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REVIEW ARTICLE

Endocrine Disrupting Chemicals (EDCs) and Human Reproductive Health

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Abstract

Production and synthesis of chemicals initiated during the Industrial Revolution in the 19th century. With the discovery and extraction of crude oil, synthesis of several chemicals, along with petroleum products was started. Many types of industrial solvents, pharmaceuticals, agricultural chemicals, having persistent and lipophilic properties, contaminated and entered in our food chain causing varieties of ill effects. Some chemicals even behave-like or mimic our natural hormones; often alter their important function and resulting in abnormal changes in the homeostatic systems of organisms. These chemicals are designated as Endocrine Disrupting Chemicals (EDCs). Many studies showed that there is an increase in the non-communicable diseases like diabetes, obesity, male and female infertility, reproductive anomalies and cancers of reproductive organs and breast, during the last five decades. EDCs are being considered as a main culprit for the causation of these diseases.

In the article an attempt has been made to review the literature pertaining to the relationship between exposure to the EDCs and their consequences with regard to human reproductive health.

Keywords: Endocrine disrupting chemicals, Human reproduction, Persistent organic pollutants, Reproductive toxicity

Abbreviations: BBP: Butyl benzyl phthalate; BPA: Bisphenol A; BPS: Bisphenol S; DDD: Dichlorodiphenyldichloroethane; DDE: Dichlorodiphenyldichloroethylene; DDT: Dichloro-diphenyltrichloroethane; DEHP: Di-(ethylhexyl) phthalate; DES: Diethylstilbestrol; DnBP: Di-n-butyl phthalate; FBS: Fetal bovine serum; FSH: Follicle-stimulating hormone; HCH: Hexachloro hexane; HDL: High-density lipoproteins; ICSI: Intracytoplasmic sperm injection; LDL: low-density lipoprotein; LH: Luteinizing hormone; OCP: Organochlorine pesticides; OP: Organophosphate pesticides; PAH: Polycyclic aromatic hydrocarbons; PBDE: Polybrominated diphenyl ethers; PCBs: Polychlorinated Biphenyls; PCOS: Polycystic ovarian syndrome; PEs: Phthalates esters; PFAS: Perfluoroalkyl substances; PFNA: Perfluorononanoic acid; PFO: Perfuorooctane sulfonate; PFOA: Perfluorooctanoic acid; POF: Premature ovarian failure; PVC: Polyvinyl chloride; TSH: Thyroid stimulating hormone; WHO: World health organization.

Introduction

The synthetic chemicals have taken an important place in our society. They have become an integral part of our life. We are exposed to some types of the chemicals during our day to day activities. Many of these synthetic chemicals can influence our hormonal system and are known as Endocrine Disrupting Chemicals (EDCs) (sometimes also referred to as hormonally active agents) posing a significant threat to human health. We are exposed to them through various consumer products including food. EDCs interfere with our hormone biosynthesis or their action.

There are some evidence showing effects of EDCs affect on thyroid metabolism, reproductive organs and their functions, develop cancers of breast, prostate, or of female reproductive organs and also cause obesity (Fig. 1). In some cases, they are also related to the onset of type II diabetes.

Several clinical and epidemiological studies provide significant evidence to implicate these chemicals as a potential threat to public health. Their mechanism of action involves many pathways of hormonal action; particularly of estrogenic or anti-androgenic. EDCs also act through affecting nuclear and neurotransmitter receptors and steroidogenic enzymes.

A variety of molecules belongs to EDCs. Some important ones are organochlorine pesticides, fungicides, herbicides, plastics, plasticizers, industrial chemicals, fuels, synthetic or natural hormones, pharmaceutical drugs and many more (Zlatanic *et al.*, 2015). All these chemicals are present in our environment posing significant threat to human health. Though the amount of EDCs in the environment may be very low, they are capable of showing their toxicity in organisms along with other toxic elements present in different forms in the environment (Fig. 2).

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As per the definition of Environment Protection Agency (EPA), USA - EDC is an exogenous agent that interferes with the synthesis, secretion, transport, metabolism, binding action or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and development processes. Some of the important EDCs are listed in table1.

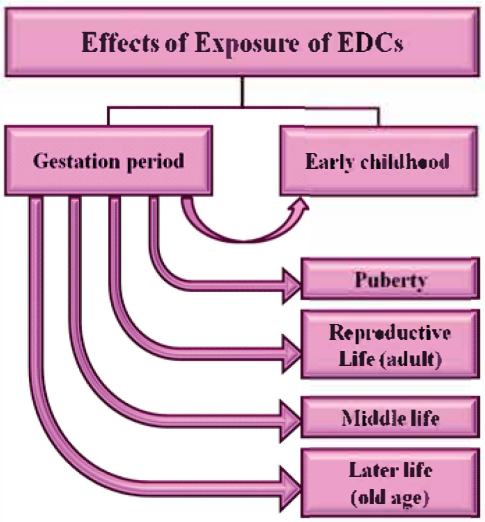
Mode of Action

Initially, it was thought that these chemicals act through nuclear hormone receptors, like thyroid, progesterone, androgen, and retinoid receptors. Recent researches indicate that EDCs act on other receptors also that include non-nuclear steroid hormone, non-steroid (serotonin, dopamine, norepinephrine) hormones. They also interfere with the enzymatic pathways of steroid biosynthesis. It has been reported that EDC attach to the receptors of the natural hormones, for example, bisphenol A (BPA) binds to receptors of estrogen (Heindel *et al*., 2013). After binding with the receptors, these EDCs activate or turn off the actions of the receptor disturbing the normal hormonal activity (Kabir *et al*., 2015). Alternatively, EDCs can interact with hormonal pathways, bypassing the receptor and activating or inactivating second messenger systems, or interfering with activation of genes, or by changing levels of hormone-binding proteins. In short, an EDC is a compound which alters the hormonal and homeostatic system of an organism.

This review will focus on the relation between the environmental exposure of EDCs and human reproductive health.

Reproduction

In the last few decades, there has been a significant increase in the problems related to the human reproduction observed in many regions of the world. Many unidentified environmental factors, mainly chemicals, may be involved in the disease etiology. During the



EDCs can act any times during human life- fetal development, infancy, early childhood, puberty, adulthood and old age. In adult, EDC has an effect when it is present, but when it is withdrawn, the effects diminishes. Exposure of EDCs during gestation period or at early childhood can have permanent effects, particularly during organo-genetic period, when a specific tissue/organ is developing. These effects may appear later in life.

Fig. 1. The effects of EDCs exposure during gestation or early life may be manifested at any time in life

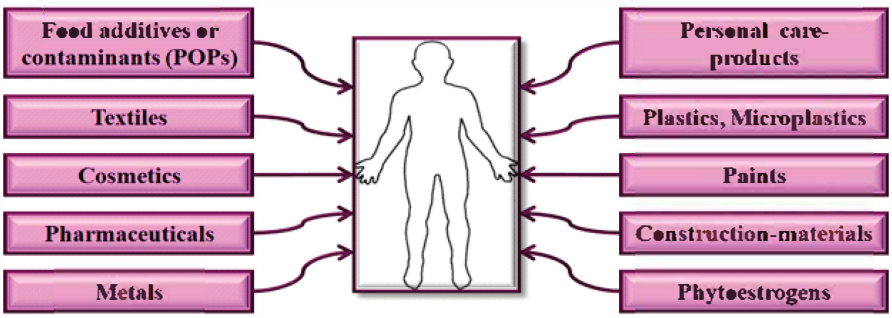


Fig. 2. Human exposure to EDCs

industrial revolution, there are many fold increase in the variety of chemicals, with which the human population is exposed, particularly in industrialized urban areas.

Incidences of various types of cancers modulated by endocrine disrupting chemicals (EDCs), like testicular and breast and cases of PCOS and endometriosis have also increased during the same period while human fertility rate has decreased within a generation.

Female Reproduction

The entire reproduction cycle in females depends on the coordinated processes. Any change caused by endogenous or exogenous agents or any other factor during the sensitive periods of development or any phase of life, may affect womens reproductive health. During the sensitive period, which is the first trimester, cell migration and differentiation take place. Any abnormal interference during this stage may result in abnormal functioning of the ovary which may cause serious consequences in the reproductive functions in later life. These may include POF (premature ovarian failure) and differentiation of uterus, cervix and upper vagina. These events are mostly postnatal, take place in response to steroid hormones beginning at puberty. Any alteration in the hormone function at this time can predispose women to infertility or poor pregnancy outcomes or other disorders related to reproduction. EDCs have the ability to alter the functions of these hormones, so it can be believed that they can cause harmful effects on the female reproductive system.

Sufficient data on laboratory animals is available which shows the role of EDCs in the pathogenesis of female reproductive disorders like tract anomalies, uterine fibroids, polycystic ovarian syndrome (PCOS), premature ovarian failure (POF), endometriosis etc. The findings in animal studies have been reviewed by many researchers (McLachlan *et al.* (2006); Caserta *et al.* (2008), Crain *et al.*

Table 1. Common EDC, their applications and hazards

EDC	Chemical Formula	Applications	Hazards
Bisphenol A	$C_{15}H_{16}O_2$	Manufacturing polycarbonate plastics, food packaging, water containers, dental sealants	Cancer, infertility, diabetes, obesity, some neuro- behavioral effects
Phthalates [dieters of 1,2-benzene-di-carboxylic acid (phathalic acid)]	$C_nH_nO_4^{-2}$	Plasticizers, packaging, cosmetics, industrial plastics, medicals devices, pharmaceuticals, flexible vinyl plastics, perfumes, lotions, varnishes	Changes sex hormone level, alteration in genital development, low sperm count and quality
Parabens (Eg. Butyl parabens)	$C_{11}H_{14}O_3$	Food preservatives, cosmetics, toiletries, medicines	Breast cancer, reproductive toxicity, low estrogen level
Insecticides (Dichlorodiphenyl, Trichloroethane)	$C_{14}H_9Cl_5$, $C_2H_3Cl_3$	Agriculture, water treatment plants	Leukemia, lymphoma, cancer of brain, breast, prostate, testis, ovaries, birth defects, spontaneous abortion, sterility, infertility
Tributyltin chloride	$C_{12}H_{27}ClSn$	Consumer goods and industrial products	Respiratory tract irritation, skin irritation, eye infections
Polychlorinated biphenyls (PCBs)	$C_{12}H_{10}$-nCln	Paints, lubricants, wooden floor finishes, coating of electric wiring, plastic water & and baby bottles, food & beverage can lining, dental sealants	Reproductive toxicity, cancer of liver, gallbladder biliary tract, gastrointestinal tract, and brain, and may be linked to breast cancer also
Polybrominated biphenyls (PBBs)	$C_{12}H_{(10\text{-}n\text{-}m)}Br_{n+m}$	Flame retardants, home electric appliances, textiles	Associated with earlier pubertal stages, skin disorders, nervous and immune systems effects, and effects on the liver, kidneys, and thyroid gland
Diethylstilbestrol	$C_{18}H_{20}O_2$	For treatment of recurrent miscarriages & advance breast & prostate cancer	Headache, dizziness, nausea, vomiting, weakness, and irritability; reproductive tract anomalies, an increased infertility rate, and poor pregnancy outcomes
Vinclozolin (Fungicide)	$C_{12}H_9Cl_2NO_3$	Control diseases, such as blights, rots and molds in vineyards, and on fruits and vegetables such as raspberries, lettuce, kiwi, snap beans, and onions; also used on turf on golf courses	Low acute oral/ dermal/ inhalation toxicity, reproductive toxicity, cancer, damage organs of unborn children
Dioxins	$C_4H_4O_2$,	Mostly exist as by-products of pulp and paper industry, pesticides. Dioxins also released while heating food in the microwave with plastic containers	Reproduction and development toxicity, damages the immune system, and interferes with hormones causing cancer

(2008); Foster *et al.* (2008); Mendola *et al.* (2008); Woodruff *et al.* (2008); Woodruff and Walker (2008). In these studies the mechanism of action of EDCs on female reproductive system was understood. Researchers have tried to extrapolate their results for humans.

Polycystic Ovarian Syndrome (PCOS)

Many EDCs were studied for their association with polycystic ovarian syndrome, but the strongest positive association was observed with various PFAS (Perfluoroalkyl substances). Recently, Wang *et al.* (2019) could relate exposure of Perfluoroalkyl substances (perfluorododecanoic acid) and risk of PCOS related infertility in Chinese women. In a case-control study, Vagi *et al.,* (2014), explored potential association between brominated diphenyl ethers, PCBs, Organochlorine pesticides, perfluorinated compounds, phthalates and bisphenol A in the American women having PCOS. In a study conducted on the women having PCOS in UK undergoing fertility treatment, showed the presence of perfluorinated alkyl acids in their serum and follicular fluid (Heffernan *et al.,* 2018)

Akgül *et al.,* 2019 evaluated the levels of Bisphenol A (BPA) and phthalates in adolescent girls-aged 12-18 years having PCOS. Girls having PCOS had significantly high levels of BPA in their urine in comparison of controls. They could not find any positive association with other phthalates like DEHP and MEHP in patients with PCOS.

Akin *et al.,* (2015) also reported a positive relation between BPA levels in the serum and PCOS in 61 girls aged between 13 and 19 years. In their study they also found the correlation between serum concentrations of BPA and androgen level but did not found correlation between BPA and obesity. Therefore, it is possible that BPA may play a role in aetiopathogenesis of PCOS in adolescent girls.

Hossein *et al.* (2017) could co-relate the higher level of BPA in the urine of women of reproductive age with PCOS. Konieczna *et al.* (2018) monitored the concentration of BPA in the serum of 106 women aged between 18-40 years having PCOS to evaluate the impact of BPA on their hormonal and metabolic profile. They found that women with PCOS had significantly higher levels of BPA in their serum compared with the controls. But they could not find any significant correlation between serum BPA and BMI, serum glucose insulin and lipid profile.

A study carried out by Vahedi *et al.* (2016) in 62 women suffering from PCOS in which a patients blood was evaluated for fasting blood sugar, cholesterol triglycerides, TSH & LH: FSH ratio along with BPA. Researchers were able to find a significantly higher amount of BPA in the serum of women having PCOS than the control group. They also observed higher levels of triglycerides, cholesterol and LH: FSH and significantly lower concentration of TSH in the patients. They did not observe any significant differences in the FBS, LDL, and HDL levels between patients and control groups.

Takeuchi *et al.* (2004) observed a strong relationship between BPA, and total testosterone, free testosterone and androstenedione in the patients having PCOS, because their levels in serum were significantly higher than the healthy women.

Studies carried out, taking other EDCs like PBDEs, phthalates, PAHs, and triclosan could not establish very conclusive association with regards to PCOS in women. But occurrence of this disease in a large number of the women, particularly in young girls is a matter of concern. The studies done with laboratory animals on this aspect, clearly establish a positive association between PCOS and exposure to EDCs (Diamanti-Kandarakis *et al.,* 2009).

Uterine Leiomyomas

Leimyomas (fibroids) are tumors of myometrium, these benign tumors may cause menorrhagia, pain in the abdomen, pelvic prolapse and infertility and even miscarriage (Buttram and Reiter, 1981). In one of the studies undertaken by the Agency of Health Care Research and Quality in 2007, reported the prevalence rate of uterine fibroids is 25-50 % in African- American women. It may be because of the chronic exposure to estrogen. The *in-utero* exposure of DES causes development of uterine fibroids in women later in life is still not established (Wise *et al.,* 2005). But there are many studies on animals which support that *in-utero* exposure of DES increases the risk of developing uterine fibroids during adulthood. (Crain *et al.,* 2008, Woodruff *et al.,* 2008, Woodruff and Walker, 2008).

Endometriosis

It is a gynecological disorder associated with pelvic pain and infertility, dependent on estrogen level. There is evidence that *in-utero* exposure to DES may increase the risk of infertility in the later life of women. A correlation between the presence of phthalates esters (PEs) in the plasma of women and endometriosis was observed. Cobellis *et al.*(2003) showed the association between Di-(2-ethylhexyl) phthalate (DEHP) (commonly used plasticizer in flexible polyvinyl chloride (PVC) formulations), plasma concentrations and endometriosis. In another study, blood of 49 infertile Indian women with endometriosis was analyzed for phthalate esters [di-n-butyl phthalates (DnBP), butyl benzyl phthalates (BBP), di-n-octyl phthalates (DnOP) and diethyl hexyl-phthalates (DEHP). Reddy *et al.* (2006) suggested an aetiological association of PEs with endometriosis in these Indian ladies. There was significant association between endocrine active perfluoroalkyl substances (PFAS) and endometriosis diagnosed in women aged between 20-50

years. Campbell *et al.* (2016) reported geometric mean levels of 3 PFASs; perfluorononanoic acid (PFNA), perfluorooctane sulfonate (PFOS) in the non- Hispanic white women. Louis *et al.* (2012) found positive association between the exposure with PFOS, PFOA, PFNA and endometriosis in 495 women (aged between 18-44 years) from Salt Lake City and San Francisco, USA, during 2007-2009. Chinese women suffering from endometriosis also showed positive association with perfluoroheptanoic acid (Wang *et al.*, 2017).

Breast Cancer

Girls of Puerto Rico having significantly higher levels of di-isocytl phthalate in their blood showed premature breast development. Colon *et al.* (2000) suggested it is due to the possible association between plasticizers having estrogenic and androgenic activity. There are possibilities that the association may lead to development of cancer in breasts, later in life.

Data on the relationship between prenatal exposure of estrogen and breast cancer risk in the ladies from the USA born to mothers treated with (diethylstilbestrol) DES during their pregnancy was gathered (Palmer *et al.*, 2002; 2006).

In a very important recent study, Cohn and coworkers (2020) worked on the hypothesis that maternal prenatal exposure of PFASs causes subsequent breast cancer on daughters. They found a positive association of N-ethyl-perfluorooctane sulfonamide acetic acid, a precursor of PFOS with breast cancer in daughters.

Earlier also, in many epidemiological studies, scientists found positive links between exposure to EDCs and incidences of breast cancer. Prolonged exposure of toxaphene (Høyer *et al.*, 1998) and DDT (Cohn *et al.*, 2007) may increase the risk of breast cancer. Today, the human population is exposed to a variety of hormonally active xenobiotics having different metabolic profiles. In a case study undertaken by Ibarluzea and coworkers reported a significant correlation between exposure to a number of chemicals present in the environment and breast cancer (Ibarluzea *et al.*, 2004).

Mancini *et al.* (2020) found that EDC like PFOS and PFOA, which they suspected to be generally present in the blood of the human population, have a positive relationship with the occurrence of post-menopausal breast cancer in the French E3N Cohort study of women born between 1925 and 1950.

In another study undertaken by Danish National Birth cohort revealed that during the first trimester, women having perfluorooctane sulfonamide in their blood are prone to develop maternal breast cancer (Bonefeld-Jørgensen *et al.*, 2014).

In one of the case studies, undertaken on 77 women from Greenland having breast cancer showed significantly high levels of persistent organic pollutants (POPs) in their serum. The levels of 14 polychlorinated biphenyls (PCBs), 11 organochlorine pesticides (OCPs), 16 perfluoroalkyl acids (PFAAs), 1 polybrominated biphenyl (PBB) and 9 polybrominated diphenyl ethers (PBDEs) were determined. Researchers concluded a positive association between breast cancer risk and PCBs and PFAAs. This association suggests that POPs present in the environment may enhance the risk for breast cancer in women (Wielsøe *et al.*, 2017).

Ecological study was undertaken by Mastrantonio *et al.* (2018) on the population that consumed water contaminated by effluents with fluorinated chemicals of a chemical manufacturing company in Veneto, Italy since 1964. They reported higher mortality rates from female breast cancers in the study area.

Studies pertaining to the exposure of organophosphate insecticides and an increased risk of breast cancer cases in women were reported from different areas with different OP pesticide. Lerro *et al.* (2015) evaluated use of OPs and cancer incidence among female spouses of pesticide

Table 2. Effect of EDC on female reproductive system

EDCs	Effects	References
Bisphenol A, Phthalates	PCOS in girls aged 12-18 years.	Akgül *et al.*, 2019
Bisphenol A	Steroidogenesis and folliculogenesis in the ovary	Akin *et al.*, 2015
Bisphenol A	Increased blood sugars, cholesterol, triglycerides and TSH & LH: FSH ratio.	Hossein *et al.*, 2017
Bisphenol A	No association with breast cancer	Yang *et al.*, 2009
Perfluoroalkyl substances	PCOS related infertility	Vagi *et al.*, 2014 Heffernan *et al.*, 2018
Di-ethyl stibestrol	Development of uterine fibroids	Wise *et al.*, 2005
Di-(2-ethyl-hexyl) phthalate	Endometriosis	Cobellis *et al.*, 2003
Di-n-butyl phthalate		
PFOS, PFOA, PFNA	Endometriosis	Reddy *et al.*, 2006
PFOS & PFOA	Endometriosis	Wang *et al.*, 2017
Perfluorooctane Sulfonamide		
	Post-menopausal breast cancer	Mancini *et al.*, 2020
	Breast cancer	Bonefeld-Jørgensen *et al.*, 2014
DDT, Toxaphene	Increased the risk of cancer	Cohn, 2007
Persistent organic pollutants	Breast cancer	Wielsøe *et al.*, 2017

applicators from North Carolina and Iowa, USA. Workers could relate increased risk of many hormonally related cancers like thyroid, ovary and breast with the exposure of Malathion and Diazinon. Engel *et al.* (2017) studied the association of insecticide use and breast cancer risk among farmers wife using pesticide. They find an elevated risk of breast cancer among women who have used chlorpyrifos. The use of fonofos by husbands was associated with the elevated risk of cancer in their wives. Though, the workers did not estimate the level of pesticides in the blood of women. Tayour *et al.* (2019) investigated the negative relation between pesticide exposure and postmenopausal breast cancer associated with the pesticide exposure in Californias Central Valley, USA.

Findings with breast cancer associated with the exposure with the phthalates are limited with inconsistent results. Similarly, results from the studies with phenols, benzophenone, parabens and carbamates and pyrethroid insecticides were scarce and could not provide any significant conclusions. There is not enough evidence available on the role of some other organophosphate pesticides on the endometrial and ovarian cancers in women to draw the conclusions.

A positive correlation between the presence of organochlorine pesticides (OCPs) residues in the blood of 135 women residing in Jaipur, India and occurrence of breast cancer was studied by Mathur *et al.*, (2002). The levels of OCPs residues like DDT and its metabolites DDD and DDE, heptachloride, dieldrin and isomers of HCH (α,β & γ) were significantly high in the blood of breast cancer patients irrespective of age. Hundred women from the same city suffering from various reproductive tract cancers, like cervical, uterine, vaginal and ovarian showed higher levels of total OCPs in their blood (Mathur *et al.*, 2008). Authors attributed it to the widespread dissemination of OCPs in the study areas and contamination of the food chain with these insecticides. Studies on effect of EDCs on Female reproductive system is demonstrated in Table 2.

Male Reproduction

Semen Quality

An extensive epidemiological studies on male partners of sub-fertile couples was carried by Duty *et al.* (2003) and Hauser *et al.* (2006) in the infertility clinic of Massachusetts, USA. They found a positive relationship between mono-butyl phthalates and semen quality which was below WHO reference values of sperm concentration and mortality.

Synthetic chemicals belonging to the PCB family were extensively used in lubricants, culling oils, and insulators for many decades. These chemicals are lipophilic, persistent, halogenated-aromatic compounds. Owing to their extensive use and persistent nature, they remain very potent environmental contaminants. Due to their lipophilicity, they bioaccumulate in the food chain. Human population consumes these pollutants through food such as dairy products, fish and meat. PCBs are found in a large section of the human population in a measurable amount.

Table 3. Effect of EDC on male reproductive system

EDCs	Effects	References
Organophosphates	Decrease in sperm concentration and degraded sperm quality	Perry *et al.*, 2011
Organophosphates	Affected Sperm concentration, sperm motility, semen volume, sperm morphology, LH-TSH levels	Meeker *et al.*, 2004
Organochlorine (DDT, DDEs)	Abnormal motility, sperm concentration and morphology	Hauser *et al.*, 2003
DDT/DDE, Insecticides, Herbicides	Genital malformation, micropenis, Cryptorchidism, hypospadias	Gaspari *et al.*, 2012
Butyl & Benzyl phthalates, Methyl phthalates	Decreased sperm motility, concentration and altered sperm morphology	Duty *et al.*, 2003
BPA	Negative association with sperm quality parameters	Hu *et al.*, 2017
BPA DDT/DDE	Degraded semen quality Affected semen motility	Sharma *et al.*, 2020
Dialkyl phosphates (Organophosphates)	Aneuploid sperm	Figueroa *et al.*, 2015
Phthalates	Increased LH, Leydig cells, and steroid production. Decreased testosterone	Akingbemi *et al.*, 2004
Phthalates	Decreased serum free testosterone	Pan *et al.*, 2006
BPA	Shorter anal Scrotal distance	Mammadov *et al.*, 2018
Phthalate	Higher molecular weight phthalates were negatively correlated with the testis volume	Hart *et al.*, 2018
Bisphenol A	Reduction in Leydig cells capacity, increased LH levels, decreased sperm count.	Li *et al.*, 2011
Bisphenol S	Negative association with semen quality and embryo development	Knez *et al.*, 2014

Epidemiological evidences are available to establish the relationship between PCBs and poor semen quality like reduced sperm quality in the human population in India, the Netherlands, Taiwan, USA, and Sweden due to the consumption of contaminant fish and rice oil (Dallinga *et al.*, 2002; Guo *et al.*, 2000; Hauser *et al.*, 2003; Hsu *et al.*, 2003; Richthoff *et al.*, 2003; Rignell *et al.*, 2004).

Hart *et al.*(2018) conducted a study on human males of Western Australia (Raine) with the aim to correlate antenatal phthalate exposure with the testicular volume, reproductive hormone concentration in serum and semen parameters. They could detect 11 phthalate metabolites in the semen. The amount of total metabolites of the higher molecular weight phthalates was negatively correlated with the testis volume.

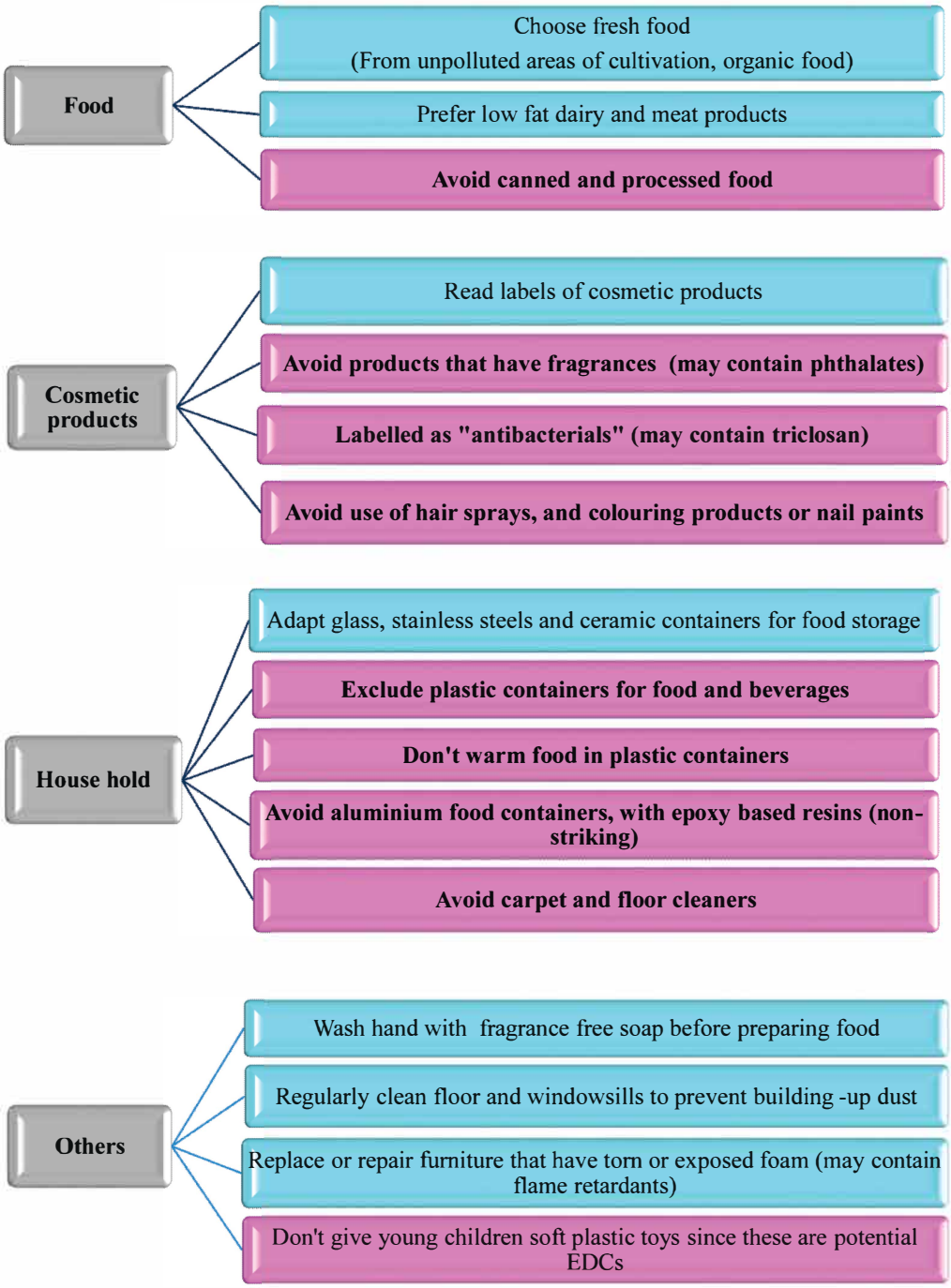


Fig. 3. Measures to lower the exposure of EDCs

Li *et al*. (2011) found a positive association of BPA on semen of workers from four different regions of China where they were exposed to high quantities of BPA. Adoamnei *et al*.(2018) reported that BPA exposure may be associated with the reduction of the capcity of Leydig cells due to the increased LH levels which resulted in a decrease in sperm count in man.

Studies were carried out on the man undergoing intra-cytoplasmic sperm injection (ICSI) procedures in a fertility clinic in which BPA was measured in their urine. No conclusive association was observed between the presence of BPA in urine and semen quality and embryo development in his partner (Knez *et al*., 2014). Ghayda *et al*. (2019) investigated Bisphenol-S (BPS) concentrations in the urine of men attending fertility center and their semen quality. They found negative association between BPS and semen parameters like sperm concentration, morphology and sperm motility.

Studies with carbamate and organophosphate insecticide and PFAs showed negative association with semen quality (Meeker *et al*., 2004; Yucra *et al*., 2008; Joensen *et al*., 2009; Louis *et al*., 2015; Song *et al*., 2018).

Prostate Cancer

It was found that occupational exposure to pesticides invariably caused prostate cancer in the agriculture workers of USA, Canada and France (Meyer *et al*.,2007; Kachuri *et al*.,2017; and Lemarchand *et al*., 2017). Results were less consistent for non-persistent insecticides and some other chemicals like PAHs and BPA, with regard to prostate cancer. Studies on effect of EDCs on male reproductive system are demonstrated in Table 3.

Measures to Lower the Exposure of EDCs

Many types of endocrine disrupting chemicals are present in the environment which are directly or indirectly entering our body. By using some measures we can reduce exposure of these chemicals to avoid their harmful effects (Fig. 3)

There is a need for further research to know precisely the effects of EDCs in combination with other synthetic chemicals on the health of humans because EDCs are generally released in the environment as a mixture. Other chemicals may interact additively, synergistically or antagonistically. Therefore, it becomes necessary to understand the effects of EDC in combination with other chemicals present in the environment.

Conclusion

EDCs mimics hormones, therefore like hormone, act via binding to receptors at very low concentrations. EDCs can influence the action of estrogen, androgen and hormones released by thyroid. EDCs can show additive or synergistic effects in the presence of other chemical pollutants present in the environment. Data on human evidence show their exposure during gestation period or during puberty may enhance reproductive diseases and endocrine related cancers.

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