testicle and its adjoining supporting tissue is severed. Leydig cells within the testicle begin secreting testosterone, which is responsible for the masculinization of the Wolffian ducts into the vasa deferentia, seminal vesicles, and epididymides as well as the morphogenesis of the penis and scrotum [129]. Along with Insulin-like growth factor 3 (INSL3), testosterone is crucial for testicular descent from the abdomen into the scrotum via the inguinal canals [130]. After the testicles complete their descent, Sertoli cells differentiate and polarize, eventually forming a true lumen during early puberty. While testicular development is not completely understood, it is clear that hormones play a pivotal role in the proper formation and descent of these organs from their earliest developmental stages. Interruption of hormonal function within the developing tissues have been shown to lead to undescended testicles (cryptorchidism) [111], improper positioning of the urethral opening (hypospadia) and sterility [131].

4.1.1 Testicular Dysgenesis Syndrome (TDS)—Based on epidemiological, clinical and laboratory findings, Skakkebaek et al. described the Testicular Dysgenesis Syndrome (TDS) consisting of varying degrees of cryptorchidism, hypospadias, and impaired spermatogenesis. These features are closely associated with TC susceptibility and it was claimed that these features result from altered prenatal testicular development [132]. This hypothesis fits well within the TOFT in the sense that, as mentioned above, cancer is “development gone awry”; TDS qualifies as a representative example of an *inborn induced error of development* [68]. Human TDS may be further exacerbated by exposure to EDCs during childhood and adult life [85].

Alteration of the hormonal milieu during gestation or perinatal life by exposure to exogenous estrogens or anti-androgens resulted in the malformations described in TDS as well as Leydig cell tumors and teratomas [111]. Several male CD-1 mouse offspring exposed to DES through daily prenatal injections (100ug/kg/d) became infertile and 15 of 24 males had noticeable testicular abnormalities including intra-abdominal testes at 9–10 months of age [133]. In a trans-generational study, twenty percent of F2 male CD-1 offspring borne from mice exposed *in utero* to DES presented with exposed urethral flaps, analogous to hypospadias, compared to 0% from oil-exposed controls, implicating parental exposure as a source of TDS characteristics [134]. BALB/c mice exposed to DES by means of a subcutaneous pellet displayed interstitial cell tumors, marked by hyperplastic Leydig cells, after 180 days of treatment [135].

4.1.2 Testicular Development and Cancer—TC is the most common type of malignancy in men aged 15–40 years in industrialized countries and is the most frequent cause of death from solid tumors in this age group. Approximately 95–98% of all TCs are germ cell tumors (TGCTs), and 1–5% of TC result from hyperplasia of testicular somatic

cells (Sertoli and Leydig cells). TGCTs consist of a diverse group of neoplasms, based on the different anatomical locations within the testis where they appear. Histopathologically, they have been classified into two main categories - seminomas, which have features similar to those of PGCs and non-seminomas, which include mixed germ cell tumors (the most common), embryonal carcinomas, teratomas, choriocarcinomas and yolk sac tumors [32, 136]. The incidence of TC has increased worldwide over the last 40 years, with an incidence peak in young adults [136, 137]. The most consistently identified risk factor associated with TC is cryptorchidism, which increases men's risk of developing TC by almost 5-fold [126].

TC consists of carcinoma *in situ* (CIS) cells that supposedly derive from PGCs that did not differentiate into spermatogonia *in utero*. This interpretation is supported by findings that human TGCTs show similar gene expression profiles and DNA methylation patterns to PGCs and embryonic stem cells [32]. In fact, the only mouse model to develop experimentally-induced TC, the 129/SvJ strain, have tumors arising from PGC populations [138]. There is also strong evidence that developmental arrest in the early germ cell lineage is necessary for neoplastic transformation of cells to CIS [136]. The findings that miRs involved in testicular development show aberrant expression in TGCTs also lend support to the link between TC and abnormal development of the testes [32]. This type of evidence is consistent with the notion that in addition to the classic *sporadic* cancers, inborn induced errors of development are responsible for the appearance of tumors or malformations in the initial decades of life in humans [68].

4.2.0 Are EDCs linked to TC and TDS in humans?

The TDS hypothesis posits that EDC exposures cause developmental disorders and TC (see above). EDCs can alter testicular development because they interfere with hormone action by mimicking and/or antagonizing hormones, and altering their production or metabolism. It has also been suggested that low and high androgen levels and/or excessive estrogen exposure during development can give rise to CIS in the testes [139]. In this regard, a meta-analysis of seven case control studies showed a statistically significant association between subfertility, possibly due to low sperm quality, and increased risk of TC [140].

By exploring the link between EDC exposure and TC, epidemiological data implied how EDC-specific effects can be associated with a carcinogenic outcome. However, in some cases, while a trend is obvious, it may not become statistically significant. For example, a meta-analysis of nine studies showed an increased risk of TC associated with prenatal exposure to DES, but this increase was not statistically significant [141]. Maternal exposure to DES during early pregnancy also increased the risk of factors linked with TC, such as male genital defects, cryptorchidism and impaired sperm quality [142]. A few case control studies have found a positive association between blood levels of p,p′-DDE, a partial estrogen agonist and androgen antagonist and the primary metabolite of DDT, and risk of TC [136]. Korean newborn boys with hypospadias had significantly higher levels DEHP and n-nonylphenol in urine and BPA and phthalic acid in plasma compared to that of newborns without hypospadias [143]. Although higher levels of BPA were not initially detected in male newborns with undescended testes in France, a negative correlation between cord blood BPA concentration and INSL3 levels was observed recently [144].

Altogether, links between PCBs and TC remain uncertain. A Swedish hospital study noted no differences in PCB levels in men with or without TC; serum from mothers of men with TC, however, showed significantly increased concentrations of several PCB congeners when compared to healthy controls [145]. In contrast, a US study found an inverse correlation between PCB congeners and TC [146], whereas a Norwegian study found epidemiologic evidence that some PCB congeners (99 and 167) may be linked to TC risk [147]. Finally, a recent case control study (125 patients vs. 103 controls) concluded that serum concentration of PCBs and hexachlorobenzene were tied to a statistically significant increase in TC risk and lower semen quality [148].

The anogenital distance (AGD) is a parameter of proper masculinization of external genitalia, and is considered a marker of testicular function. Swan et al. presented the first evidence that AGD was correlated with incomplete testicular descent in infants exposed prenatally to phthalates [149]. Chinese males whose mothers were occupationally exposed to BPA during pregnancy showed shorter AGD [150]. AGD has been confirmed to be a good readout for fetal androgen exposure in humans by several meta-analyses [151].

4.3.0 Animal Studies linking EDCs to TDS and TC

Currently there are no experimental models to study the effects of EDCs on TC, nor are there rodent models that develop TC spontaneously. These factors make it difficult to study TC in the context of endocrine disruption given that experimentally induced TGCTs through genetic manipulation in rodents do not reflect the mode of EDC action.

Although further investigation is required to establish a causative link between TC and EDCs, animal studies have linked EDC exposure to TC risk factors such as TDS. *In utero* exposure to phthalates, inhibitors of androgen synthesis, has been shown to induce characteristics of TDS in male rats, such as cryptorchidism, hypospadias, impaired spermatogenesis, and reduced male fertility, along with lower levels of testicular testosterone indicating dysfunctional fetal Leydig cells [152]. AGD in rodents has been shown to be a sensitive end-point for phthalates and anti-androgens such as flutamide and finasteride [129]. CD rats exposed to DBP *in utero* showed reduced AGD compared to controls, along with hypospadias and aberrant development of the male reproductive tract [153]. Embryonic mouse testes exposed *in utero* to DES showed a delay in testicular descent and alterations in Sertoli cells [154]. Exposure to zeranol (a non-steroidal estrogen used by cattle handlers in the U.S. and a metabolite of the fungicide zearalenone) *in utero* resulted in accelerated differentiation in mouse embryonic testes along with fetal Leydig cell hyperplasia [154]. Male Long-Evans and Holtzman rats, and Syrian hamsters exposed to TCDD perinatally showed dose-dependent developmental defects that ranged from reduced epididymis weights to reduced AGD, delayed testicular descent and reduced sperm number and quality [155].

The effects of BPA on TC and testicular development remain suggestive but not yet definitive. A 1982 National Toxicology Program study reported an increased incidence of testicular interstitial cancers in mice and rats exposed through diet to doses of BPA similar to oral LD50 levels [156]. However, the controls of the study also showed an elevated baseline of tumor incidence when compared to controls in preceding studies. In contrast,

other studies showed that dietary BPA exposure was insufficient to result in TC or aberrant lesions in the testes of Sprague-Dawley rats [157]. Long-Evans rats exposed to low doses of BPA perinatally showed an increase in the number of Leydig cells and altered androgen secretion, although the development of testicular neoplasias was unexplored [158]. *In utero* exposure to BPA did not result in changes in sperm production, seminiferous tubules, germ cell apoptosis and testosterone levels in C57Bl/6 mice [159]; but neonatal CD-1 and C3H/HeJ mice exposed to BPA orally showed aberrant meiotic recombination events in the testicular meiocytes [160]. Male rat pups exposed to BPA *in utero* showed a lower level of serum testosterone compared to non-exposed pups, although the decrease in serum testosterone did not change with various doses of BPA [161]. While an earlier study did not find any effects on AGD in Sprague-Dawley rats exposed to BPA perinatally [162], a more recent one showed that AGD was reduced in male Wistar-Furth rats, examined at PND4, when exposed to BPA *in utero* [163]. It should be noted that these studies were not designed to test whether BPA increased the risk of testicular carcinogenesis or the development of TDS.

5.0.0 EDCs in Male Mammary Gland Development and Cancer

The female rodent MG has been the model of choice to study the relation between endocrine disruptors and breast development and cancer. Combined with the rarity of male breast cancers (MBCs), there exists a paucity of knowledge on the effects of EDCs on the development of the male breast and its pathologies.

5.1.0 Male Mammary Gland Development

In humans, the male breast is primarily composed of adipose tissue with sparse ducts and periductal stroma. This contrasts with the female breast, which is predominantly comprised of ducts, glandular epithelium, and non-adipose stroma [164]. In mice, the male and female MGs develop similarly until embryonic day 13 (E13). The testosterone surge observed at E14 causes the mammary mesenchyme to condense around the epithelial stalk causing detachment of the glandular epithelium from the epidermis, which leads to a lack of nipples in males [164]. While this lack of nipples has created doubts as to whether the male mouse MG may be used as a representative model to study diseases of the male breast, studies that examined the effects of pre-pubertal exposure to hormones and pharmaceuticals on the male MG concluded that it is still amenable to such studies [165]. Rat MGs show distinct sexual dimorphism; histological analyses from different rat strains show the male MG epithelium to be squamous type with abundant vacuoles, highly eosinophilic cytoplasm and indistinct lumena that occasionally contain secreted materials. The male MG epithelium is also lacking in organization and has large and contiguous groups of alveoli, in contrast to the ductal organization observed in female rat MGs [166].

5.2.0 Cancer and associated diseases of the male breast

MBC is a rare form of cancer with a reported frequency of less than 1% in the population [167]. It is estimated that in 2015, 2,350 new cases of invasive breast cancer will be diagnosed in the U.S. male population, resulting in 440 mortalities [168]. Male breast cancer typically manifests itself around 70 years of age, with 40% of individuals advancing to

stages III or IV [169]. MBCs are mostly ER positive (up to 90%), with ductal carcinoma being the most common subtype. Other subtypes such as lobular, inflammatory, medullary, papillary and trabecular duct carcinomas have also been reported [167]. Multiple factors have been associated with development of breast cancer in men. These include *inborn inherited errors of development* [68] (e.g. *BRCA1/2* germline mutations, Klinefelter and Cowden syndrome), lifestyles (obesity, excessive alcohol intake, hormone manipulation), and occupational hazards (exhaust emissions, high temperatures). Diseases such as pituitary adenoma, testicular inflammation or damage, liver disease causing hyperestrogenism, as well as exposure of the chest to radiation have also been shown to increase risks for MBCs [167].

The most common condition of the male breast is gynecomastia, i.e. the benign enlargement of the breast due to proliferation of the ductal epithelium that affects 48–64% of boys around puberty; the condition is normally resolved spontaneously within 3 years [170]. Pseudo-gynecomastia, the benign enlargement of the breast due to excessive adipose tissue, is also observed in the male breast [165]. Recently, MBC risk was significantly associated with gynecomastia in the Male Breast Cancer Pooling Project, a consortium of 11 case-control and 10 cohort investigations involving 2,405 case patients and 52,013 control subjects [171].

5.3.0 EDCs and human MBC cases

While there are clear examples of EDC exposure linked to breast cancer in women [64, 172], there is no direct evidence of EDCs causing MBCs. In a small number of cases, patients with no family history of breast cancer treated with DES for PC later developed bilateral gynecomastia and breast cancer [173]. A case-control study on the 71 reported cases of MBC in residents (1950–1985) of Camp Lejeune, North Carolina, suggested associations between vinyl chloride, tricholoroethylene (TCE) and tetrachloroethylene (PCE) found in the drinking water of Camp Lejeune residents and MBC risk in that population. Exposure to vinyl chloride, TCE, PCE and t-1,2-dichloroethylene (DCE, also found in Camp Lejeune water) was also associated with earlier age onset of MBC [174].

5.3.1 EDCs linked to conditions associated with MBCs in humans—EDCs have been linked to higher incidences of gynecomastia in humans. Case studies suggest that exposures to environmental estrogens or estrogen mimics can contribute to the development of gynecomastia in adult males [175]. For example, 20% of male workers at an oral contraceptive plant in Puerto Rico reported cases of gynecomastia when they were exposed to aerosolized estrogen during the manufacturing process [176]. Environmental anti-androgens have also been associated with increased incidences of gynecomastia; phenothrin used as a delousing agent for treating bedding and clothing provided to Haitian refugees led to significantly higher rates of gynecomastia in that population [177]. A retrospective epidemiologic study of adult men who were administered low doses of DES during treatment of castration-resistant PC showed that 59% of them went on to develop gynecomastia [178]. Reports of pubertal gynecomastia have been linked to exposures to health care products with estrogenic or anti-estrogenic properties [179]. Additionally, a case-control study showed levels of two phthalates were higher in adolescent boys with gynecomastia compared to boys without this condition [180].

5.4.0 EDCs and MBCs and associated conditions – evidence from animal studies

Few studies have addressed the effects of endocrine disruptors on male MG development and MBC. Vandenberg et al. [165] showed that the mammary tissue of male CD-1 mice exposed prenatally to BPA displayed an age-dependent NMDR. At 3–4 months of age, animals exposed to 0.25 ug BPA/kg BW/d and 2.5 ug BPA/kg BW/d showed more advanced gland development than controls, but 25 and 250 ug BPA/kg BW/d groups were indistinguishable from controls. More specifically, the 0.25 and 2.5 ug groups showed more epithelial tree branching points and 2.5 ug group also showed increased ductal area relative to controls. The 2.5 ug group was most severely affected presenting a 4.5-fold increase in branching points and 7.7 fold increase in ductal area, compared to controls. However, at 7–9 months age, the NMDR had shifted such that animals treated with 2.5 and 25 ug BPA/kg BW/d were the most affected. Glands from 25 ug BPA-exposed males had a 3.6-fold increase in branching points and 4.8-fold increase in ductal area. At 12–15 months age, 25 and 250 ug group animals had more branching points compared to controls, and although there was a trend of increase in ductal area, the difference was not significant. The significance of this data is highlighted at the end of section 2.1.

Male Sprague-Dawley rats exposed chronically (*in utero*, nursing and dietary) to genistein showed ductal and alveolar hyperplasia and hypertrophy in their MGs, with significant effects observed at 25 ppm and above [181]. These effects were observed across generations where hyperplasias were sustained but did not increase in magnitude or result in neoplasias [182]. The administration of flutamide, primarily used to treat PC, and also present in pesticides, resulted in persistence of nipples and mammary epithelium in male Sprague-Dawley rats exposed *in utero* [183]. Pre-pubertal male Sprague-Dawley rats showed increased lateral budding in MGs when exposed to methoxychlor or genistein and methoxychlor *in utero* and through diet [184]. In adult male Sprague-Dawley rats, exposure to methoxychlor or a combination of genistein and methoxychlor resulted in increased longitudinal growth, density and size of the MGs, increased number of ductal branches and alveolar mass, and exhibited ductal hyperplasia [185].

6.0.0 Critical Analysis of EDC Research

Extensive evidence obtained from epidemiological studies in human populations have identified DES and DDT as carcinogens in women; animal studies have presented ample evidence to suspect BPA as a carcinogen for the prostate and MGs [172]. However, as the Endocrine Society has recently asserted [186], more research is required to establish the link between defects of the male reproductive system, including cancers, and EDCs, such as the ones discussed above. Currently, there exists a public controversy surrounding the effects of EDCs that originates from confounding results described across multiple studies. In this section, we will describe the sources of such confounding data and whether a connection between EDCs and carcinogenesis and defects of the male reproductive system can be verified.

A major source of confounding data arises from the choice of models to study the link between EDCs, developmental defects and carcinogenesis. Models for hormone-induced carcinogenesis were originally developed to obtain high tumor yields with a short latency

period; this goal was achieved by treating animals with supra-physiological levels of hormones with or without additional chemical carcinogens [187]. Therefore, these models do not accurately represent how EDCs may affect hormonal action in human populations. Studies on carcinogens have traditionally used a linear dose scale, a method that largely masks those effects seen at low doses [188]. This may explain why EDCs, which may not have significant effects at high doses due to their NMDR, had been ignored as potential carcinogens in early studies. Similarly, traditional toxicological studies that operate under the premise that larger doses should have greater effects also failed to describe the low dose effects of EDCs [84]. Given that the regulation of a chemical is based on the no-observed-adverse-effect-level, which is extrapolated from the LD50 doses, it is not surprising that the low dose effects of EDCs were ignored given their NMDR nature.

While these comments may address why EDCs and their carcinogenic potential and low dose effects were not discovered earlier, it does not resolve the contradictory results observed in practice. This issue can be partially resolved by taking into consideration the model's sensitivity to candidate EDCs. For example, *in vitro* assays to detect the estrogenicity (E-SCREEN) and androgenicity (A-SCREEN) of environmental chemicals employ cell lines growing in 2D conditions [189]; however, the characteristics of these cell lines differ based on the source they are obtained from and, depending on laboratory practices, can give differing results. For instance, a comparative analysis of MCF-7 cell lines obtained from four different sources showed only one line of MCF-7 cells to be estrogen responsive and suitable for use to screen potential xenoestrogens [190]. Rodent models have long been used to study the effects of EDCs in the laboratory. However, different strains of laboratory mice and rats do not show the same sensitivity to EDCs. For example, while Wistar-Furth rats exposed to 250 ug/kg BW/day of BPA show a shorter AGD and other developmental defects [163], Sprague-Dawley rats exposed up to 40 mg/kg BW/day of BPA did not show any changes in AGD [162]; studies have suggested that the Charles River Sprague-Dawley rat strain is relatively insensitive to estrogen and therefore, cannot be used to detect low dose effects of BPA [191]. Different inbred mouse strains also exhibit different sensitivity to EDCs, as seen in the case of BPA [157].

The study design, such as administration route, window and duration of exposure and assessment of endpoints can also influence the outcome of a study [82, 192–194]. For example, oral gavage is widely used by regulatory bodies in risk assessment and hazard identification studies; however, this method of chemical administration does not mimic human dietary exposure to BPA and other EDCs and can affect the endocrine system by inducing stress in animal subjects [82]. Another study that used Long-Evans rats to study low dose effects of BPA lacked proper positive controls [193]. This highlights the need for novel guidelines for research on EDCs.

Research on endocrine disruptors is based on the principles of endocrinology. On the one hand, hormonal regulation is conserved among mammals; thus, rodent studies, for the most part, teach us about the human. On the other hand, there are species, strains, and individual differences that vary from quantitative differences (higher or lower doses are needed to achieve the same effect) to qualitative ones (no effect). For example, using a fetal testis assay (FeTA) culture system, it was found that phthalates do not alter testosterone

production or *INSL3* expression in human fetal testes while similar concentrations reduced testosterone production in rat fetal testes [195], however, they do affect the production of testosterone in adult testes [196]. Human fetal testes were shown to be more sensitive to BPA compared to rat and mice testes in an *in vitro* organotypic culture system. While BPA reduced testosterone production in all 3 species at high doses, only human testes were affected at low doses. Additionally, BPA treatment reduced *INSL3* mRNA levels in human testes only [10]. The knowledge gap existing between rodent experimentation and human epidemiology can only be bridged by selecting models that more closely mimic human biology.

While independent research groups have confirmed the low-dose effects of EDCs, the public debate on this issue is partly fueled on by industry influence. This has become evident, especially in the case of BPA, one of the highest volume chemicals synthesized in the world [194]. Recently, the Food & Drug Administration claimed that low-dose effects of BPA are not amenable to study due to ubiquitous contamination issues [197], a move that marked an apparent end to the debate. However, vom Saal et al. [198] and others [82, 199] were able to show that studying low-dose effects of BPA is perfectly possible without any contamination issues. This emphasizes that the Good Laboratory Practices paradigm exercised by the regulatory bodies is not a reliable indicator of a study's quality when gauging public health risks for endocrine disruptors in a lab setting [194].

We have presented here a summary of the ever-growing body of information on EDCs and their potential and actual deleterious effects on the human male reproductive system. A fair assessment of this subject is challenged by its biological complexity, limitations of animal models and, of course, economic interests. We have discussed how manipulation of systemic hormone synthesis, residential reduction or aromatization of circulating hormones, and receptor function or expression in rodents results in distinct changes in organ structure, function, and development. The safety of candidate EDCs, and those which have yet to be investigated, deserves further questioning in the proper experimental context.

7.0.0 Conclusions

This review highlights the carcinogenic properties of EDCs on the male genital tract and breast. However, animal studies for the most part address a single chemical and a single window of exposure, whereas in the "real world" humans and wildlife are exposed to a mixture of EDCs that act jointly and contextually. As humans continue to release chemicals into the environment without proper evaluation of the consequences of these decisions, science is ill-prepared for tackling this newly created situation. Most chemicals are not traceable, for lack of sensitive assays, and their effects cannot be studied using classical methods because unexposed controls do not exist, either as a result of direct exposure or transgenerational effects. In addition, the concept of exposome (i.e. tracking all exposures throughout life), created to bridge this gap, has yet to be properly described, developed and tested.

Regardless of whether or not this concept will materialize as a useful tool, the quandary still remains that in order to understand the problem we created, novel experimental approaches

will have to be implemented. These new methods should integrate the effects of different doses of structurally different chemicals that for the most part show non-monotonic dose-response curves with the fact that EDCs act at different ages on different target tissues. Would mathematical modeling and computer simulations help to arrive at more definitive answers? While this question awaits resolution, the existing body of evidence justifies the application of the precautionary principle. Therefore, preventive measures should be effectively adopted by those who are genuinely concerned with and are responsible for the public's health to reduce exposure to EDCs.

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List of Abbreviations

AGD	anogenital distance
AR	androgen receptor
BPA	bisphenol A
BPH	benign prostatic hyperplasia
CIS	carcinoma *in situ*
DBP	dibutyl phthalate
DCE	t-1,2-dichloroethylene
DDT	dichlorodiphenyltrichloroethane
DEHP	diethylhexyl phthalate
DES	diethylstilbestrol
EDC	endocrine disrupting chemical
ER	estrogen receptor
INSL3	insulin-like growth factor 3
MBC	male breast cancer
MEHP	mono(2-ethylhexyl) phthalate
MG	mammary gland
miR	micro-RNA
NMDR	non-monotonic dose response
PC	prostate cancer
PCB	polychlorinated biphenyls
PCE	tetrachloroethylene

PGC	primordial germ cells
SMT	somatic mutation theory of carcinogenesis
TC	testicular cancer
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCE	trichloroethylene
TDS	testicular dysgenesis syndrome
TGCT	testicular germ cell tumors
TOFT	tissue organization field theory of carcinogenesis

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