Review Article

Endocrine disrupting chemicals and impact on male reproductive health

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Abstract: Endocrine disrupting chemicals (EDCs) have been known to adversely affect the endocrine system leading to compromised functions of hormones. The presence of these compounds in everyday products such as canned food, water bottles, plastics, cosmetics, fertilizers, kid's toys and many others goods is a greater concern for general population. The persistent and long-term use of EDCs has deleterious effects on human reproductive health by interfering with the synthesis and mechanism of action of sex hormones. Any change during the synthesis or action of the sex hormones may result in abnormal reproductive functions which includes developmental anomalies in the reproductive tract and decline in semen quality. The present paper provides an overview of the EDCs and their possible impact on male reproductive health with major focus on semen quality which leads to male infertility.

Keywords: Endocrine; chemicals; reproductive; semen; anomalies

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Introduction

The endocrine system maintains homeostasis of the bodily systems through hormones that can travel long distances in the body and often have amplified effects. Endocrine disrupting chemicals (EDCs) are the substances which change the course of endocrine systems in a way that adversely affects the organism itself or its progeny (1). These chemicals can be found in a variety of everyday products and goods, such as in foods, water, plastics, shampoos, clothes, toothpastes, soaps, fertilizers, paper, textiles, carpets, utensils, bedding, toy, cosmetics, deodorant, etc. (2-4). Because of the use of EDCs in several consumer goods and personal care products, humans are exposed to the harmful effects of these substances in a variety of ways which include ingestion, germination, inhalation, and dermal contact. Hence, EDCs call for greater attention because of their increasing utility in daily products and possible correlation with compromised male reproductive health. The endocrine system is particularly important for male reproductive development because androgens (such as testosterone) promote the maturation of male secondary characteristics as well as the process of spermatogenesis. Male reproductive health- specifically sperm count and testosterone-have been declining (5,6), which is correlated with an increase in a variety of EDCs, such as perfluoroalkyl compounds (2). Regional differences have also been reported in urban versus rural areas showing a statistical correlation

Table 1 Decline in reference values of semen parameters from WHO 1999 to WHO 2010 guidelines

Parameter	WHO 1999	WHO 2010	% Decline
Volume (mL)	2	1.5	25
Concentration (million/mL)	20	15	25
Motility, %	50	40	20
Normal forms, %	14	4	71
Live forms, %	60	58	3

between poor semen quality and higher levels of EDCs found in pesticides, such as alachlor, diazinon, atrazine, metolachlor, and 2,4-dichlorophenoxyacetic acid (7). Such evidence linking the increasing prevalence of EDCs to declining semen quality and male reproductive health calls attention to the detrimental effects of EDCs.

Semen parameters

Semen parameters are used to measure the quality of sperm and are important because they can be used to predict male infertility, which is defined as the inability to fertilize an egg after 12 months of unprotected intercourse. From 1999 till 2010, the reference values defined in the WHO 1999 manual were used to consider a semen analysis normal or abnormal. In 2010, these values were re-evaluated and new cutoffs were introduced which are lower than WHO 1999 (*Table 1*). A conventional semen analysis report is considered the first diagnostic test in male infertility. Based on the semen parameters results assessed against WHO 2010 criteria, a decision of abnormal and normal is declared. However, it is not feasible to certify a male fertile or infertile just based on the results of a conventional semen analysis. Low quality semen can be used as a predictor for male infertility, but such men can still be fertile. Similarly, men with high quality semen may still be infertile. However, according to the WHO, only 30% of men with high quality semen are infertile, whereas men with low quality semen are much more likely to be infertile. Thus, the semen parameters are significant as indicators of compromised male fertility.

Decline in semen parameters and EDCs

Over the past several years, male reproductive health has been on the decline (5,8). Globally, incidences of testicular cancer (TC), cryptorchidism, and hypospadias have been rising, and sperm quality has been decreasing (5). Male fertility is measured, in large part, by qualitative and quantitative measures of semen parameters (9). A continuous decrease in sperm count, volume, motility, morphology, and concentration has been reported, which has contributed to an increase in male infertility (5,8-10). For instance, Auger *et al.* (1995) showed a 2.1% decrease in sperm count and a 0.6% per year decrease in sperm motility from 1973 to 1992 (11). Swan *et al.* (2000) reported that mean sperm concentration has declined 1.5% per year in the U.S. from 1938 to 1988, and 3.1% per year in Europe from 1971 to 1990 (12). Rolland *et al.* (2013) showed a 32.2% decrease in sperm concentration, and 33.4% in sperm morphology from 1989 to 2005 (13).

EDC levels have simultaneously been rising, supporting the argument that EDC exposure contributes to decreased semen quality and thus increased male infertility. For instance, polybrominated diphenyl ethers (PBDE) have been increasing globally over the past 30 years; dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenylethane (DDE) use has been increased in Africa and other parts of the world; and multiple EDCs such as bisphenol A (BPA), alkylphenols, pentachlorophenol (PCP), and triclosan have become more prominent in the environment because of manufacturing and because of their presence in widespread consumer products such as soaps, toothpastes, and wood preservations (14-16). Associations between decreasing male fertility and increasing EDC levels suggest that the decline of male reproductive health over the past few decades is due not only to genetic but also environmental factors.

EDC's leading to decreased semen quality

Phthalate metabolites, used in plastic to soften PVC polymers, have been identified in 75% of Americans. Children have shown 2–4 times higher levels as compared to adults (17). Similarly, the plasticizer BPA has been detected in urine samples of at least 90% of subjects in the United States, Germany, and Canada (1). Both phthalates and BPA have been studied as EDCs which negatively affect male reproductive health. The pre and neonatal exposure and subsequent effects of these chemicals are especially striking.

Phthalate exposure in neonatal male rats has been shown to reduce testicular testosterone levels, which results in down regulation of certain genes associated with steroidogenesis (1). Similarly, exposure to the metabolite di(n-butyl) phthalate (DBP) has shown reduction in testosterone production in rodents (18). In neonatal marmosets, DBP exposure induced significant Leydig cell aggregation (LCA), which can be an indicator of potential conditions such as cryptorchidism, hypospadias, TC, and reduced semen quality collectively grouped as testicular dysgenesis syndrome (TDS) (18). The adverse effects of phthalates on steroidogenesis in neonatal rodent primates, including humans, is a matter of great concern because higher levels of phthalates have been identified in younger children (1). Exposure to EDCs during critical periods of neonatal development has been an issue which warrants attention to the idea that prenatal exposure may be an even more significant factor than neonatal exposure in the development of TDS (1). Furthermore, in women 2–4 times higher phthalates have been reported as compared to men, suggesting a greater risk of exposing the developing child to such higher phthalates levels (17). In utero exposure to phthalate esters DBP and di-(2-ethylhexyl) phthalate (DEHP) caused inhibition of testosterone production as well as increased LCA, both conditions which are indicators of impaired spermatogenesis (7). However, in utero exposure resulted in abnormal seminiferous cord formation and multinucleation of spermatogonia in cryptorchid boys (7). Embryonic exposure to DEHP has been linked to a decrease in sperm motility, disruption of testicular germ cell organization and spermatogonial stem cell function (17). Shortened anogenital distance (AGD) and impaired testicular descent have also been reported as a result of phthalates exposure (19).

BPA has been associated with an increased risk of cryptorchidism and reduced semen quality (3). Bilateral cryptorchidism is associated with greater risk of azoospermia, poor semen quality, increased risk of TC and reduced paternal fertility rates, even after treatment (20). Increased prostate cancer progression has also been correlated with BPA exposure. The prostate gland has a crucial role in sperm motility by providing prostatic fluid (1,21). Prostate cancer is rated as the second most common male malignancy in North America (21). BPA has shown higher levels in prostate cancer patients compared to non-prostate cancer men. Further, BPA exposure has shown reduction in normal sperm morphology and motility in mice model (3).

Like rodents, human exposure to EDCs has also been correlated with decreased semen quality. For example, Faure *et al.* 2013 found that men exposed to dioxins had a greater number of morphologically abnormal sperm and low linear motility (9). Jurewicz *et al.* reported that increased exposure to polychlorinated biphenyls (PCBs) was associated with decreased sperm count, motility, and normal morphology (22). Additionally, pesticides have shown decreased normal sperm morphology, count, volume and motility (15,22). Organophosphate exposure also reduced semen volume and increased pH, and exposure to phthalates decreased concentration, normal morphology, and motility (22). These findings in humans indicate that EDC exposure does affect human semen quality in a way that is similarly modeled by rodents in other studies.

Though the effects of individual EDCs have been reported, it is important to consider the fact that humans can be simultaneously exposed to a large variety of these chemicals. EDCs can have dose-additive effects that can result in as large as a 50% discrepancy in terms of malformation in men (1). The combined effect of EDCs is more alarming and calls for greater attention because it is more realistic in mimicking human exposure.

Mechanisms of action

Different EDCs impact semen quality through various mechanisms. It has been shown that phthalates, BPA, dioxins, and PCB are all associated with decreased semen quality; however, their mechanisms of action affect different parts of the endocrine system in relation to semen quality and male reproduction.

Phthalates are of particular health concern due to their presence in common consumer goods and their impact on male reproduction. For example, several studies have shown that mono-(2-ethyl-hexyl) phthalate (MEHP), the reactive metabolite of DEHP, activates both PPAR (peroxisome proliferator-activated receptor) α and PPARγ pathways (23,24). This stimulates PPAR:RXR (retinoid X receptor) heterodimers to compete for binding sites on DNA and limited coactivators required for gene transcription, thereby inhibiting the transcription of aromatase, an enzyme involved in sexual development (23,25). Additionally, MEHP-activated PPARγ ligands decrease cAMP response element-binding protein (CREB) and Sp1 from binding to DNA for transcription, thereby preventing them from positively regulating the transcription of steroidogenic genes (24). StAR and p450c17 in particular are tightly regulated by cAMP. PPARγ ligands significantly diminish these steroidogenic proteins, leading to low sperm quality (24). StAR's function is to mediate the rate-limiting step in steroidogenesis by transporting cholesterol into Leydig cells' mitochondria, while p450scc and p450c17 are steroid-converting enzymes (24,26). MEHP decreases the production of these proteins through the PPAR pathways, thus negatively impacting male reproductive health. It has also been shown that high levels of MEHP (2,000 µM and over) inhibit the activity of these steroidogenic proteins (in addition to inhibiting 3β- and 17β-HSD enzymes specific to Leydig cell function) by inducing overloaded oxidative stress in Leydig cells, which decreases testosterone synthesis (26).

Phthalates' interference with cholesterol in Leydig cells poses a major issue. StAR helps in the transport of cholesterol to Leydig cell mitochondria. High levels of MEHP decrease the production of StAR and reduce cholesterol transport to mitochondria, which is a necessary step for testosterone production (24). MEHP also decreases the production of p450scc, which converts cholesterol into pregnenolone, an essential step in testosterone synthesis (27). Furthermore, DBP, another phthalate, decreases fetal plasma cholesterol levels, consequently leading to low fetal testosterone synthesis, which can impair testicular descendance and secondary sexual characters (27) (*Figure 1*).

In addition to decreasing fetal plasma cholesterol levels, DBP has been shown to cause lesions in seminiferous cords and multinucleated gonocytes (27). Sertoli cells carry stem cell factor (SCF) ligands while gonocytes carry c-kit receptors required for interaction between Sertoli cells and gonocytes. DBP decreases the expression of both SCF ligands and c-kit receptors, thereby preventing interaction of Sertoli cells and gonocytes. In a similar mode of action, MEHP inhibits Sertoli cell-gonocyte interactions. It inhibits Sertoli cell proliferation by decreasing cyclin D2 mRNA production, which is involved in the G1 phase of the cell cycle (28). MEHP also causes abnormal vacuolation in Sertoli cells and disrupts the intermediate filament vimentin, which normally allows spermatogenic cells to anchor to Sertoli cells (28,29). MEHP affects spermatogenesis by decreasing the number of Sertoli cells, reducing the Sertoli cell proliferation, disrupting the interactions with gonocytes, and triggering testicular apoptosis by increased expression of the Fas ligand (28,30,31).

The negative role of MEHP on semen quality has also been documented by its passing through the blood-testis barrier (BTB), which distinguishes the basal from the adluminal component of the seminiferous epithelium (31). This separation is essential in creating a specialized microenvironment in the adluminal compartment in which germ cells can undergo meiosis and maturation (31). Tight junctions between Sertoli cells and tight junction-related proteins in these cells, including claudin-11, occludin, and zonula occludens-1 (ZO-1), contribute to BTB formation. Disruptions in these tight junctions significantly decrease the division of germ cells and the production of sperm and may lead to development of autoimmunity. MEHP greatly reduces the levels of claudin-11 and occludin mRNA expression in Sertoli cells by activating the p44/42 MAPK pathway, thereby disrupting tight junctions and thus spermatogenesis (31). BPA similarly induces reduction of occludin and ZO-1 in Sertoli cells through activation of the p44/42 MAPK pathway (31).

BPA also affects estrogen (ERα and ERβ) and androgen receptors (25,32-35). For instance, BPA competes with estrogens such as 17β-estradiol and E2, which normally bind to estrogen receptors in the testis and trigger transcription of steroidogenic genes (25,32,33,36). Normally, the 3-hydroxyl group of E2 interacts with Glu353 and Arg394 via hydrogen bonding to ERα, and the 17β-estradiol interacts with His524; the 4-hydroxyl group of BPA competitively interacts with these amino acids and thus decreases steroidogenesis (34). Additionally, the hydrophobic propane and B-ring moieties of BPA help it bind to the hydrophobic binding sites of estrogen receptors (37). BPA also interacts with ASC1 to inhibit binding of androgens to receptors, which is detrimental to prostate development (33). Another receptor that BPA interferes with is the luteinizing hormone (LH) receptor in Leydig cells (33). BPA prevents LH receptors and adenylate cyclase from coupling in Leydig cells, thus inhibiting testosterone synthesis (33).

BPA also affects sperm quality by upregulating the mRNA level of the aryl hydrocarbon receptor (AhR) repressor (37). AhR is a transcription factor whose function is to induce expression of the *CYP1* gene, which encodes aromatase, an enzyme that biosynthesizes steroids. By suppressing AhR, BPA inhibits aromatase activity and steroidogenesis (37) (*Figure 1*). Additionally, AhR usually mediates the effects of other endocrine disruptors such as polyaromatic hydrocarbons, dioxins, and PCBs (37).

BPA also leads to the accumulation of reactive oxygen species (ROS), which affects mitochondria and the endoplasmic reticulum (ER) (38). Pathological levels of ROS damage the ER and compromise its function of

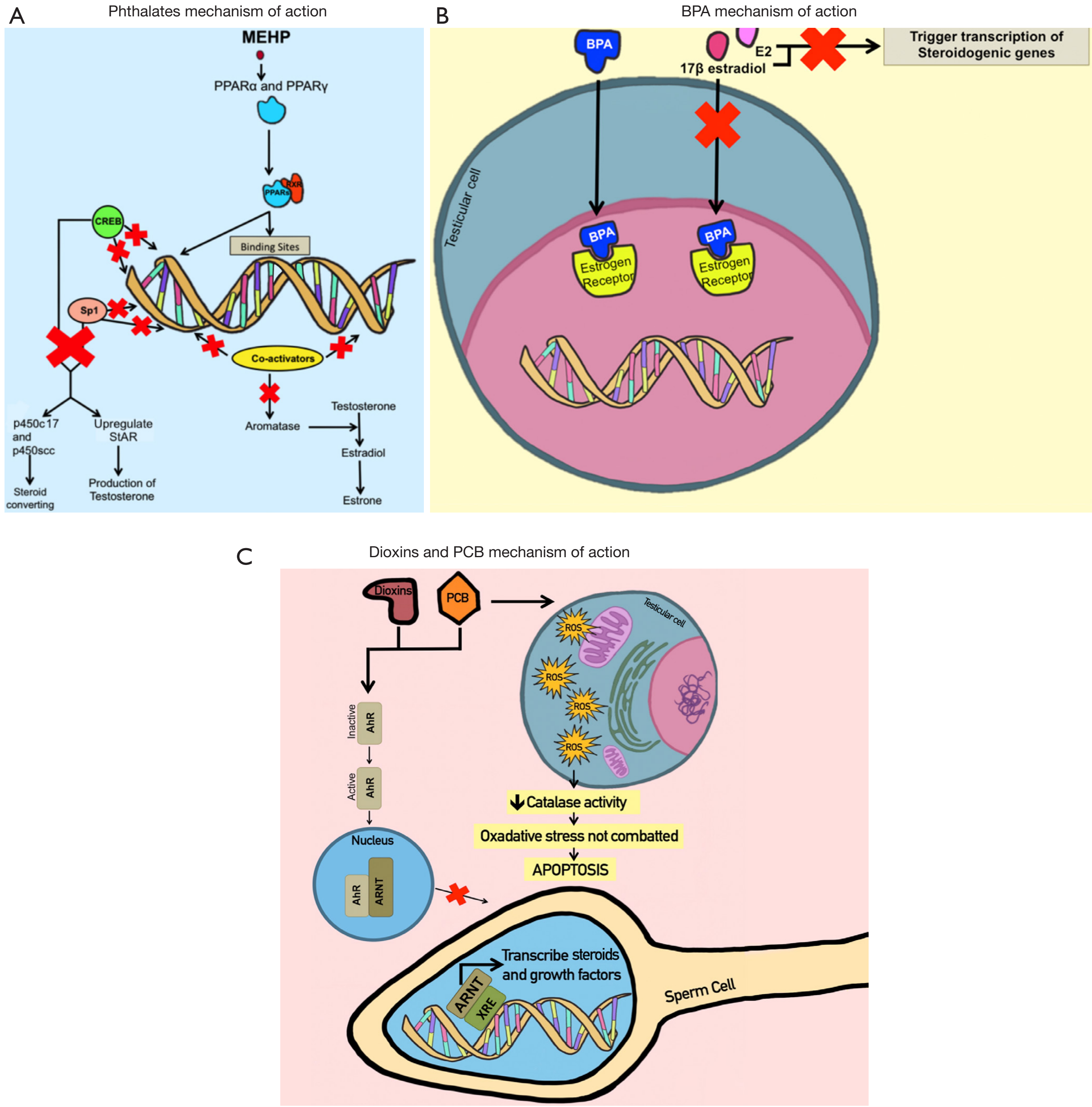

Figure 1 EDCs' mechanisms of action during leading to decrease semen quality. Panel A illustrates how MEHP (phthalates) initiates PPAR heterodimerization, thereby blocking binding sites on DNA and coactivators needed for transcription of steroid-producing genes. Panel B illustrates how BPA blocks estrogen receptors so that transcription of steroidogenic genes is blocked. Panel C illustrates how dioxins and PCB block transcription of steroid-related genes by preventing the ARNT complex from binding to XRE on DNA. It also shows how PCB specifically causes oxidative stress that leads to apoptosis of testicular cells. EDCs, endocrine disrupting chemicals; MEHP, mono-(2-ethyl-hexyl) phthalate; PPAR, peroxisome proliferator-activated receptor; BPA, bisphenol A; PCB, polychlorinated biphenyl; ARNT, AhR nuclear translocator; XRE, xenobiotic responsive element.

protein folding, thereby triggering the unfolded protein response (UPR) (38). The UPR favors binding of glucose-regulated protein 78 (GRP78) to unfolded and misfolded proteins. This binding in turn stimulates the production of ER stress transducers protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) (38,39). These stress transducers collectively stimulate apoptotic factors in the testicular cells. IRE1 activates the apoptotic transcription factor Chop; ATF6 activates apoptotic genes such as *BiP*, *GRP94*, and *Chop*; and PERK triggers the translation of ATF4, which then drives the activation of Chop (38). All these events lead to raised ROS levels, causing a condition called oxidative stress which negatively affects spermatogenesis and semen quality (38). ROS accumulation also triggers mitochondrial apoptosis in testicular cells by activating the Fas/FasL apoptotic signaling pathway, further debilitating spermatogenesis (38,40). BPA also suppresses the Akt/mTOR pathway in testicular mitochondria, which is crucial in spermatogenesis (40).

Dioxins and PCB are two more EDCs that negatively impact semen quality using similar mechanisms of action. Dioxins and PCBs bind to the AhR, which is normally inactive (9). They activate AhR, causing it to translocate to the nucleus and dimerize with the AhR nuclear translocator (ARNT) complex (41). The ARNT complex normally binds to the xenobiotic responsive element (XRE) on target DNA to transcribe steroids and growth factors. In cases of high dioxins and PCB levels, AhR blocks the ARNT complex, leading to impaired steroidogenesis (41). Since sperm possess AhR, dioxins and PCBs interfere with these receptors and cause detrimental consequences for male reproductive health in terms of capacitation, the acrosome reaction, sperm-egg binding, and fertilization (9). Further, dioxins and PCBs inhibit Sertoli cell proliferation and the development of seminiferous tubules, which results in reduced semen production (42). Additionally, dioxins and PCBs interrupt the hypothalamic-pituitary-thyroid (HPT) axis, which is responsible for regulating hormones and steroid production (43). Disruption of the HPT axis decreases spermatogenesis, Leydig cell number, and plasma testosterone (43). PCBs specifically also produce free radicals in testicular cells that decrease catalase activity which is meant to combat oxidative stress (43). PCBs are known to inhibit gene expression of steroidogenic enzymes by binding to AhR and androgen receptors, thus resulting in oxidative stress and ultimately apoptosis (43,44) (*Figure 1*).

Against argument

Though there is much evidence to support the assertion that EDCs are detrimental to semen quality and overall male reproductive health, there are some who claim that current studies on the effects of EDCs are inaccurate or unrealistic in their findings. One such concern is that current studies do not report the body mass indexes (BMIs) of their subjects, which could be problematic because BMI and body fat percentages have been correlated with variations in both semen quality and levels of reproductive hormones (12). Past work, however, has addressed this concern in different ways. For example, one study compensated for differences among subjects by normalizing weight in terms of AGD so that individuals could be compared to each other on the basis of an anogenital index (AGI), and results showed that AGD was shorter in boys whose mothers had experienced heightened exposure to phthalates (19). It was acknowledged in this study that humans have greater potential sensitivity to toxins because of their slower metabolic rates as compared to rats and other rodents that are often used as test subjects in similar studies (19). It follows that the subject of varying metabolic rates among humans must account for some of the different responses to EDC exposure, and this is an especially important point considering that metabolic rates can vary greatly between individuals with different weights and body fat percentages. To address this issue, one study determined the ratio of metabolized EDC as compared to the amount of un-metabolized chemical (45). In this work, it was found that overweight subjects had lower levels of the metabolized form of di-2-ethylhexyl (DEHP)—MEHP—as compared to normal and underweight individuals (45). These results are important not only because they call attention to the higher health risks associated with overweight exposure to EDCs, but because they also compensate for the confounding effects of differing weights among test subjects. Another concern regarding these studies is that they do not report on the confounding effects of smoking (12). Though past studies, such as the one regarding MEHP, have taken note of smoking versus non-smoking test subjects, the results of these studies are still limited because they fail to take into account the fact that many of these same test subjects are also on prescription medications that could interfere with the results of the EDC exposure (45). Such concerns limit the findings of studies that report on the effects of EDCs, but the mounting amount of evidence still seems to point toward the direction of these chemicals as harmful agents against human hormonal systems.

Conclusions

Overall, the evidence on EDC exposure points toward the negative effects they have on humans. The rise of EDCs in the environment as well as the simultaneous rise of male reproductive disorders and infertility calls attention to the idea that EDCs may be responsible for the decline in male reproductive health (2,5,6). EDCs have been incorporated into a wide array of consumables and products (foods, water, plastics, shampoos, clothes, toothpastes, soaps, fertilizers, paper, textiles, carpets, utensils, bedding, toy, cosmetics, deodorant, etc.), which puts all people at greater risk for exposure in daily life (2-4). Additionally, there is an increasing amount of research to suggest that male children are more likely to develop reproductive disorders in response to neonatal and especially prenatal exposure; such exposures are even more likely to occur now with the increasing prevalence of EDCs in general consumer goods (1,7,17-19). In order to tackle this issue, some countries have already established regulations to remove EDCs from everyday products. For example, as of January 2015, the French parliament outlawed the use of BPA in any containers that come into contact with food. France has also outlawed the use of phthalate DEHP in toys and products related to childcare. In the United States, legislation such as the Toxic Substances Control Act, the Food Quality Protection Act of 1996, and the Safe Drinking Water Act of 1996 gives the Environmental Protection Agency (EPA) the power to evaluate and place regulations upon substances that may act as endocrine disruptors. Similarly, the Endocrine Disruptor Screening Program introduced by the EPA in 1998 has allowed for the testing of over 85,000 chemicals. A comprehensive list of EDCs and their potential effects on male reproductive health in relevance to the published studies are listed in *Table 2*. Clearly, the EDC issue has inspired much legal change, but it is still necessary that more countries adopt these regulations and that a wider range of chemicals are screened for the potential enactment of new legislation. Unless more laws are put in place to control the increase of EDCs in the environment, humans and animals alike could be facing the consequences of decreased health and fertility. The way in which EDCs have been shown to negatively affect semen parameters and reproductive health in male subjects is just one of the many ways in which EDCs have been shown to be a detriment to humans. These facts warrant the use of alternatives to EDCs.

Table 2 Endocrine disrupting chemicals and their impact on the male reproductive system

EDCs	Reference	Population	Effects					
			Anogenital distance	Cancers (prostate, testicular, etc.)	Testes	Hypospadias	Cryptorchidism	Semen quality
BPA	(32)	Mouse spermatocyte-derived GC2 cells from American tissue culture collection and 32 adult male Kunming mice	–	–	Shrinkage and vacuolation of seminiferous tubules	–	–	Reduction in the number of spermatogenic cells and sperm
BPA	(3)	Male offspring (70 days of age) of 60 Calomys laucha mice	No effect	–	Induced testicular spermatogenic cellular apoptosis	–	–	Decreased sperm concentration
BPA	(46)	79 human newborns recruited between 2000 and 2002	–	–	–	–	–	Reduction of normal sperm morphology, sperm motility, and sperm membrane integrity
BPA	(47)	153 boys	Significant decrease in AGD	–	–	Increased incidence of hypospadias	Increased incidence of cryptorchidism	–

Table 2 *(continued)*

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EDCs	Reference	Population	Effects					
			Anogenital distance	Cancers (prostate, testicular, etc.)	Testes	Hypospadias	Cryptorchidism	Semen quality
BPA	(21)	60 patients from the urologic clinic at the University of Cincinnati Medical Center	–	–	–	–	–	–
Dioxins	(48)	82 male field mice	–	Increased incidence of prostate cancer (especially significant in younger patients <65) Decreased prostate-specific antigen (PSA)	–	–	–	Could possibly reduce sperm motility
Dioxins	(9)	251 men living in Besancon, France, between 2001 and 2007	–	–	–	–	–	Could possibly decrease the number of active spermatozoa (decreased motility)
Dioxins	(49)	39 sons born between 1977 and 1984 to mother exposed to dioxin after the accident in Seveso, Italy (1976); 58 sons born to mothers exposed to only background dioxin	–	–	–	–	–	Could possibly negatively impact sperm morphology
Dioxins	(50)	135 males exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at three age groups; 184 healthy male comparisons	–	–	Inhibits Sertoli cell proliferation in the testes	–	–	Decreased sperm concentration, progressive motility, and total motile count
PCB	(50)	A review of 11 previous studies on PCB	–	–	No effect on testosterone concentration	–	–	Reduced sperm count, progressive motility, and total number of motile sperm
PCB	(51)	Four Simmental bulls (aged 2–4) in Turkey	–	–	Associated with reduced testosterone levels	–	–	Could possibly reduce sperm motility
PFOS	(2)	Male Sprague Dawley rats	–	–	Exposure associated with reduced testicular weight	–	–	Decreased total motility and progressive motility
PFOS and PFOA	(52)	105 Danish from general population (median age = 19 years)	–	–	Impaired fetal Leydig cell (FLC) function Reduced FLC number Decreased T production	–	–	–

Table 2 (*continued*)

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EDCs	Reference	Population	Effects					
			Anogenital distance	Cancers (prostate, testicular, etc.)	Testes	Hypospadias	Cryptorchidism	Semen quality
PFOS	(53)	645 Danish boys (1980–1996)	–	–	–	–	–	Reduced normal sperm count in ejaculate (6.2 million in men with high PFOS-PFOA as compared to low PFOS-PFOA at 15.5 million) Significant decrease in normal sperm morphology Nonsignificant decrease in sperm concentration, total sperm count, and sperm motility
PFOA	(54)	169 human males (ages 19–21 years)	–	–	Increased testosterone production	No association	No association	–
PFOA and PFOS	(55)	Males in Italy	–	–	Higher levels of LH and FSH	–	–	Lower sperm concentration, total sperm count,
TCS	(56)	Sea urchin (Strongylocentrotus nudus)	–	–	–	–	–	Decreased sperm concentration, progressive motility, and normal morphology
TCS	(57)	LNCaP, PC-3, and DU145 prostate cancer cell lines	–	–	–	–	–	Decreased sperm viability
TCS	(4)	Human children (3 months of age)	Reduced AGD	Promotion of prostate cancer tumor growth	–	–	–	–
TCS	(58)	471 men in a male reproductive health clinic in China	–	–	–	–	–	–
Vinclozolin	(59)	Male rats	–	–	–	–	–	Decrease in progressive motility, sperm concentration, sperm count, sperm density, and percentage of sperm with normal morphology
Vinclozolin	(18)	Male rats	Significantly decreased AGD	–	–	–	Significantly increased incidence of cryptorchidism, unilaterally and bilaterally undescended testes	–

Table 2 (*continued*)

Table 2 (continued)

EDCs	Reference	Population	Effects					
			Anogenital distance	Cancers (prostate, testicular, etc.)	Testes	Hypospadias	Cryptorchidism	Semen quality
DBP/MBP	(60)	Fetal testis explants from rats (gestation day =19.5)	–	Prostate inflammation	–	–	–	Reduction in elongated spermatid number
DEHP	(29)	Male mice	–	–	Major decrease in levels of intratesticular testosterone Increased Leydig cell aggregation (LCA)	–	–	–
MEHP	(61)	21-day-old mice	–	–	Disruption of testicular germ cell association and spermatogonial stem cell function	–	–	Decreased sperm count, motility
DEHP DINP	(27)	Male Rats	–	–	Increased spermatogenic cells apoptosis	–	–	Decreased sperm count
DBP	(62)	13 rats	–	–	Germ cell apoptosis in testes	–	–	–
Finasteride	(63)	Male rats	–	–	Decreased T leads to impaired spermatogenesis	–	–	–
BBzp DBP DEHP	(64)	Rodent species	Decreased AGD	–	–	Higher occurrence of hypospadias	Ectopic testes at high dose	–
DDE DDT DEHP	(65)	Rats and alligators	–	–	Decreased testes weight	Malformations of the epididymis and vas deferens	Malformations of the epididymis and vas deferens	Reduced Sperm production
DBP DEP DPP DMIP	(66)	Male mice	–	–	–	Hinders reproductive tract development	DDE and DTT caused cryptorchidism in alligators	Declined Semen quality and fertility
MBP	(19)	Non-human primate, marmoset	–	–	Inhibits fetal testicular testosterone production	Possible effects	Possible effects	Decreased T production so possibly affected semen parameters
MBP MiBP	(67)	134 boys, 2–36 months of age	Decreased AGD (18% shorter than expected)	–	Testicular morphology was not affected	–	–	Not affected

Table 2 (continued)

Table 2 *(continued)*

EDCs	Reference	Population	Effects					
			Anogenital distance	Cancers (prostate, testicular, etc.)	Testes	Hypospadias	Cryptorchidism	Semen quality
Review of 61 articles	(68)	14,979 men from 1938–1991	–	–	–	–	–	–
Phthalates in general along with other EDC's like BPA	(69)	Extensive review article (human)	–	–	–	–	–	Decline in sperm density and volume

AGD, anogenital distance; PCB, polychlorinated biphenyl; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; LH, luteinizing hormone; FSH, follicle-stimulating hormone; DDE, dichlorodiphenylethane; DBP, di(n-butyl) phthalate; MBP, mono(n-butyl) phthalate; MiBP, mono-isobutyl phthalate; DEHP, di-(2-ethylhexyl) phthalate; MEHP, mono-(2-ethyl-hexyl) phthalate; DINP, disononyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEP, diethyl phthalate; DPP, diphenyl phthalate; DMIP, dimethyl isophthalate; BPA, bisphenol A; EDC, endocrine disrupting chemical; DTT, dithiothreitol; TCS, trichlorosilane; BBzp, benzyl butyl phthalate.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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