The effect of endocrine disruptors on reproductive health

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THE EFFECT OF ENDOCRINE DISRUPTORS ON REPRODUCTIVE HEALTH

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Abbreviations

ACOG - American College of Obstetrics and Gynecology

APEs - Alkylphenol Ethoxylates

ASRM - the American Society for Reproductive Medicine

BPA - Bisphenol A

DDT - Dichlorodiphenyl Trichloroethane

DEP - Diethyl Phthalate

DES - Diethylstilbestrol

DMP - Phthalates Dimethyl Phthalate

EPA - US Environmental Agency

FIGO - International Federation of Gynecology and Obstetrics

FVs - Fruits and Vegetables

HBCDD - Hexabromocyclododecane

HCB - Hexachlorobenzene

NPE - Nonylphenoxypoly (ethy1eneoxy) Ethanol

NPnEOs - Nonylphenol Ethoxylates

OCP - Organochlorine Pesticides

PBDE - Polybrominated Diphenyl Ether

PCDDs - Polychlorinated Dibenzo Dioxins

PCDFs - Polychlorinated Dibenzofurans

PFAS - Perfluoroalkyl and Polyfluoroalkyl Substances

PFCs - Polyfluoroalkyl Compounds

PFHxS - Perfluorohexane Sulfonate

PFOA - Perfluorooctanoate

PFOS - Perfluorooctane Sulfonate

PVC - Polyvinyl Chloride

TBBPA - Organophosphate Esters

TBT - Tributyltin Chloride

TCDD - Tetrachlorodibenzo-p-dioxin

TPTO - Bis(triphenyltin) oxide

USEPA - United States Environmental Protection Agency

WHO - World Health Organization

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1. Summary

Title: The effect of endocrine disruptors on reproductive health

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Synthetic chemicals are causing significant environmental contamination in several industrial and agricultural applications. Pesticides, plasticizers, antimicrobials, and flame retardants have positive purposes, but their consequences on human health are a global issue. Endocrine-disrupting chemicals (EDCs) can alter hormonal homeostasis, leading to developmental and reproductive problems. Human EDC exposure is linked to obesity, metabolic syndrome, and type 2 diabetes in new in vitro, in vivo, and epidemiological research. The effect of endocrine disruptors on reproductive health is an important subject that must be controlled, researched, and known to the public. Human exposure to different substances through air, water, food, plastics, and pesticides causes various. Reproductive health is also affected by different substances that cause damage and changes in the system. This review summarizes the most important endocrine disruptors known today and their effects. This topic is critical due to its impact on women's reproductive health and future generations.

1. Sažetak

Naslov: Učinak endokrinih disruptora na reprodukajsko zdravlje

Autor: Dor Yanai

Sintetičke kemikalije uzrokuju značajno onečišćenje okoliša u industeiji i poljoprivredi. Pesticidi, plastifikatori, antimikrobna sredstva i usporivači plamena imaju pozitivne svrhe, ali njihove opasne posljedice na zdravlje ljudi globalno su pitanje. Kemikalije koje ometaju rad endokrinog sustava mogu promijeniti hormonskij homeostazu, što dovodi do razvojnih i reprodukij skim poremećaja. Izloženost je povezana s pretilošću, metaboličkim sindromom i dijabetesom tipa 2 u novim in vitro, in vivo i epidemiološkim istraživanjima. Učinak endokrinih disruptora na reprodukcijskog zdravlje važna je tema koja se mora istraživati a resiltati tih istraživanja moraju biti dostvan javnosti. Izloženost ljudi različitim tvarima kroz zrak, vodu, hranu, plastiku, pesticide i drugo uzrokuje razne. Na reprodukcijsko zdravlje utječu različite tvari koje uzrokuju oštećenja i funkcionalne promjene. Ovaj pregledni članak sažima najvažnije endokrine disruptore poznate danas i njihove učinke. Ova je tema kritična zbog svog utjecaja na reproduktivno zdravlje žena i buduće generacije.

2. Introduction

The effect of endocrine disruptors on reproductive health is a wide field that is studied by researchers around the world for many decades. Researchers in this field are trying to determine and understand the mechanisms and specific effects of endocrine disruptors on the body. Products created by humans can cause damage to the body and can affect people through dietary consumption, breathing, skin exposure, and other routes of exposure. This topic is becoming increasingly important to understand and research due to the development of the world, allowing for an increase in the production of various products such as plastics, pesticides, and the high use of those products in the industrial world, which causes increased exposure in the society. In the last decades, it has been more pronounced that there is a reduction in the fertility rates among women, and progress in research has proven that there is a significant correlation between decreased fertility and endocrine disruptors which are released from industries or by pesticides that found in our food or the environment we are exposed to.

This review paper aims to review and discuss the most relevant endocrine disruptors, those with the most significant role in reproductive health. The endocrine disruptors reviewed here have a significant role in some specific populations, and some others, have more worldwide effects which might play a major role globally. It is highly important to make this information more accessible to the general public and emphasize the importance of regulation procedures in different industries to minimize the negative effects of endocrine disruptors described in this paper. Moreover, our society needs to be aware and focus on avoidance and prevention to minimize the health effects on humans and animals.

When considering the effects of endocrine disruptors on reproductive health, a major problem is the inability to research the subject effectively in a satisfactory manner. We are unable to properly examine all the possible vulnerabilities of the various substances on the health of the reproductive system. Beyond the fact that endocrine disruptors can be the cause of various injuries, many other factors can affect the same way. Therefore, researchers cannot reliably cover all the harmful factors as well as all the possible vulnerabilities. Most of the studies done in the past and until this date are being done on specific populations and yet cannot determine whether harm is made due to exposure to endocrine disruptors or due to exposure to other environmental factors, which can go unrecognized.

Reproductive health refers to the women's and male condition of the reproductive system during their lives. The reproductive system is composed of organs and hormones that control the system and work together to create a healthy reproductive system [19].

Health is defined by the world health organization (WHO) as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." This definition concerning reproductive health is defined as a state in which reproduction health does not depend only on the state of absence of disease but also on the ability of people to control their health by learning how to control their system, how to enjoy intercourse, and their relationships and by that to create a healthier mental environment that will influence their reproductive health [19].

Many factors in today's world are defined under reproductive health. One of the main issues nowadays is the fertility problems increasing around the world. Fertility, by definition, is "The ability to conceive and bear children, the ability to become pregnant through normal sexual activity." one of the reasons for infertility is Unsafe sex, which produces a lot of sexual diseases that affect the woman and her reproductive health. In non-developed countries, this risk is much higher than in developed countries. Many measures have been taken to reduce this risk worldwide, starting with education about safe sex, increasing the use of contraception, increasing the use of barrier contraception to reduce sexual diseases, and educating women about their rights in sexual intercourse [16]. Some RCTs and meta-analyses have been made to study this problem, and still, it is hard to find enough and good enough information due to the problems arising in researching this subject sufficiently.

3. Endocrine Disruptors

An endocrine disruptor is “an exogenous agent that interferes with 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 developmental process” (US environmental agency). Endocrine disruptors are compounds that are found in industries such as the plastic industry, fuels industry, pesticides industry, and in environments such as plants and animals that can cause damage to the endocrine and reproductive systems of women and men [11].

Synthetic chemicals that industries and agriculture produce are causing contamination of the environment and are being the main concern regarding abnormalities in reproductive health and various health conditions such as cancers, metabolic diseases (including obesity), and cardiovascular diseases. Endocrine disruptors can cause damage to the process of hormone production, and hormones release, and can exacerbate bodily changes by acting the same as some hormones in the body. Endocrine disruptors act on different neurological pathways in the body and can mimic the action of serotonin, norepinephrine, and dopamine. Additionally, endocrine disruptors can mimic the action of thyroid hormone on its receptors, they can activate nuclear receptors such as estrogen hormone receptor and progesterone hormone receptor, and they can act on the peroxisome. All the hormonal and neurotransmitter activities of the endocrine disruptors can cause changes in the body and disruptions that are assumed to negatively affect the reproductive health [11].

When discussing the effect of endocrine disruptors, one shall note that some factors influence the end effect of exposure to a specific endocrine disruptor. Those factors are the duration of exposure to the disruptor and the age at which one has been exposed. It is well established that infants will be affected differently from adults and will present different symptoms and may show severe disruptions if the exposure was at the time of critical development time in fetus life. Moreover, an infant that was exposed to endocrine disruptors may not show any sign of disruption until later in life. Notably, most of the exposers to endocrine disruptors are not to just one substance but rather a mix of compounds that can be found in the environment or being consumed without the harmed person even knowing about it [11].

Upon exposure to the mixture of endocrine disruptors, they can have an additive or synergistic effect that will influence the rate and severity of health issues and abnormalities. It is important to

remember that not only the people that are exposed are at risk of developing different endocrine abnormalities but the effect can travel through generations. Recent evidence shows that people who were exposed to some endocrine disruptors can develop a mutation that changes factors of regulation and gene expression. In turn, those mutant genes will be transmitted onward and cause changes in methylation and acetylation, which inhibited or activate different sequences in DNA and cause changes in the organism [11].

Endocrine disruptors are chemicals that are frequently used in everyone's life. All these elements can be found around the world and can be stored for a long time in animal fat, or human fat, or can be products that are found only for a short period before disappearing. We can categorize the endocrine disruptors differently by their effect, their use in our lives, and their structural properties [20].

Table 1 shows human exposure to endocrine disruptors by the level of exposure, way of exposure, and half-life of the disruptors compared to levels that are used experimentally. This table is important because it emphasizes the amplitude of exposure people are experiencing, which can help us understand its effects on the body.

EDCs	Human exposure	Levels in the human body	Biological half-life	Concentrations experimentally used	References
Organochlorines (e.g., DDT)	Banned Soil half-life: 22 to 30 years	DDE: very variable range from <5 to >15,000 mg (kg BW)$^{-1}$	5 years	In cells: 20 μM *p,p′*-DTT	20, 24, 157
Dioxins (e.g., TCDD)	TDI: 1–4 pg (kg BW)$^{-1}$ (WHO)	In adipose tissue: 3.6 pg (g lipid)$^{-1}$ In blood: 2.2 ppt	7–11 years	In mice: doses of 5–500 ng (kg BW)$^{-1}$ day^{-1} affect energy metabolism	17, 119, 158
Organotins (e.g., TBT)	TDI: 1.6 mg (kg BW)$^{-1}$ (Welfare Ministry of Japan)	In serum: 27 nM In human tissue: 3–100 nM	From 23 to 30 days	In mice: induce adipogenesis at 0.05–0.5 mg (kg BW)$^{-1}$ In vitro: EC_{50}: 3–10 nM for RXR/PPARγ	11, 28
PFCs	Indoor air levels: PFOS: 5 ppm PFOA: 3.7 ppm	Serum-level medians: PFOS: 19.9 μg liter^{-1} PFOA: 3.9 μg liter^{-1}	PFOS: 5.4 years PFOA: 3.8 years	In rodents: PFOA prenatal exposure effects in a range of 0.01–5 mg (kg BW)$^{-1}$	10, 14, 40, 141, 142
BFRs (e.g., PBDE)	Exposure through diet: 37–97 ng day^{-1} Exposure through house dust: Adults: 16.7 ng day^{-1}; children: 191.3 ng day^{-1}	Mean levels in adipose tissue: Europe and Asia: <5 ng (g lipid)$^{-1}$ North America: >200 ng (g lipid)$^{-1}$ In fetal liver: range of 4–98.5 ng (g lipid)$^{-1}$ (in the United States) In breast milk: range of 1.57–73.9 ng (g lipid)$^{-1}$ (worldwide)	In serum: from weeks to months In fat: several years	In rats: exposure to 14 mg (kg BW)$^{-1}$ day^{-1} for four weeks alters lipolysis and glucose oxydation	13, 67, 95
Alkylphenols	NP's TDI: 7.5 mg day^{-1} (Germany)	In urine: range of 0.4–13.9 ng ml^{-1} In adipose tissue: median level of 57 ng g^{-1} (Spain)	NP in blood: 2–3 h	In vitro: lowest effect concentrations in the 10–1000-nM range	52, 55, 56
BPA	TDI: <50 μg (kg BW)$^{-1}$ day^{-1} (U.S. Environmental Protection Agency)	Range of 0.1–10 ng ml^{-1} in blood, urine, fat, and fetal tissue	6 h	In vitro: lowest effect concentrations in the 0.1–1-nM range In mice: weight increase correlated with in utero exposure to 2.4–500 μg (kg BW)$^{-1}$ day^{-1}	55, 67, 89, 156
Phthalates	DBP's TDI: 10 mg (kg BW)$^{-1}$ day^{-1} (European Food Safety Authority)	Range of prenatal phthalate metabolite mean levels in urine of mothers: 2.54–816 μg liter^{-1} Monoesters of DEHP in children's urine: 91.3 μg liter^{-1} (NHANES)	From hours to days	In cells: 50-μM DEHP, DBP, and metabolites In mice: DEHP: 1,000 mg kg^{-1} day^{-1}; DBP: 2,000 mg kg^{-1} day^{-1}	32, 67, 134

[a]Abbreviations used: BFR, brominated flame retardant; BPA, bisphenol A; BW, body weight; DBP, dibutyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEHP, diethylhexyl phthalate; EDC, endocrine-disrupting chemical; NHANES, National Health and Nutrition Examination Survey; NP, 4-nonylphenol; PBDE, polybrominated diphenyl ether; PFC, polyfluoroalkyl compound; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PPAR, peroxisome proliferator–activated receptor; ppt, parts per trillion; RXR, retinoid X receptor; TBT, tributyltin chloride; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TDI, tolerable daily intake; WHO, World Health Organization.

Table 1. Human exposure to EDCs compared with concentrations experimentally used (Casals-Casas & Desvergne B, 2011).

3.1 Pesticides

"Pesticide law defines a "pesticide" (with certain minor exceptions) as Any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, Any nitrogen stabilizer" (US environmental agency). Pesticides include organochlorine pesticides (OCP) that can mostly be found in agriculture and include dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), chlordane. Also, contemporary organophosphate-based agents, triazines, pyrethroids, and more. Exposure to those pesticides as any other agent that may be in our environment can occur through dietary

and water consumption, occupational setting, and agricultural field and crop that may release into the air the people breathe. All these agents have a deleterious impact on women's fertility and reproductive health. Leading experts and organizations (FIGO, ACOG, and ASRM) describe the high risk of the aforementioned pesticides on women's health as they can cause various types of endocrinological abnormalities (i.e thyroid and steroid hormone signaling), an increase in oxidative stress, disruption of gonadotropin receptor, sexual development, fertility, and pregnancy maintenance [13].

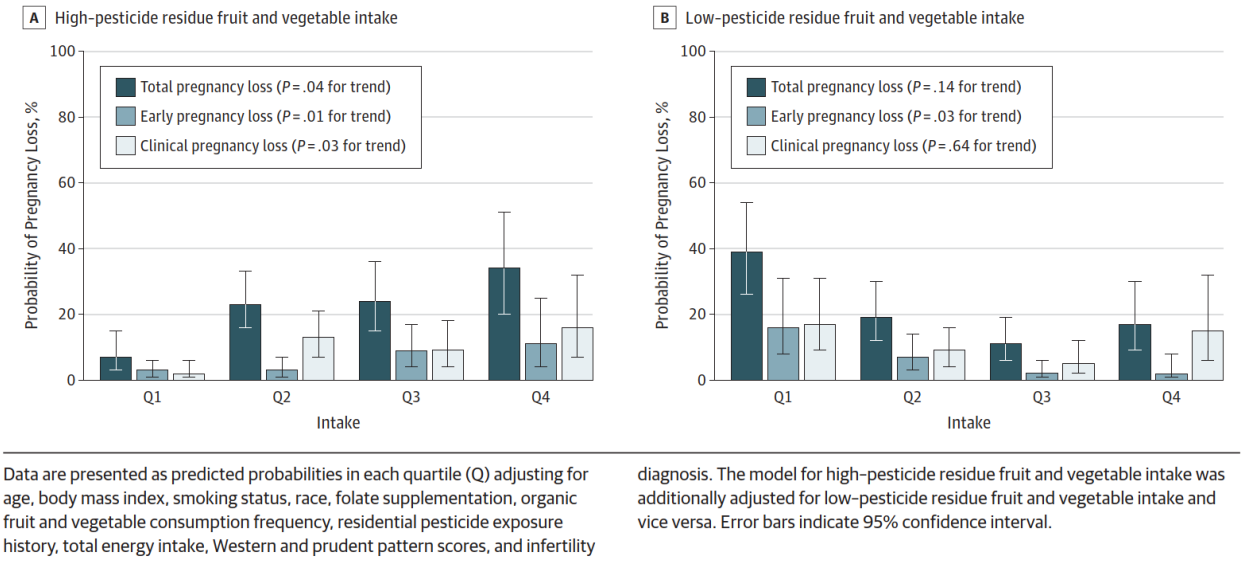
In recent years we see a high connection between pesticide exposure and reproductive dysfunction. It is now known that the fertility rate is not only decreasing in developed countries but also developing countries. Contributing factors for the reduction of fertility and childbirth can be connected to the increased focus of people in their careers and the increased use of contraceptives. Though, a major concern is that other factors in our environment play a significant role in the ability to conceive and stay fertile. The epidemiological study by Clementi M and colleagues describes different effects of pesticides that can interfere with the ability of women to become fertile. It can change the hormonal balance, interfere with implantation, damage the gamete, and even cause damage to the development of the reproductive system. An important key in the fertility of a woman is the hormonal balance and the amount and time interval of hormone needed to be at the appropriate level to create the endometrium in the right state for implantation. When pesticides cause changes in those hormones, we have an alteration in the menstrual cycle, regulation of implantation, and fertilization [7].

The connection between pesticides and female infertility was first suggested by a study that examined the occupational history of 280 women with a confirmed diagnosis of infertility. In this study, it was shown that there is a significant correlation between women with a working history in agriculture, greenhouses, spraying pesticides, and damage to the reproductive system. Other epidemiological studies that have been done later prove that pesticide is also a risk factor for abortions with an estimation that 30% of pregnancies end before week 6 [7].

Another way in which pesticides reach women who do not work and are freely exposed to these substances is through food. The food we eat is constantly sprayed with various pesticides to maintain product quality. In the United States, pesticides can be detected in more than 90 percent of people in urine and blood. Research studying 235 women who consumed FV's with a high amount of pesticides has found that those women were more likely to report disturbances in pregnancy and fertility. On the

other hand, women that consumed a low amount of FVs with pesticides had a lower risk of problems during pregnancy. The results of the research suggest that reducing the amount of pesticide intake will allow for better pregnancy progress, with a decreased likelihood of pregnancy loss. The following graph (Graph 1.) shows the results of the research from the EARTH study regarding stages of pregnancy loss in women that consumed a high or low amount of pesticide fruit or vegetables [5].

The EARTH study is a collection of more than 130 papers published in peer-reviewed journals that covers the impact of environmental exposures and consumption of foods on fertility and pregnancy process and outcomes. Scientific groups and government organizations have used this study to conclude about environmental risk factors for infertility and poor pregnancy outcomes. This study aims to use the results to improve the knowledge we have about those factors and how can we improve the clinical practice and policies.



Data are presented as predicted probabilities in each quartile (Q) adjusting for age, body mass index, smoking status, race, folate supplementation, organic fruit and vegetable consumption frequency, residential pesticide exposure history, total energy intake, Western and prudent pattern scores, and infertility diagnosis. The model for high-pesticide residue fruit and vegetable intake was additionally adjusted for low-pesticide residue fruit and vegetable intake and vice versa. Error bars indicate 95% confidence interval.

Graph 1. Probabilities of Total, Early, and Clinical Pregnancy Loss According to High– or Low–Pesticide Residue Fruit and Vegetable Intake Among 256 Women With Successful Implantation (316 Cycles) From the EARTH Study (Chiu YH, et al, 2018).

3.2 Dioxins

A dioxin is a group of organochlorines that can produce naturally in nature but also by humans. In nature, it can be released by volcano or forest fire and humans usually produce this substance by creating substance as polyvinyl chloride (PVC) or bleached paper production. The dioxin group contains PCDD, PCDFs, and PCBs. The most toxic dioxin is TCDD which was used in the Vietnam war and caused to severe effect on society [20]. Digoxin toxicity can occur both during and after long-term treatment with the drug. Even though the digoxin concentration is within the therapeutic range. Anorexia, nausea, vomiting, and neurological problems are all indicators of toxicity. More than that, it can potentially cause life-threatening arrhythmias. In severe toxicity, digoxin-specific antibody fragments are safe and effective [27].

For all stages of development, precise integration of different endocrine systems is essential. The involvement of estrogens, progestins, gonadotropins, and androgens, among other hormones, are key elements of the endocrine system development and function. The brain, endocrine organs, reproductive organs, and peripheral tissues all play a role in the organism's normal functioning throughout its lifespan. Given the importance of hormones in many areas of development, exogenous environmental substances that imitate, inhibit, or alter endogenous chemical messengers are likely to have developmental consequences. The polyhalogenated aromatic hydrocarbons (PHAHs), are a very important family of such environmental pollutants. They have been demonstrated to be developmental and reproductive toxicants in many species [1].

Although dioxin has long been known to be a reproductive toxin, little work has been put into understanding how it affects fertility and reproduction until recently. This is due in part to the focus on overt structural defects; nevertheless, some of the impacts do not manifest themselves until puberty or even later. Gray and Ostby looked at the effects of TCDD exposure on female rat offspring during pregnancy and lactation. In addition to being delayed in puberty, the pups' external genitalia had anatomical deformities. In addition to partial clefting of the phallus, there was a continuous thread of tissue across the vaginal opening. First matings were challenging and frequently resulted in vaginal bleeding as a result of these changes. The weight of the ovaries was also permanently lowered [14].

Robert J. Biggar, Jan Wohlfahrt, and Mads Melbye made a research on Digoxin use and the risk of cancers of the corpus uteri, ovary, and cervix. They hypothesize that there is a connection between those cancers and the usage of Digoxin.

The study looked at the risks of uterus, ovarian, and cervix cancer in a cohort of all women aged 20 who lived in Denmark at some time between 1995 and 2008, Using data from the Danish Medicinal Product Statistics Register. Theis results were that uterus cancer risks were significantly higher in women who were now taking digoxin and potentially in prior users. Digoxin users, on the other hand, did not have an elevated risk of ovarian or cervix cancer. Cancer incidences for uterine, ovary, and cervix were not elevated among other angina medication users. Women who took digoxin or angina medication were almost all post-menopauses. As a result, the comparisons to women who did not use these medicines were carefully adjusted for age and calendar period. The incidence of uterine cancer increased soon after exposure to digoxin [2].

3.3 Organotins

Organotins are a group of organic pollutants that are used in agricultural fungicides, paint for ships, rodent repellents, and fishing nets. Organotins include TBT and TPRO. Humen exposure to organotins can be from dietary products mostly from the sea as shellfish, fish, or other contaminated food or water [4].

TBT causes different changes in reproductive health. It is known that exposure of sea snails to TBT cause to change in reproductive development that is called imposex. Other research that has been done on female rats its shown that rats that were treated with seafood with imposex alteration in the reproductive tract were shown in less than a month. Also, the female rate show increase in the lipid body layer due to changes in the Hypothalamus-Pituitary axis [30].

3.4 Plastics

Plastic is a polymeric substance that may be molded or sculpted by applying heat and pressure. Plasticity, which is frequently combined with other specific features like low density, low electrical conductivity, transparency, and toughness, allows plastics to be produced in a wide range of items.

Plastic is one of the most used products in the world. When in 2010 more than 300 million tons of plastic were produced. Many studies have shown and are still researching the effects of plastic on the human body and with an emphasis on the effect of endocrine disruptors. Different types of plastic

include polyfluoroalkyl compounds, brominated flame retardants, alkylphenols, bisphenol A, and phthalates known as endocrine disruptors [4].

3.4.1 Polyfluoroalkyl Compounds

Polyfluoroalkyl compounds (PFCs) are compounds found in different industries such as leather, firefighting foam, paper, textile, and more. PFCs is known to cause chemical attraction with the liver and different protein. In past research that had been done on rodents in a laboratory, it was found that PFCs cause neonatal mortality and decrease normal births. More than that in rats it is shown to cause hormonal disturbances such as decreased testosterone levels and increase estradiol. In addition, it was proven that it can cause a problem with lipid metabolism and decrease cholesterol and triglyceride levels [4].

Sources	**Pathways**
Dietary sources	
Fish and shellfish	Environment/Ingestion
Drinking water	Ingestion
Food-packaging materials	Ingestion
Non-stick cookware	Ingestion
Others (including dairy products, eggs, beverages and vegetables)	Ingestion
Non-dietary sources	
Indoor air	Inhalation
Indoor dust	Inhalation/ingestion
Soil and sediment	Environment
Impregnation spray (for furniture and carpet)	Inhalation/dermal absorption
Cosmetics	Dermal absorption
Other consumer products (including skin waxes, leather samples andoutdoor textiles)	Dermal absorption

Table 2. Sources and pathways of human exposure to PFAS (Ding N, et al, 2020).

The three most known PFCs are perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorohexane sulfonate (PFHxS) are known to have a risk on fetal development. it is possible to find PFCs in breast milk, blood, and human serum when the woman was exposed to a high amount of PFCs. The amount of PFCs found in the serum is associated with birth weight and length. As high the amount of PFCs in the serum the weight and the length will be lower. This fact indicates the adverse effect of

PFCs on pregnant women and on the changes that occur in the women's bodies that disrupt reproductive health [22].

A few randomized control trials have been done on PFAs exposure and can prove that there is a high connection between exposure to PFAs to late menarche, earlier menopause, irregular menstrual cycle, and reduced level of hormones. One of the main adverse effects is the defect in ovarian folliculogenesis and disturbances in the gap junction between oocytes and granulosa cells. PFAs exposure causes damage to oocyte development by activation of peroxisome proliferator-activated receptor (PPAR) signaling pathways which cause the creation of oxidative stress that damages the connection between the oocyte and the granulosa cells and causes to inhibition of oocyte meiosis, which is an important stage the gamete development [12].

Figure 2 below shows normal follicle development and oogenesis and explains where in those processes the PFAS may interfere with the female reproductive system.

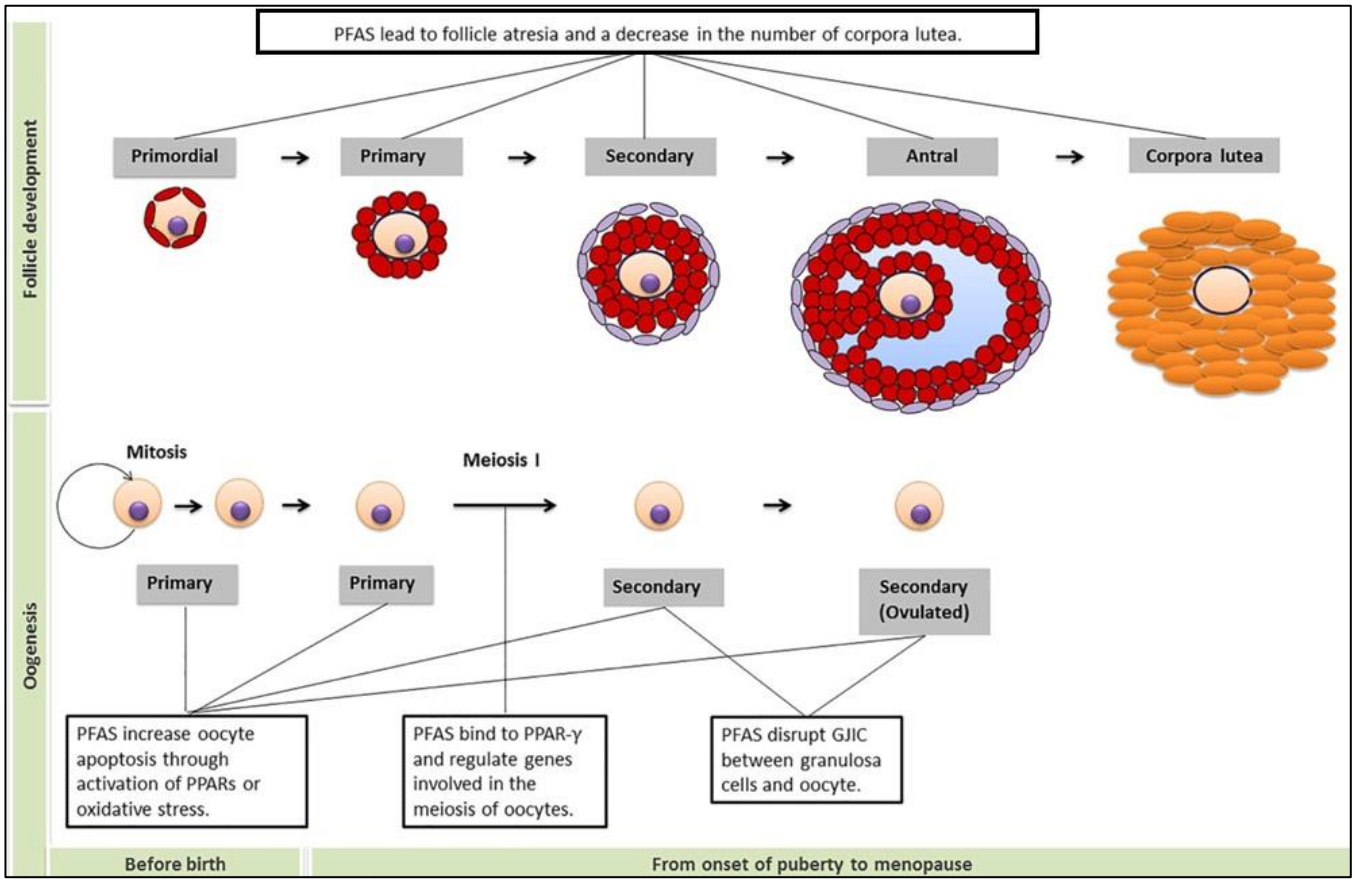


Figure 2. PFAS disrupts folliculogenesis (Ding N, et al, 2020).

3.4.2 Brominated Flame Retardants

Organohalogens are a wide class of compounds that include brominated flame retardants (BFRs). Due to their great performance efficiency and low cost, BFRs are currently the most widely used flame retardant category. Brominated flame retardants (BFRs) are chemical mixes that are added to a wide range of products, including industrial applications, to make them less combustible. Plastics, textiles, and electrical/electronic equipment all use them. BFRs are divided into five categories, each with its own set of applications -Plastics, fabrics, electronic castings, and circuitry all contain polybrominated diphenyl ethers (PBDEs). Hexabromocyclododecanes (HBCDDs) is a type of thermal insulation used in construction. Printed circuit boards, thermoplastics – tetrabromobisphenol A (TBBPA) and other phenols (mainly in TVs). PBBs are found in consumer electronics, fabrics, and plastic foams. Certain BFRs are banned or limited in the European Union but due to their persistence in the environment, they are still used.

Flame retardants have been introduced to a wide range of consumer products and can now be found in almost every area. Polybrominated diphenyl ether (PBDE) flame retardants have been found to have a deleterious influence on human health in epidemiological, in vivo, and in vitro investigations, resulting in their phase-out and replacement. Alternative flame retardants such as hexabromocyclododecane (HBCDD) and tetrabromobisphenol A can be used instead. Their Acute toxicity appears to be minimal. Oral exposure to HBCDs, on the other hand, appears to increase drug-metabolizing enzymes in rats, such as hepatic cytochrome P450 (CYP), indicating that HBCDs may cause cancer through a nonmutagenic route. The thyroid hormone system and thyroid hormone receptor-mediated gene expression has been reported to be disrupted by HBCDs. Developmental neurotoxic effects, such as abnormalities in spontaneous behavior, learning, and memory function, can be generated in rats following neonatal exposure experiments. HBCDs can also affect neurotransmitter absorption in the rat brain. More investigation into the precise amounts at which these effects manifest is required [8]. Some of these substances have been shown to cause ovarian cancer. The effects of many of these flame reignite may be adverse to female fertility. However, the full effect on the ovaries is not completely known [33].

PBDEs (polybrominated diphenyl ethers) were widely utilized as flame retardants. Based on studies on experimental animals, evidence has accumulated that PBDE exposure may have harmful impacts on human health. As a result, their use has been regulated. These consequences come in a variety

of forms as neurotoxicity, carcinogenicity, phytotoxicity, as well as developmental and reproductive effects toxicity to the reproductive system [21].

As a result, they have been replaced with alternatives such as hexabromocyclododecane (HBCDD), tetrabromobicyclododecane(TBCDD), tetrabromobicyclododecane (TBCDD), tetrabromobicyclo Organophosphate esters (OPEs) and bisphenol A (TBBPA) that frequently used as flame retardants replacements [10].

Some PBDEs have been associated with decreased fecundity in women, as well as a higher rate of in vitro fertilization failure (IVF) [18]. Similarly, maternal exposure to OPEs is harmful and has been linked to poor pregnancy outcomes. To date, HBCDD or TBBPA exposure has been linked to human reproduction. Epidemiological data is scarce, which implies that flame retardants may have negative effects on women However, little is known about the effect on the ovaries [6].

Table 3. listed the Brominated flame retardants and organophosphate ester flame retardants that are known to be harmful to the human body.

	Chemical (acronym)	CAS#
Brominated flame retardants	2,2′,4,4′-Tetrabromodiphenyl ether (BDE-47)	5436−43-1
	2,2′,4,4′,5-Pentabromodiphenyl ether (BDE-99)	60348−60-9
	2,2′,4,4′,6-Pentabromodiphenyl ether (BDE-100)	189084−64-8
	2,2′,4,4′,5,5′-Hexabromodiphenyl ether (BDE-153)	68631−49-2
	Decabromodiphenyl ether (BDE-209)	1163−19-5
	Hexabromocyclododecane (HBCDD or HBCD)	3194−55-6
	Tetrabromobisphenol A (TBBPA)	79−94-7
Organophosphate ester flame retardants	Tris(2-butoxyethyl) phosphate (TBOEP)	78−51-3
	Tris(methylphenyl) phosphate (TMPP) or tricresyl phosphate	1330−78-5
	Tri-o-cresyl phosphate (TOCP)	78−30-8
	Tris(chloropropyl) phosphate (TCPP)	13674−84-5
	Isopropylated triphenyl phosphate (IPPP)	68937−41-7
	Tris(dichloro-isopropyl) phosphate (TDCPP)	13674−87-8
	Triphenyl phosphate (TPHP)	115−86-6
	Tris(2-chloroethyl) phosphate (TCEP)	115−96-8
	Ethylhexyl diphenyl phosphate (EHDPHP)	1241−94-7
	Tert-butylphenyl diphenyl phosphate (BPDP)	56803−37-3
	Tris(3,5-xylenyl) phosphate (TXP)	25155−23-1

Table 3. List of chemicals of interest (Wang X, et al, 2021)

3.4.3 Alkylphenols

Nonionic surfactants are mainly used for industrial cleaners, agrochemical emulsifiers, metal cleaners, stabilizers, Wetting agents, and sanitizers. Nonionic surfactants such as alkylphenol ethoxylates (APEs) account for 6% of overall surfactant production and 25% of total nonionic surfactant production in the United States. The alkylphenol hydrophobe and a para-substituted long chain of repeated ethylene oxide units as the hydrophilic moiety provide them surfactant action. One to 100 repeating units make up an ethoxylate chain; the longer the chain, the more water-soluble the molecule. A branched nonyl, octyl, or dodecyl chain is commonly used as an alkyl group. Nonoxynol, ethononylphenol, polyoxyethylene nonylphenol ether, or nonylphenoxypoly(ethy1eneoxy) ethanol are the most common of the APEs, accounting for 82 percent of production. They are also known as nonoxynol, ethononylphenol, polyoxyethylene nonylphenol ether, or nonylphenoxypoly (ethy1eneoxy) ethanol [23].

APEs and their degradation products can reach humans through the water supply, sewage sludge used as fertilizer, aquatic flora and fauna that serve as food, and directly through the use of APE spermicides. The US FDA has also approved APEs for use in the production of food packaging [24].

High levels of alkylphenols, which are endocrine disruptive substances, have been linked to reproductive hormone imbalance in infertile women (EDCs). MicroRNAs (miRs), short non-coding RNAs that target mRNAs encoding enzymes in the hormone production pathway, have been found to interfere with gene expression in previous research. This effect, however, is dependent on the target organ, dose, and whether the drugs are used alone or in combination. The study done by Patiño-García D confirmed that miR-200b-3p targets Cyp19a1, the mRNA encoding CYP19A1, the enzyme that generates estradiol, utilizing primary granulosa cell culture. These findings suggest that chronic exposure to alkylphenols modifies ovary miR biogenesis and increases the expression of miRs involved in steroid hormone synthesis control in female mice, potentially contributing to reproductive disorders [25].

Endometrial cancer has been linked to exposure to environmental substances that have oestrogenic properties (EMCa). The most often diagnosed cancer of the female genital tract is EMCa (Endometrial cancer). A study that conducted a case-control trial between 2011 and 2014 check the potential link between environmental endocrine disruptors and the development of EMCa. The study searches for the connection between any differences in concentrations of alkylphenol, a recognized

hormone disruptor, and women who had EMCa or uterine leiomyoma and those who didn't. A similar connection was seen when pre-and post-menopausal groups were stratified. The findings indicate that NP/OP exposure is linked to EMCa [34].

3.4.4 Bisphenol A

BPA is one of the most widely used compounds on the planet. According to current estimates, more than 8 billion pounds of BPA are manufactured each year, with around 100 tons being emitted into the environment. BPA is utilized in the production of plastics and epoxy resins, both of which are ubiquitous in our surroundings and daily lives. BPA has been identified as an endocrine disruptor. A.P. Dianin was the first to synthesize it in 1891, and it was examined for commercial usage in the 1930s as part of a hunt for synthetic estrogens. Although BPA's estrogenic activity was confirmed, testing of diethylstilbestrol (DES), a structurally comparable synthetic chemical, revealed that DES was a significantly more potent estrogen than BPA in a traditional vaginal cornification estrogenicity assay. After correlations to vaginal and cervical malignancies were discovered in the exposed women, the treatment was discontinued [29].

The bisphenol-A (BPA) chemical has been linked to female infertility. Indeed, BPA has been reported to be more frequently discovered in infertile women, prompting speculation about whether BPA influences natural conception and spontaneous pregnancies. Furthermore, BPA exposure was found to be inversely linked with peak serum estradiol levels after gonadotropin stimulation, number of retrieved oocytes, number of properly fertilized oocytes, and implantation in medically assisted reproduction operations. BPA has more harmful effects during perinatal exposure, producing disruption of the hypothalamic-pituitary-ovarian axis, as well as an early maturity of the axis due to damage to the GnRH axis, gonadotropin signaling, and sex steroid hormone synthesis. Studies that have been done on female adult animals and offspring, prenatal, perinatal, and postnatal exposure to BPA has been shown to disrupt numerous stages of ovarian development and ovarian function, notably folliculogenesis, as well as uterus morphology and function. Finally, research in animal models has shown the formation of endometriosis-like lesions following BPA exposure [26].

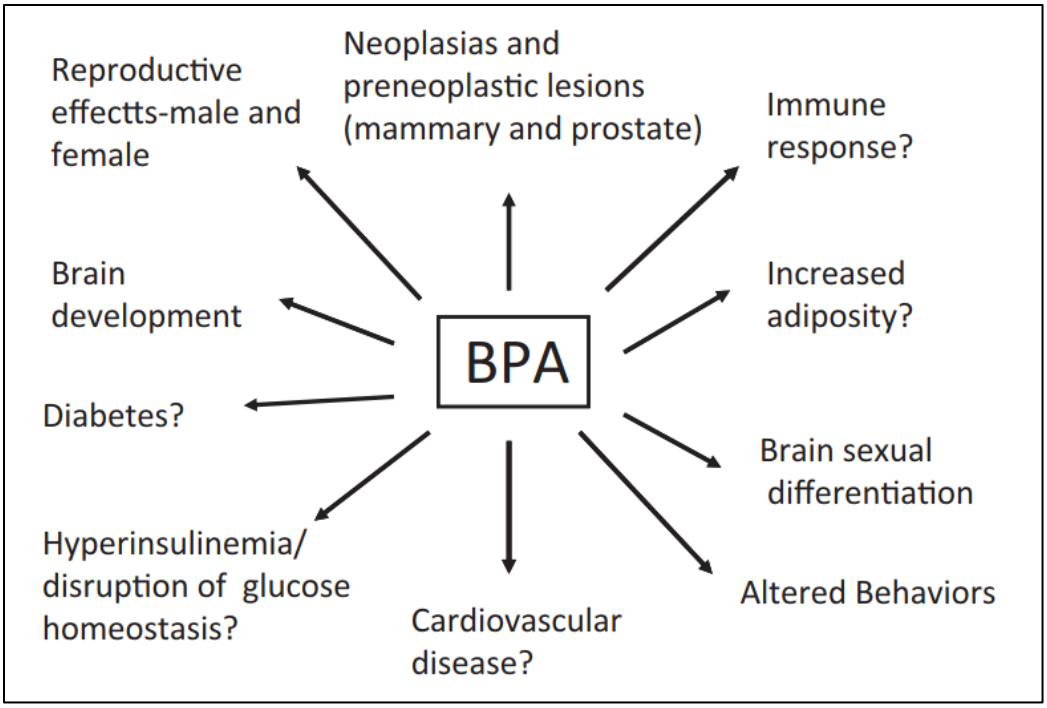


Figure 3. effects of BPA exposure (Rubin BS, et al, 2011).

Increased levels of BPA in adults have been linked to a variety of diseases, health outcomes, and medical disorders in humans. Diabetes, which is consistent with the report that low levels of BPA limit adiponectin release from human adipose tissue, cardiovascular disease, and altered liver enzymes have all been linked to greater levels of BPA exposure. Increased BPA levels have also been linked to recurrent miscarriages and an increase in the number of premature births in women. Increasing BPA levels were linked to lower peak estradiol levels and fewer oocyte retrieval numbers in IVF women, while increased BPA levels were linked to increased inflammation and oxidative stress in postmenopausal women [31].

3.4.5 Phthalates

Phthalates are phthalic acid diesters that are widely used in cosmetics, food packaging, and medical items as plasticizers to increase the flexibility, pliability, and elasticity of plastics. Phthalates have been found in water, air, sediments, soil, food, human blood plasma, breast milk, urine, and other places, with an annual generation of roughly 6.0 million tons. Because of their high production volume and widespread use, phthalates have become practically ubiquitous. Recent research has demonstrated that phthalates are obesogens (compounds that cause weight gain) [3]. The phthalates dimethyl phthalate (DMP), diethyl phthalate (DEP), DBP, BBP, DEHP, and DNOP are recognized as priority environmental contaminants by the United States Environmental Protection Agency (USEPA) [28].

Phthalates, which were long thought to be safe, are now causing widespread worry due to their hormone-disrupting properties, which have negative health impacts. Some phthalates have been linked to premature breast development in girls, as well as shorter pregnancies and shorter anogenital distance in newborn males [9]; [32]. The estrogen-disrupting effect of some phthalates is most likely to blame for these reproductive abnormalities. Though studies on the estrogenic endocrine disrupting activity of phthalates have been conducted, and some phthalates, such as DEP, DBP, BBP, and DEHP, have been reported to have estrogenic activity in vitro, the toxicity and estrogenic endocrine-disrupting potency of some phthalates and phthalate mixtures in vivo systems remain unknown [28].

Di(2-Ethylhexyl) phthalate (DEHP), one of the most prevalent phthalates, is a specific public health issue because 100% of the US population has detectable amounts of this EDC2. DEHP has previously been linked to significantly earlier menopause in women, implying that DEHP has a deleterious impact on reproduction. Phthalate exposure has also been linked to lower couple fertility, low birth weight, preterm birth, and pregnancy loss. The placenta is exposed to phthalates throughout pregnancy, and this EDC passes the placental barrier, raising concerns regarding the chemical's impact on placental and fetal development (15).

4. Conclusion

After reviewing the effects of hormone disruptors on reproductive health, considering many other demographic factors and factors in the environment and the affected individuals, we can conclude that reproductive health is affected negatively by endocrine disruptors. Many studies support these conclusions, for example, pesticides in agriculture cause fertility abnormalities (via the disruption of thyroid and steroid hormone signaling pathways), increasing oxidative stress and changes in gonadotropin receptors, sexual development, and pregnancy maintenance. Digoxin which has recently been studied was associated with an increased risk of uterine, ovarian, and cervical cancer. Organotins on experimental animals are found to cause imposex and increase in lipid body layer due to changes in the hypothalamic-pituitary axis. Plastic compounds such as Polyfluoroalkyl Compounds, Brominated Flame Retardants, Alkylphenols, Bisphenol-A, and Phthalates have been associated with decreased levels of testosterone, increased estradiol, lipid metabolism abnormalities, changes in birth weight and birth length, irregular menstrual cycles, reduced hormonal activity, defect in folliculogenesis, oocyte development abnormalities, neurotoxicity, cardiotoxicity, carcinogenesis, hyperinsulinemia, neoplasia, alterations in behavior, placental and fetal development abnormalities.

In summary, endocrine disruptors can be concluded to affect reproductive health negatively in various ways. We can encounter endocrine disruptors in agriculture, food, water, etc. Even though it is a complicated task to research this subject sufficiently, though, very important to continuously improve the knowledge of the population about endocrine disruptors and their effects and to continue researching it and find more information that can help us in the future to improve and maintain reproductive health and other aspects of the environmental health.

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7. Biography

My name is Dor Yanai, I was born in Israel on April 13th, 1994. After high school, I served in the army as commander for 2 years. Since my childhood, I knew that my dream is to become a doctor and after the army, I started my studies at the University of Zagreb, School of Medicine in 2016. In the year 2018, I volunteered to join “Team 5” medical team to do a mission in Guatemala in which we gave medical assistance to remote villages after the devastating Volcanic eruption. This is my graduation thesis to become officially Dr of medicine.