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# The effect of endocrine disruptors on the reproductive system – current knowledge

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**Abstract. – OBJECTIVE: Chemicals that disrupt the endocrine homeostasis of the human body, otherwise known as endocrine disruptors (EDCs), are found in the blood, urine, amniotic fluid, or adipose tissue. This paper presents the current knowledge about EDCs and the reproductive system.**

**MATERIALS AND METHODS: The article is an overview of the impact of EDCs and their mechanism of action, with particular emphasis on gonads, based on the information available on medical databases (PubMed, Web of Science, EMBASE and Google Scholar, EMBASE and Web of Science) until May 2021.**

**RESULTS: EDCs occur in everyday life, e.g., they are components of adhesives, brake fluids, and flame retardants; they are used in the production of polyvinyl chloride (PVC), plastic food boxes, pacifiers, medicines, cosmetics (bisphenol A, phthalates), hydraulic fluids, printing inks (polychlorinated biphenyls – PCBs), receipts (bisphenol A, BSA) and raincoats (phthalates); they are also a component of polyvinyl products (e.g. toys) (phthalates), air fresheners and cleaning agents (phthalates); moreover, they can be found in the smoke from burning wood (dioxins), and in soil or plants (pesticides). EDCs are part of our diet and can be found in vegetables, fruits, green tea, chocolate and red wine (phytoestrogens). In addition to infertility, they can lead to premature puberty and even cause uterine and ovarian cancer. However, in men, they reduce testosterone levels, reduce the quality of sperm, and cause benign testicular tumors.**

**CONCLUSIONS: Therefore, this article submits that EDCs negatively affect our health, disrupting the functioning of the endocrine system, and particularly affecting the functioning of the gonads.**

*Key Words:*
Endocrine disruptors, Reproductive system, Mechanistic studies, Human studies.

## Introduction

Endocrine-disruptor chemicals/compounds (EDCs) are chemicals that disrupt the body's hormonal homeostasis. They play an important role in the functioning of the endocrine system, including the hypothalamic-pituitary-gonadal axis (HPG axis). Some common and widely studied EDCs have a negative effect and a broad spectrum of activity on the endocrine system. These include: (1) plasticizers such as (a) bisphenol A (BPA) used in the production


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of polycarbonates and epoxy resins with a very wide range of applications, and b) phthalates used in the production of phthalic varnishes and paints, adhesives and laminates, and used as plasticizers; (2) polychlorinated biphenyls (PCBs) used as plasticizers, hydraulic fluids and lubricants, in the production of packaging, as a component of printing inks, as an additive to insecticides, adhesives and plastics, and as an insulation material; (3) polybrominated diethyl ethers; (4) dioxins (a product of the incineration of municipal waste or volcanic eruptions); (5) pesticides (insecticides, herbicides and fungicides) used in the protection of plants, farm animals and food during storage and transport, in the paper and textile industry, in cosmetics; (6) phytoestrogens which are commonly found in our diet, e.g., some vegetables (soybeans, broccoli, onions, tomatoes), fruits, red wine, chocolate and green tea[1,2].

The mechanism of action of EDCs is not fully understood. They may impair the functioning of the endocrine system[2]. However, it is known that in the case of the female gonad, they may cause changes in the estrogen signaling pathways or interact with estrogen receptors (ER). Similarly, in the case of the male gonad, EDCs may interfere with natural hormones via androgen and its receptor[3]. EDCs can act as agonists, mimicking the natural hormone by binding to and activating various hormone receptors (i.e., hydrocarbon receptor [AhR], ER, the pregnane X receptor [PXR, NR1I2], constitutive androstane receptor [CAR, NR1I3]). EDCs can bind to these receptors without activating them (antagonistic activity). Moreover, EDCs, especially in pesticides, can reduce the concentration of hormones by influencing their synthesis, transport, metabolism and elimination, and interrupt critical cellular processes (Figure 1)[4-7].

EDCs can lead to the development of uterine (BPA) and ovarian cancer (BPA), premature puberty (BPA, phtatalates) and fertility disorders (BPA). In men, however, they reduce the sperm count (phthalates) and testosterone levels (phthalates) and cause benign testicular tumors (phthalates). Furthermore, EDCs reduce the quality of the sperm, which can result in the development of prostate cancer (BPA). The omnipresence of EDCs, which results in environmental pollution, can lead to many future diseases for which we do not yet have accurate knowledge. It has been demonstrated that some EDCs have thyrogenic, estrogenic and antiandrogenic properties[8]. In an era of increasing infertility problems for both men and women, we would like to show any associations between EDCs and fertility. This review analyzes how EDCs influence human health, focusing mainly on the human reproductive system.

## Materials and Methods

The article is an overview of the impact of endocrine disruptors on the male and female reproductive systems based on the information available on the medical databases PubMed, Web of Science, EMBASE and Google Scholar, EMBASE and Web of Science until May 1, 2021. Publications in Polish and English were taken into account. During the search of the relevant literature, the following keywords and their combinations were used: "endocrine disruptors", "male gonads", "female gonads", "bisphenols", "dioxins", "isoflavones", "perchlorate", "perfluoroalkyl substances", "pesticides", "phthalates", "polybrominated diphenyl ethers", "phytoestrogens". Original research papers and review papers related to the presented topic qualified for the review.

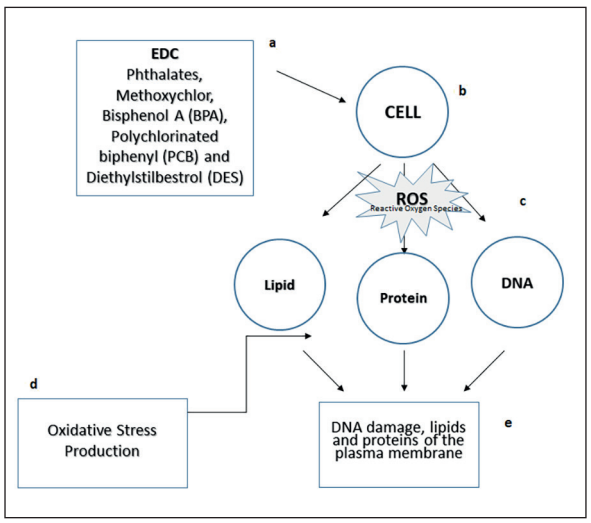


**Figure 1.** The mechanism of action of endocrine-disrupting chemicals on a human cell: **(a)** Multiple examples of EDCs: phthalates, methoxychlor, bisphenol A (BPA), polychlorinated biphenyl (PCB), diethylstilbestrol; **(b)** Cell exposure to EDCs; **(c)** reactive oxygen species (ROS); **(d)** Oxidative stress production; **(e)** Excessive ROS production leads to oxidative stress which may result in DNA damage, lipid oxidation, protein carbonylation and may cause defects to other cellular components.

## Results

### Plasticizers: (a) bisphenol A (BPA) and (b) phthalates

#### *(a) Bisphenol A (BPA)*

Bisphenol A (BPA, 4,4′-isopropylidenediphenol) is an organic compound from the phenol group. It is widely used in the production of polycarbonate plastics, epoxy resins, as a flame retardant and as a component in the production of other flame retardants. It is also used as a fungicide. It plays an important role in the electronics industry (as a component of adhesives for electronic components, in PVC production, as a component of brake fluids) and as a component in the lining of food cans and coatings for drinking water tanks. It should be mentioned that it is also present in everyday objects such as paper for thermal printers or receipts (ATM prints, cash registers). BPA is widely used in the food industry (e.g., lining of food cans, food packaging, plastic food storage containers, bottles [including children's bottles], toys, plates and pacifiers for children), and in plastics (electronic parts, DVDs and CDs), as well as in the medical (dental sealant) and cosmetics (perfumes, deodorants, shampoos) industries[9]. BPA has been found in the placenta and umbilical cord blood, breast milk, urine, neonatal blood and amniotic fluid[10].

#### *Mechanistic and Human Studies*

BPA is a chemical produced in large quantities[11] and, therefore, human exposure to BPA is very high[12]. BPA is a xenoestrogen (it imitates the activity of estrogens) which disrupts the endocrine metabolism by binding to nuclear estrogen receptors (ERs) – estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). It is defined as a selective ER modulator because its effects are pro-estrogenic in some tissues, but it causes antagonistic effects in others[13,14]. Its affinity to ERα and ERβ is 1,000-10,000 times lower. Nevertheless, it may negatively affect the female and male reproductive systems[15]. It has been proven that 2,2-Bis (4-hydroxyphenyl) propane may contribute to the development of uterine and ovarian cancer and premature puberty in humans. It may also affect the occurrence of polycystic ovary syndrome. In men, on the other hand, it may impair fertility and contribute to the formation of prostate cancer[16,17].

#### *Phthalates*

Phthalates, phthalic acid esters (PAEs), are widely used as compounds which increase the plasticity of polyvinyl chloride (PVC) products, including cosmetics (e.g., shampoos, soap, perfumes), glue and certain detergents. Interestingly, they play a unique role as a component of medical products (drains, probes, catheters, syringes, blood and intravenous bags, surgical gloves, dialysis equipment), and even for the enteric coating of oral medications and dietary supplements (from certain fish oils to probiotics)[18]. Furthermore, PAEs are frequently used in the production of beverage containers, elements of equipment, vinyl, for the production of floor coverings, window and door joinery, accessories (in the form of various finishing strips), pipes and fittings for installation in buildings, for covering sports and other surfaces; in electrical engineering, PVC is used as insulation for wires and cables, small objects and plastic toys[19,20].

PAEs are divided into: I. the parent compound: (a) bis(2-ethylhexyl) phthalate (DEHP), (b) dibutyl phthalate (DBP), (c) diethyl phthalate (DEP), (d) benzyl butyl phthalate (BBP), (e) diisobutyl phthalate (DIBP), (f) diisononyl phthalate (DINP); and II. A monoester metabolite**:** (a) mono(2-ethylhexyl) phthalate (MEHP), (b) monobutyl phthalate (MBP), (c) monoethyl phthalate (MEP), (d) monobenzyl phthalate (MBzP), (e) monoisobutyl phthalate (MIBP), (f) monoisonyl phthalate (MiNP). The most commonly used plasticizers are phthalate plasticizers (orthophthalates) known as di (2-propylheptyl) phthalates (also known as bis(2-propylheptyl) benzene-1,2-dicarboxylate, di (propylheptyl) orthophthalate, or DPHP)[16,18].

#### *Mechanistic and Human Studies*

Acting as endocrine disruptors, PAEs have an antiandrogenic effect in men *via* the androgen receptor (agonist and antagonist). They reduce the testosterone concentration (by reducing the production of androgens by the testis) in the blood, thus reducing the sperm count. Moreover, these compounds cause cryptorchidism, hypospadias, and testicular dysgenesis syndrome, leading to testicular cancer[21-24]. This research included the study of animal models and humans[25-27]. It has been proven that two PAEs – DEHP and DBP – could disrupt androgen in the reproductive tract[28,29]. Previous epidemiological studies[30,31] demonstrated that phthalate metabolites (namely MBP, MBzP, MEHP and

MiNP) caused a shorter anogenital distance (AGD) in 194 male infants at 22 months of age. These studies were performed for 20 suspected or proven EDCs detected in the 1st-trimester urine/serum of more than 2,300 mothers (SELMA study). PAEs (including DEPH) may affect testicular steroidogenesis by impairing the function of Leydig cells. Additionally, apart from inhibiting testosterone production in the adult human testis, *DEHP* and *MEHP* affect Leydig cells' expression of *INSL3*[32]. Paradoxically, the mechanism of PAE action on male reproduction is better understood than the similar mechanism in female reproduction. This is strange because women are often exposed to higher levels of phthalates than men through the more extensive use of personal hygiene and cosmetic products. Furthermore, the environmental contaminant DEHP (di-2-ethylhexyl phthalate), through its metabolite MEHP (mono-2-ethylhexyl phthalate), acts through a receptor-mediated signaling pathway (PPAR-γ) to suppress estradiol production in the ovary, leading to anovulation[33]. PAEs could also act *via* the PPAR-α and PPAR-α-independent pathways[34]. PAEs also seem to be involved in the pathogenesis of insulin resistance, obesity, and T2DM[35,36].

PAEs, including DEHP, have also been shown to disrupt the growth rate of primordial follicles to the growing amount of follicles due to various factors, including an increase in the ovarian mRNA levels of 3-phosphoinositide-dependent protein kinase-1 (PDPK1), a decrease in the mRNA levels of phosphatase and tensin homolog (PTEN) and tuberous sclerosis 1 (TSC1), and an increase in phosphorylated protein kinase B (AKT)[37]. Interestingly, there was a negative correlation between urine phthalate exposure (MEHP, MEP, MBP, MBzP) and an increased likelihood of polycystic ovary syndrome (PCOS)[38]. Also, an analogous negative association was found between maternal levels of MEP and anti-Müllerian hormone (AMH)[39]. Nevertheless, there are reports that phthalates may stimulate steroidogenesis[40-46].

### Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are used as plasticizers, hydraulic fluids, lubricants for the production of packaging materials, as a component of printing inks, and additive insecticides, adhesives, plastics and insulation materials[12,47]. PCBs are common in the environment as they do not degrade easily, are lipophilic and have a low evaporation rate[47,48].

### Human Study

A study by Richthof et al[49] showed decreased sperm motility which correlated with a high serum PCB concentration (as an inhibitor of testosterone synthesis)[48]. PCBs, dioxins and polychlorinated biphenyls negatively affected the course of pregnancies (spontaneous miscarriages, fetus development negatively impacted, pregnancy duration shortened), which resulted in babies with low birth weight[49]. Moreover, there was high infant mortality and congenital defects, such as hydronephrosis and cleft palate, were also present. In addition, faster thymus involution was observed. The disorders were also accompanied by cognitive impairment and delayed puberty[50-52]. In adulthood, the exposure of pregnant women to PCBs caused intellectual disturbances in children[53,54]. At the same time, Schantz et al[55] observed that adults who consumed PCB-contaminated fish had a reduced IQ and memory impairment.

### Dioxins

Dioxins are derivatives of organic chemical compounds containing chlorine which are usually the by-product of municipal waste incineration but are also produced during forest burning or volcanic eruptions[56,57]. Dioxins are considered to be substances that accumulate in the environment. Therefore, 90% of human dioxin exposure comes from eating food contaminated with dioxins, especially those derived from animals[58]. These compounds are known as highly toxic substances, negatively affecting many organs and systems in the human body, including the reproductive system[59].

### Mechanistic Studies

The toxic mechanism of dioxins is based on stimulation of the acrylic hydrocarbon receptor (AhR), a transcription factor that controls cell growth and differentiation[56]. The AhR receptor is stimulated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a substance considered to be highly teratogenic[60]. The fetuses of mice treated with TCDD had reduced mRNA transcription of LH and FSH gonadotropin mRNA. TCDD also weakened the transcription of genes for the transport protein, StAR, which plays a key role in the synthesis of gonadal hormones[61,62]. In addition, a reduction in testosterone levels was demonstrated in the fetuses of TCDD-treated mice. Importantly, the work shows that the toxic effects of TCDD are due to stimulation of the AhR receptor[62].

### Human Study

A neonatal weight study showed there was a decrease in the birth weight when the mother had an increased TCDD concentration, but only in correlation with concomitant genotypes increasing the risk of increased AhR activation[63]. This suggests the possible influence of dioxins on the development of normal birth weight in newborns. However, further research is required to confirm this thesis. Another study showed the negative effects of dioxins on sex hormones in pregnant women. There was a reduction in the umbilical cord testosterone concentration in the fetuses of pregnant women detected with high TCDD levels, regardless of the sex of the fetus. However, the same study did not show an effect of dioxins on the estradiol concentration[64]. Nevertheless, dioxins are substances that are present everywhere in the modern, industrialized world. Therefore, scientists are always looking for substances that have a protective effect on the reproductive system, despite exposure to dioxins.

### Pesticides

Pesticides are common in the human environment; residues are found in the soil as well as the plants we eat. The following types can be distinguished: insecticides, herbicides, biopesticides, those classified by type of pest, and other types. The most famous pesticides are dieldrin, chlordane, DDT, DDE, β-hexachlorocyclohexane, carbon tetrachloride, heptachlor, γ-hexachlorocyclohexane (lindane)[65]. All of these are banned in the European Union (EU).

Between 1960-2001, a significant increase in infertility was observed in developed countries, even by as much as 60%. The most common environmental contaminants are organophosphorus pesticides and carbamates. On the other hand, it should be noted that the use of pesticides is very beneficial for human health, for example, in the control of agricultural pests (weeds and diseases) and vectors of plant diseases and of human and livestock diseases[66].

### Human Study

Since it has also been demonstrated that endocrine disruptor pesticides disrupt reproductive and sexual development, the effects related to the level of endocrine hormones have mainly been observed in humans[67]. It should be noted that the impact of pesticides depends on several factors, including gender, age, diet, and occupation. The data show that infertility caused by constant contact with products for protecting plants affects men more than women. This may be because the exact causes of childlessness in women are not fully understood[68]. Grosicka-Maciąg[68] states that women's exposure to pesticides causes ovulation cycle disorders at various stages.

Several cohort studies, meta-analyses and case-control studies have shown the effect of pesticides on gonadal dysfunction and fertility problems. They can affect spermatogenesis leading to poor semen quality and reduced male fertility and significantly influence female organogenesis and reproduction.

The following have all been demonstrated: An increase in aromatase activity and estrogen production[4,69]; reproductive tract damage; reduced fertility[4]; binding to the sex hormone[70]; induction of aromatase activity; increased estrogen production[71]; decreased estrogen production and increased androgen availability[72,73]; competitive binding to cellular estrogen receptors[74]; increased proliferation of estrogen-sensitive cells and inhibition of corticosterone synthesis in the adrenal cortex[4,72,75].

In some cases, pesticide by-products may have even more side effects than the parent compound itself; the oxons of methyl-parathion, chlorpyrifos and diazinone are 10 to 15 times more toxic to sperm DNA than their corresponding parent compounds[76]. For example, 2,4-dichlorophenoxyacetic acid (2,4-D) is a known estrogen receptor ligand[77]. The vinclozolin derivatives 2-(((3,5-Dichlorophenyl)carbamoyl)oxy)-2-methyl-3-butenoic acid and 3',5'-Dichloro-2-hydroxy-2-methyl-but-3-enanilide, whose metabolites are present in both the soil and plants and in animal organisms, are antiandrogenic compounds[78].

There are many studies where people exposed to pesticides, such as those working in agriculture and in factories or due to their geographic location, were found to have higher levels (e.g.in breast milk, maternal blood, serum, urine, hair, umbilical cord blood) than those not exposed[79-84].

Pesticides may contribute to gonadal cancer, and an increased risk of breast cancer in women with high levels of PCBs, DDE[85] and DDE[86] has been found. Similarly, in men, various studies have consistently shown a statistically significantly higher incident rate of prostate cancer in the exposed population (e.g., farmers) than in the general population[2,87-90]. However, according to the analysis by Rzeszutek et al[91] pesticides increase the incidence of three different cancers

– prostate, testes or kidney – by up to 75%. These pesticides (dichlorvos, fipronil and fungicides, among others) probably affect DNA methylation, leading to a change in the mRNA expression profile, and also disturb the modification of histones that are involved in the formation of chromatin (epigenetic memory transmitter) which also leads to a change in expression.

### Phytoestrogens

Phytoestrogens have been used as an alternative form of estrogen replacement therapy for many years. They are part of our diet and can be found in vegetables (beans, parsley, celery, peppers, kale, broccoli, onions, tomatoes, lettuce), fruit (apples, grapes, apricots, cherries), red wine, chocolate and green tea. Phytoestrogens are natural plant compounds whose structure is similar to 17β-estradiol and its active metabolites. Phytoestrogens include flavonoids (flavanones, flavones, flavonols, catechins) and isoflavonoids (isoflavones, isoflavans, coumestans)[92].

### Mechanistic Studies

Numerous studies have shown that phytoestrogens bind in vitro to ERα and ERβ, leading to the activation of ER-dependent gene transcription[93-96]. Phytoestrogens can also influence steroid transport and biosynthesis via SHBG (stimulating hormone-binding globulin)[97] and, competitively, testosterone and 17β-estradiol from plasma SHBG[98].

### Human Study

On the one hand, phytoestrogens have many benefits because they protect against cancer, have a prophylactic effect on atherosclerosis and a protective effect against osteoporosis[99-103]. On the other hand, they may pose a threat to unborn children or infants[104-106]. Therefore, when quoting Patisaul and Jefferson, it is worth asking, "So are they helpful or harmful?"[92]. The occurrence of deformities of the male external genitalia (hypospadias) and a vegetarian diet in mothers may indicate that phytoestrogens which disrupt the hormonal balance are involved in causing fetal defects[92,107]. It should be noted that soy is an ingredient of infant nutrition formula[108-110] and, if breastfeeding is not possible, it is the preparation of choice[110].

### Limitations

One limitation of our study is that we do not have conclusive data to thoroughly analyze the effects of EDCs on gonads. Secondly, while the mechanism of action and impact of EDCs can be demonstrated in many animal studies, this becomes a significant problem in human reproductive health. Thirdly, longer follow-up is needed to determine how ECDs affect both male and female gonads.

## Conclusions

As human beings, we are constantly exposed to many environmental chemical substances, including the many EDCs found in body fluids and tissues. Several studies indicate their additive or synergistic effects. Hence, their action may have unpredictable effects on humans. More and more reliable data indicates that EDCs have side effects on our health, even at low doses. While many epidemiological studies have previously focused mainly on people at risk of persistent exposure to EDCs due to their occupation or those affected by accidental exposure (Soveso, Italy), recent studies have suggested far-reaching effects of EDCs in the general population. The reproductive systems of both women and men are complex and require the proper structure and functioning of many organs, including the pituitary-gonadal axis. EDCs can interfere with reproduction by adversely affecting the organs of the female and male reproductive systems and/or their function.

It should be noted that the chemical industry is interested in results that have a positive effect on the industry itself, indicating that the produced chemical is safe for humans. Often, tests on various chemical products are carried out to prove the safety of the chemical compounds they contain, and the negative results obtained are considered favorable and published. In addition, government-funded research is usually a test of a preconceived hypothesis and it is not necessarily intended to prove or deny that a chemical is safe for humans or the environment.

**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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### Authors' Contribution

Conceptualization, A.C., K.J., B.C. and A.O.; methodology, M.Z-S., P.Z. and K.J.; software, E.F.; formal analysis, M.R.; resources, N.S-G. and P.Z.; writing, reviewing and editing, A.C., K.J. and A.O.; supervision, I.K-K., P.G. and M.R. All authors have read and agreed to the published version of the manuscript.

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