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REVIEW PAPER

ENVIRONMENTAL EXPOSITION TO XENOESTROGENS AND RELATED HEALTH EFFECTS*

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Abstract

The aim of this study is to present the impact of environmental pollutants disrupting the human endocrine system and their negative effects on human health. Xenoestrogens are a group of chemical compounds structurally similar to natural estrogens that mimic the action of natural hormones. Xenoestrogens include substances such as diphenol A (BPA), dimethylacrylated diphenol A (BAD), triethyl dimethyl acrylate glycol (TEGDMA), herbicides, pesticides, PCBs, plasticizers and polystyrenes. These chemicals are widely used in industry, agriculture and households. Environmental research conducted for years has shown that substances that disrupt the functioning of the endocrine system accumulate in the environment in an increasing amount, and thus also in the human body. To provide information on the environmental impact of chemicals, including xenoestrogens, on human health at work, the issues related to occupational health hazards related to the use of pesticides, phthalate release and associated health risks, the health impact of polychlorinated dibenzodioxins and dibenzofurans and the health impact of pollutants released into the environment as a result of landfill fires, were addressed in this study. It has been shown that xenoestrogens, classified as endocrine disruptors, are present as pollutants practically everywhere: in sewage, water, soil, air, food and in everyday products, including household chemicals and cosmetics. The above means that a large part of the human population around the world is exposed to xenoestrogens both, in private and professional life (at work). Long-term exposure to even low doses of xenoestrogens may ultimately have

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a negative impact on human health, leading to disturbances in the endocrine system, as well as contributing to the development of neoplastic diseases. The most dangerous is the exposition to xenoestrogens in the early intrauterine period of fetal development or puberty. Considering the above facts, environmental exposure to xenoestrogens should be of particular interest to public and environmental health at every stage of human life.

Keywords: xenoestrogens, exposure, subjection, environment, health.

INTRODUCTION

Other than bringing about economic and civilizational growth, the industrial revolution, whose onset took place in the 19th century, contributed to the increase in the pollution of the environment. During the production process, chemical substances are released into the environment through elution from manufactured products, landfilling and waste disposal. In this manner, they become potential risk factors for the health. Many of these chemical substances have a detrimental effect on the physiological functions of the organism, especially the human endocrine system and they are thus referred to as endocrine disrupting compounds (EDCs). It is estimated that there are about 1000 chemicals with endocrine-acting properties (Kabir et al. 2015, Xin et al. 2015, Yilmaz et al. 2020).

The issue of endocrine disruption is the subject of a multitude of research and articles. Studies show that EDCs are related to changes in reproductive functions of men and women alike, an increased rate of breast cancer development, incorrect height patterns and neurodevelopmental retardation of children, as well as changes in the immune function. As defined by the World Health Organization, EDC is "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." Exposure to EDCs may take place during water or food product consumption, the intake of dust, inhaling gases and particles in the air, or through the skin. They can also be passed down from a mother to a developing fetus or to her child through the placenta or breast milk, respectively (Marino 2014, Stypuła-Trębas et al. 2015, Kulik-Kupka et al. 2017, Paterni et al. 2017, Ripamonti et al. 2018, Ochwanowska et al. 2019, Chmielewski et. al. 2020, 2020*a*).

The aim of the study is to present the influence of environmental pollutants which disturb the human endocrine system. To practically illustrate the purpose of the work, publications relating to pesticide exposure issues; phthalates; polychlorinated dibenzodioxins and dibenzofurans as well as pollutants released into the environment as a result of fires in landfills and the related health risks, were presented.

XENOESTROGENS

Xenoestrogens are a group of chemical compounds of exogenous origin, widespread in the environment, exhibiting the ability to interact with the endocrine system through actions that mimic natural hormones – estrogens. An xenoestrogen binds to estrogen receptors to imitate natural hormones, thereby having a possible detrimental effect on the human health. Xenoestrogens can be of synthetic or natural origin alike (Forma et al. 2013, Paterni et al. 2017, Hu et al. 2020).

Whether a compound is classified as a xenoestrogen or not is determined by the way it affects the organism rather than its chemical structure (Gałamon, Liwarska-Bizukojć 2018).

Xenoestrogens include substances used in manufacturing, agriculture and the household, such as polychlorinated biphenyls, pharmaceutical estrogens, chloroorganic compounds present in pesticides, phthalate esters, isoflavones, lignans, coumestans, stilbenes, phytoestrogens, metalloestrogens, alkylphenols, parabens and UV filters (Matejczyk, Zalewski 2011, Engler, Lemley 2013, Forma et al. 2013, Gore et al. 2015, Chmielewski et al. 2016, Sawaniewska et al. 2019).

In the Anglo-Saxon understanding, xenoestrogens are classified as endocrine disrupting compounds (EDCs) or endocrine disruptors (EDs) (Dobrzyńska 2015, Paterni et al. 2017, Słowikowska-Hilczer 2018).

In the research, Paterni et al. pose that natural xenoestrogens include compounds such as phytoestrogens (PhyEs), mycoestrogens and narcotic drugs, meanwhile they classified compounds produced through chemical synthesis as synthetic xenoestrogens. Their study included an evaluation of natural and synthetic xenoestrogens as far as their biological activity and sources are concerned, the results of which are illustrated in Table 1 and Table 2 (Paterni et al. 2017).

A literature review can also provide one with a classification of XEs into subgroups, which include: phytoestrogens, metals, pesticides and synthetic compounds (Bronowicka-Kłys et al. 2016).

Xenoestrogens include chemicals in plastics such as bisphenol-A (BPA), phthalates and polyvinyl chloride (PVC), pesticides and insecticides like DDTs, polychlorinated biphenyls (PCBs), parabens and placental extracts in cosmetics, aromatic amines, industrial solvents like benzene and toluene, and air pollutants such as polyaromatic hydrocarbons (PAHs) (Dey et al. 2010, La Marca, Gava 2017, Ripamonti et al. 2018).

XENOESTROGENS IN THE ENVIRONMENT, FOOD AND PRODUCTS OF EVERYDAY USE

The ubiquitous nature of xenoestrogens in the environment has been confirmed by research whose purpose was the indication of the level of polychlorinated biphenyl congeners in edible fungi in the Warmia and Masuria

Table 1

Selected natural xenoestrogens: biological activity and sources

Natural xenoestrogens	Compounds		Activities[1]	Sources[2]
Phytoestrogens	Lignans[3]	Lariciresinol	cardioprotective (clinical trial) reduced risk breast cancer *(in vitro)*	berries, seeds, grain, nuts, fruits and cruciferous vegetables
		Matairesinol		
		Pinoresinol		
		Secoisolariciresinol		
	Chalcones	Isoliquiritigenin	increased breast cancer risk *(in vitro)*	*Glycyrrhiza glabra*
	Other structure	Pterostilbene	neuroprotective *(in vitro)*	grapes and berries
	Flavonoids[4]	Apigenin	protective role in prostate cancer cells *(in vitro)*	parsley and mint
			protective role in colorectal cancer cells *(in vitro)*	
		Daidzin	*in vitro* estrogenic activity	*Pueraria mirifica* leaves
		Liquiritigenin	antinociceptive activity *(in vivo)*	*Glycyrrhiza uralensis* root
Mycoestrogens	Zearalenone		false pregnancy *(in vivo)*	contaminant in corn, oats, wheat, rice (produced by Fusarium species)
			decreased fertility *(in vivo)*	
			negatively affects male reproductive system *(in vitro)*	
Drugs of abuse	Δ^9-Tetrahydrocannabinol		affects ERα/ERβ ratio *(in vitro)* and reproductive behavior	marijuana

[1] The activity is mediated by interaction with ERs.
[2] For details, see USDA database. The origin is reported when specified in the reference paper.
[3] Metabolized to active enterolignans (enterolactone and enterodiol).
[4] Generally found in soybean, plants, berries, wine, seeds, grains, nuts and legumes.

region in Poland. Warmia and Masuria is a region where forests constitute over 30% of the territory, thereby it is an area referred to as the "Green Lungs of Poland". As the focus in the region's economy is on tourism, industries are poorly developed, therefore the effect of the emission of fumes or any other such risks is not large. The studies used five species of fresh fungi native to the region: Greville's bolete (*Suillus grevillei*), golden chanterelle

Table 2

Selected synthetic xenoestrogens: biological activities and sources.

Synthetic xenoestrogens	Activities	Sources
Bisphenol A (BPA)	correlated with hormone related cancer	generally found in plastic and, consequently, as contaminants in foodstuff, fruits and vegetables
	alteration neuroendocrine system	
	altered development observed in aquatic species	
	negatively affects pregnancy and development	
Bisphenol S	cardiotoxicity	
Dibutyl phtalate	negatively affects pregnancy and development	
Benzylbutylphtalate	negatively affects pregnancy and development	
Butylated hydroxyanisole	*in vitro* estrogenic/antiestrogenic activity	food preservatives
Polychlorinated biphenyls	neurological and hormonal diseases	used as coolant, plasticizers and pesticides and found in several food supplies
Ethynil estradiol	reduced fertility and fecundity	pharmaceuticals (found in aquatic environment)
	behavior changes in aquatic species	
TCDD	carcinogenicity, hepatotoxicity, immunotoxicity reproductive and developmental toxicity	environmental contaminant

(*Cantharellus cibarius*), bay bolete (*Xerocomus badius*), penny bun (*Boletus edulis*), parasol mushroom (*Macrolepiota procera*). The studies showed that fresh mushroom had the highest concentration of polychlorinated biphenyls, with 13.11 μg kg^{-1} of lipid substance. Taking into consideration the fact that PCB congeners accumulate in the human body even at small amounts, they can pose a threat to the health for a long period of time (Kotlarska et al. 2010).

Xenoestrogens as chemical compounds are commonly present in the environment. They are found in plants, food, cosmetics, pharmaceutical drugs, plastic materials, tin food containers, infants' feeding bottles and even children's toys (Marino et al. 2014, Gore et al. 2015, Bronowicka-Kłys et al. 2016, Ripamonti et al. 2018, Chmielewski et al. 2019).

The release of both industrial and domestic sewage is the source of pollution of the environment and leads to the accumulation of xenoestrogens in the soil, air, as well as surface and ground waters. Literature states that

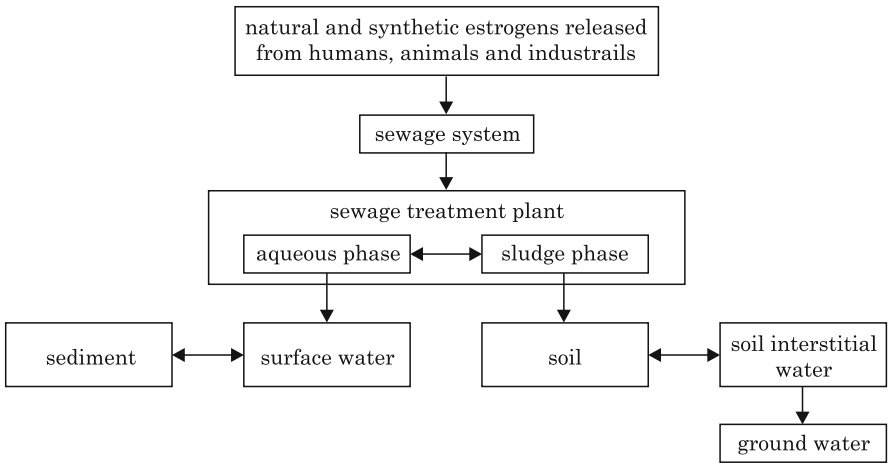

Fig. 1. EDCs distribution in the environment

xenoestrogens were identified in various aqueous environments, including sewage from treatment plants, rivers, lakes, seas, oceans and even drinking water (Citulski, Farahbakhsh 2010, Engler, Lemley 2013, Jin et al. 2013, Abdallah 2016, Kessler et al. 2019).

EDC distribution in the environment is illustrated in Figure 1 (Abdallah 2016).

As part of their research, Sodré et al. detected xenoestrogens (BPA) in water samples taken from the basin of the Atibaia river in the state of São Paulo in Brazil. BPA levels ranged from 25 to 84 ng L^{-1} (Sodré et al. 2010).

Xenoestrogen (parabens and BPA) pollution of surface waters was discovered in the Great Pittsburgh Region by Renz et al. Based on the research conducted, the authors came to the conclusion that it was caused by an obsolete sewage system. According to them, personal hygiene products and plasticizers could have potentially spread to the water through treated and untreated wastewater (Renz et al. 2013).

In their research aimed at determining potential health risks related with newly emerging chemical pollutants in the main rivers and treated water, Kessler et al. produced a summary table of the data related to EDC concentrations. Data related to EDC concentrations in surface waters, rivers, settlements, and tap water that emerged in their research are presented in Table 3 (Kessler et al. 2019).

A literature review will reveal studies related to the exposure to xenoestrogens present in the air (Liu et al. 2015). Fucic and Alberto show a relationship between traffic and the xenoestrogen pollution in the air (Fucic, Alberto 2016). The release of xenoestrogens, and consequently their pollution of air, also takes place during waste incineration as well as landfill fires (Chmielewski et al. 2020, 2020*a*).

Table 3

Concentrations of emerging contaminants (μg L^{-1}, μg kg^{-1})

EDC	Concentration (ppb)	μg L^{-1}	μg kg^{-1} (in sediments)	Presence in tap/ drinking water
Atrazine (ppb)	0.19 to 1.88 (Ohio River)			detected in 28 U.S. states
Bis-phenol A		0.016-0.5		detected in Asia, Europe, North America
Chlorpyrifos	0.24 (ground water, MN)	0-2.828		detected in drinking water
Endosulfan		<1 (WHO), 0.020-0.11		detected in drinking water
Nonyl phenol		0.1-0.5 (Ohio Tributary) 0000.1-0.0027 (tap water, Chongqing China)	75-340 (Ohio Tributary)	detected in drinking water
Buprenorphine		0.042–0.195 (sewage water, Paris)		detected in waste water

Bisphenol A (BPA) is identified in the outdoor and indoor air (Rudkowski 2013). Other studies also show a possible presence of BPA in the indoor air environment (La Marca, Gava 2017).

At room temperature, BPA has the ability to migrate from polycarbonate bottles to food or mouth plates of pacifiers, where it can spread to the organism (Aliprandini et al. 2011, Cooper et al. 2011).

Food is one of the primary exposure pathways to endocrine disrupting compounds for humans, e.g. phytoestrogens (PhyE). It is due to the presence of xenoestrogens in food products (Guzik et al. 2014, Ochwanowska et al. 2019).

Xenoestrogens are highly lipophilic substances that can accumulate in food with high fat content, red meat, milk, and dairy products. (Matejczyk, Zalewski 2011, Sawaniewska et al. 2019). Studies show that milk and dairy products are contaminated with xenoestrogens (Farke et al. 2011, Stypuła-Trębas et al. 2015, 2017).

Xenoestrogens can also be found in more complex compounds that are contained in paints, varnishes, substances coating the inside of food cans, many types of plastics as well as during the production of cosmetics, perfumes, deodorants, and shampoos (Matejczyk, Zalewski 2011, Biesterbos et al. 2013, Ripamonti et al. 2018). Studies indicate the use of phthalates in personal hygiene products (Orecchio et al. 2015) and the use of parabens as preservatives in cosmetics, pharmaceutical drugs, and food additives (Świerkot et al. 2017).

THE EFFECT OF XENOESTROGENS ON THE HEALTH

Laboratory analyses used in disease diagnosis allow one to detect the presence of chemical substances absorbed from the environment in the blood and tissues. Substances that are often detected include bisphenol A (BPA), phthalates, flame retardants, fluoropolymers, and pesticides (Rudkowski 2013).

Xenoestrogens raise much concern due to their potential effect on the human endocrine system (Kulik-Kupka et al. 2017, Paterni et al. 2017, Ripamonti et al. 2018, Kessler et al. 2019, Yilmaz et al. 2020).

The exposure of the organism to estrogenic compounds in different periods of the life may facilitate the development of dysfunctions or even tumors of hormone-dependent tissues (Hilakivi-Clarke et al. 2013).

The human body is not usually exposed to one particular substance, but rather a mixture of various substances, which may work synergically or antagonistically to each other. While estimating the potential effects of exposure, the age of the victim of exposure, type of substance, period of exposure, and size of the dose have to be taken into account. It also has to be taken into consideration that endocrine disrupting compounds are active in doses smaller than the toxic dose threshold. Moreover, it needs to be considered that a long time may elapse between the exposure to those compounds and the emergence of the first disease symptoms (Kotlarska et al. 2010, Muncke 2011, Biesterbos et al. 2013, Kulik-Kupka et al. 2017, Elonheimo et al. 2021).

Over the years, various health complications manifesting in men, such as a higher incidence of testicle cancer, decrease in sperm quality or malformations of genital organs (Toppari et al. 2010, Snoj, Majdič 2018), as well as in women, such as a higher incidence of breast cancer, reproductive system tumors (Gibson, Saunders 2014, Konduracka et al. 2014, Vogl 2015, Rogowska et al. 2019), were observed, which contributed to a significant increase of the interest in the cause of their origin. A multitude of studies showed that xenoestrogens, exogenous substances exhibiting estrogen-like properties, are responsible for many of those diseases, and have an effect on the development and condition of the human reproductive system (He et al. 2015, Sheikh et al. 2017, Yuan et al. 2018, Gonzalez et al. 2019).

Epidemiological research suggests a relationship between the consumption of dairy products (especially, whole milk) containing xenoestrogens and the risk of prostate cancer development (Pettersson et al. 2012, Song et al. 2013). Higher consumption of dairy was related to a greater risk of testicle cancer (Giannandrea et al. 2013). There is also a hypothesis that estrogens in milk play a significant role in supporting ovary cancer development (Ganmaa et al. 2012).

Xenoestrogens may embed themselves into the sperm cell membrane and, as a result, decrease the mobility of the semen (Sawaniewska et al. 2019).

Liu et al. examined the relationship between breast cancer risk and the exposure to ambient factors disrupting estrogen activity amongst the participants in a large cohort study, the California Teachers Study. They observed an elevated risk of hormone-responsive-negative tumors in the case of greater exposure to cadmium compounds and probably inorganic arsenic amongst people who have never smoked. Analyzing the results, they came to the conclusion that long-term exposure to low doses of cadmium compounds in the environment, or probably inorganic arsenic, may be a risk factor for breast cancer (Liu et al. 2015).

In the paper, Fucic and Alberto indicate a relationship between the xenoestrogen-polluted air as a result of traffic and the possible increased risk of breast cancer development (Fucic, Alberto 2016).

Exposure to xenoestrogens is primarily related to endocrine system disruptions, the dysfunction of the reproductive system, the dysfunction of the immune system, and the risk of breast, prostate and uterus cancer. Studies also show a correlation between a lower weight at birth, premature childbirth, developmental defects, behavioral changes and a lower IQ of the progeny. Xenoestrogens are also considered to have an effect on the occurrence of diabetes, obesity, metabolic syndrome, reduction of sperm cell count, lower testosterone concentration, liver, kidney and heart damage, impact on the immune system resulting in a higher susceptibility of infection (Hilakivi-Clarke et al. 2013, Fucic, Alberto 2016, Kulik-Kupka et al. 2017, Paterni et al. 2017, Ripamonti et al. 2018, Chmielewski et al. 2019, Kessler et al. 2019, Rogowska et al. 2019, Chmielewski et al. 2020, 2020*a*).

The effect of xenoestrogens on the endocrine system, and thus, on human health, has been the subject of a longitudinal study conducted by The Endocrine Society. The Endocrine Society's analyses and research resulted in the publication of the 2nd statement on the impact of environmental chemicals known to be endocrine disruptors (EDCs) on human health and possible diseases (Gore et al. 2015). The effects of EDCs on the human body are shown in Table 4 (Gore et al. 2015).

CONCLUSION

The significant development of the production sector of the economy, and consequently the growth of manufacturing and the use of chemical substances, exposed the human body to to the chemicals introduced into the environment in considerable quantities, with such consequences as the human body's dysfunctions and the development of many diseases.

Monitoring concentrations of chemical substances in different elements of the environment, as well as products of everyday use, is crucial for the health risk assessment of the exposure to endocrine disrupting compounds,

Table 4

Mode of action for EDCs

EDC	Mechanism	Mode of action
BPA	nuclear receptor	ER agonist; strong affinity for ERRγ; antiandrogen; increased PR expression; hPXR agonist
	ER-mediated nongenomic pathway	activates membrane-associated ERα, Erβ signaling cascades through PI3K-pAkt and MAPK-pErk and GPER-pErk pathways
	nonsteroidal receptor	antagonist of ThR; binds to GPR30
	ion channels	activates membrane ERβ-Ca^{2+} pathway; activates ERβ-KATP and Ca^{2+} mobilization; up-regulation of Ca^{2+} ion channel gene and protein, Orai1
	uninhibited growth	alters MaSC gene expression and induces early neoplastic lesions; induces beaded ducts and increases hyperplasia
	inflammation	induces proinflammatory cytokines and chemokines
DDT and metabolites	nuclear receptor	binds and transactivates ERα and ERβ; DDE binds AR and represses transcription
	microenvironment/stroma	induced estrogenic microenvironment in breast adipose tissue
DES	nuclear receptor	ERα agonist; AR binding; suppresses activation of ERR α, β, and γ
	ER-mediated non-genomic pathway	activates MAPK and PI3K and induces phosphorylation of ERK
	epigenetic	hypermethylation of HOXA10; DNA methylation
Dioxins	nonsteroidal receptor	binds to AhR
	coactivator recruitment	recruitment of coactivator p300
PCBs	steroid hormone biosynthesis	inhibits sulfotransferase, inhibits aromatase; increases T4 glucuronidation, competes with thyroid hormone binding proteins
	nuclear receptor	weak binding to ER, weak binding to AR
PFOA	nuclear receptor	binds to ER and EREs
	nonsteroidal receptor	PPARα agonist
	uninhibited growth	increased hyperplasia and stromal density
Phthalates	nuclear receptor	DBP weak affinity for ER
	microenvironment/stroma	MEHP induced PPARβ in adipose

Abbreviations: EREs – estrogen response elements, ERR – estrogen-related receptor, PI3K – phosphatidylinositol-3-kinase.

including xenoestrogens. As regards the broadly understood issue of public health, including the wellbeing of the population and cancer prevention, it is important to carry out large-scale educational activities for the entirety of society. The aim should be to disseminate information on existing dangers related to chemical substances in common use. Raising awareness in a society should help decrease environmental pollution and, as a consequence, depress the exposure to chemical substances and limit their detrimental effects on the health.

The data presented in this article highlight the need for an implementation of an environmental health strategy in the context of joint actions related to public health and environmental protection.

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