Xenoestrogens: environmental ubiquity, endocrine disruption, carcinogenic potential, and regulatory challenges

Martyna Zdych[1*], Zuzanna Cisowska[1], Zofia Wojciechowska[1], Maria Wiszniowska[1], Emilia Kucharczyk[1], Dagmara Gaweł-Dąbrowska[3]

*Corresponding author: martyna.zdych@student.umw.edu.pl

1. Faculty of Medicine at the Wroclaw Medical University, Wybrzeże L. Pasteura 1, 50-367 Wrocław
2. Division of Public Health, Faculty of Health Sciences Wroclaw Medical University

Received: 28 October 2024 / Accepted: 23 June 2025

Abstract. Xenoestrogens are chemicals that mimic natural estrogens and disrupt hormonal balance, posing health risks such as endocrine disruption and cancer. Recent studies have demonstrated the widespread presence of xenoestrogens in various environmental matrices, encompassing not only pesticides and industrial chemicals but also water, soil, air, and consumer products. Exposure during critical periods such as fetal development and puberty is of particular concern. Increased awareness of the effects of xenoestrogens on hormonal and reproductive health is essential to address their potential long-term health impacts. The presented paper discusses the principal sources of xenoestrogens, elucidating the endocrine mechanisms they activate, and delineating the potential risks associated with neoplastic development.
Key words: xenoestrogens, endocrine disruptors, reproductive health, hormonal homeostasis
Materials and methods: To obtain up-to-date information on trends in xenoestrogens, PubMed and Google Scholar databases, along with the latest legislative reports in Europe and Poland, were reviewed.
Aim of the study: This study aimed to explore current research on the mechanisms, health impacts, environmental implications, and potential neoplastic threats related to xenoestrogens across diverse ecosystems, with a specific emphasis on their effects on human health and well-being.

1. Introduction

Xenoestrogens, also known as Endocrine Disrupting Compounds (EDCs), are environmental hormones that resemble the activity of estrogen. Some are of natural origin, whereas others can be industrially produced. They possess the capacity to associate with intracellular estrogen receptors, thereby exerting estrogenic effects on the respective organism.

It is presumed that when an organism is exposed to xenoestrogens, it may develop negative aftermaths, such as disorders of the endocrine and reproductive systems, as well as neoplastic changes. Nevertheless, they can also be useful as inhibitory factors for some cancer-related ailments. Thus it is valid to say that these substances are clinically significant.

EDCs are a wide group of chemicals that can behave similarly to natural and synthetic estrogens. Although they have been present for a long time in the natural environment, they have been massively introduced into the global industry in recent years. Found in many commodities of ordinary use, they can be recognized in different species of plants (phytoestrogens), fungi (mycoestrogens), and types of metals (metalloestrogens), as well as in cosmetics, pharmaceuticals, and many more artificial products (e.g., bisphenol A (BPA)). As previously mentioned, not all of them have detrimental effects on living organisms (Wang et al., 2021; Wang et al., 2021).

2. Examples of xenoestrogens and their sources

Presently, there is an escalation in the environmental impact of xenoestrogens. There have been many reports on its presence in rivers, food containers, and cosmetics. Therefore, awareness of the clinical impact and knowledge of how to avoid contact with them should be raised. In this section, we focus on the sources of exemplary xenoestrogens, which come in many different forms (Figures 1 and 2).

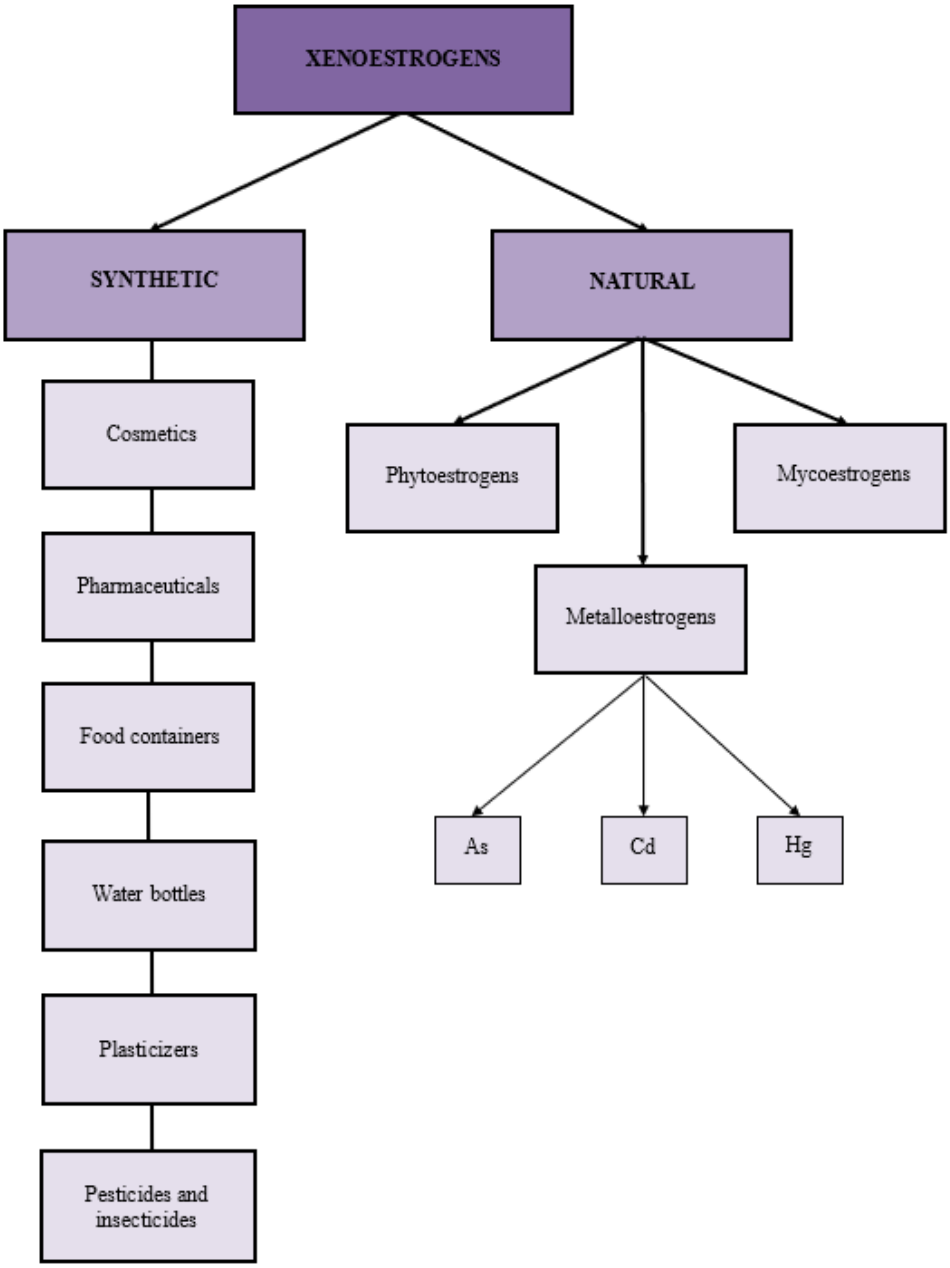

Figure 1. Types of Xenoestrogens and Their Sources

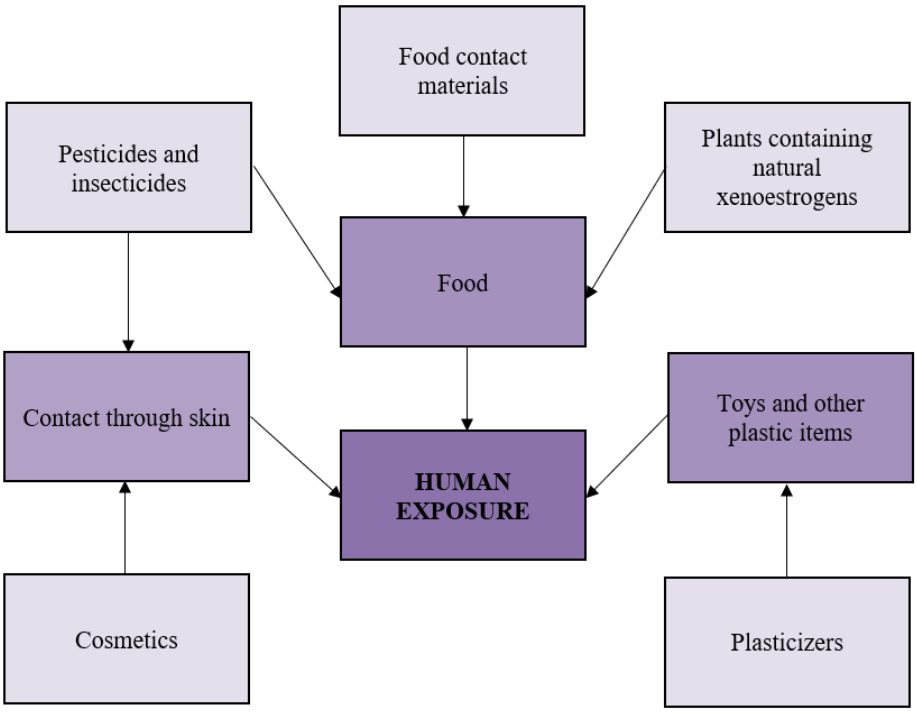

Figure 2. Main Sources of Human Exposure to Xenoestrogens

2.1 Plants

Phytoestrogens are xenoestrogens found in plants, with isoflavones being prominent examples. The most important of these are genistein (GEN), daidzein (DAI), and glycitein (Křížová et al., 2019). As shown in Table 1, many xenoestrogens are of natural origin.

Isoflavones can be found in many plants, such as red clover and alfalfa, as well as in food vegetables, such as soybean and other legumes (Křížová et al., 2019). Numerous studies have focused on the potential utility of xenoestrogens given their efficacy in disease prevention and therapy across various ailments. Nevertheless, there are still some concerns regarding the results of their application, as some side effects have been observed (Wang et al., 2021).

Vegetables are also a source of metals that can be classified as metalloestrogens. This is particularly true for heavy metals, such as arsenic (As), cadmium (Cd), and mercury (Hg) (Table 1).

Table 1. Natural Xenoestrogens: Biological Activities and Sources

Natural Xenoestrogens	Class and examples	Activities	Sources
Phytoestrogens (PhyEs)	Lignans, e.g. Lariciresinol Matairesinol Pinoresinol Secoisolariciresinol	Cardioprotective, Reduced risk of breast cancer	Berries, seeds, grains, nuts, fruits and cruciferous vegetables
	Flavonoids (main class of PhyEs), e.g. Genistein, Daidzein, Puerarin, Genistin, Glycitein	Neuroprotective, Protective role in colorectal, prostate cancer, Protective in AD and PD	Red clover, dyer's broom, lucerne, sohphlang flax, soybean and legumes, cauliflower or broccoli
	Chalcones e.g. Isoliquiritigenin	Increased breast cancer risk	Liquorice (Glycyrrhiza glabra)
	Other structure e.g. Mangiferin, Norathyniol, Oleocanthal	Activate Erα or ERβ in breast cancer cells, Anti-inflammatory, Antiproliferative, Neuroprotective	Mango fruit, Olive oil
Metalloestrogens	Arsenic (As), Cadmium (Cd), Mercury (Hg)	Cause of many systemic disruptions, e.g. gestational diabetes mellitus, Ability to bioaccumulate	Some vegetables
Mycoestrogens	Zearalenone	Decreased fertility, Negatively effects on male reproductive system, False pregnancy	Contaminant in corn, oats, wheat, rice (produced by Fusarium species)

2.2 Food and packaging

Of the many synthetic xenoestrogens presented in Table 2, one of the most well-known is bisphenol A. BPA has long been used in the industry, primarily in metal can coatings, plastic bottles, and thermal paper (Zbucka-Kretowska et al., 2018). Recent studies have highlighted its

toxicity, revealing its ability to disrupt the endocrine system and migrate from packaging to food (Tumu et al., 2023). BPA is also linked to the development of hormone-related cancers (Komarowska et al., 2022).

Another group of xenoestrogens is phthalates, which are widely used as plasticizers owing to their softening effects. They can permeate food, water, and other products that are applicable to the human body. Nevertheless, they have been found in food contact materials (FCM), medical devices, and some personal care products (Kiwitt-Cárdenas et al., 2021). Even toys for infants when sucked can be a source of these xenoestrogens (U.S. Environmental Protection Agency et al., 2017). Some bisphenols, phthalates, and their analogs are considered dangerous. To mitigate the risk of adverse human health effects, various global regulations have been implemented that impose limits on the concentration of bisphenols for application in FCM (Paterni et al., 2017).

2.3 Cosmetics

Compounds utilized in cosmetics, such as parabens, exhibit estrogenic characteristics. They are frequently integrated into makeup and personal care items, including sunscreens, deodorants, and toothpaste. Owing to their application in diverse regions of the human body, they have the potential to permeate the skin, accumulate, and cause endocrine disruption. Cosmetics are often spread around the breasts and underarms, so there are some conjectures that parabens may influence the development of breast cancer. Considering their potential involvement in activating estrogen receptor α, such a hypothesis appears plausible (Dairkee et al., 2023).

2.4 Environmental pollutants (pesticides and insecticides)

Pesticides are chemicals designed to eliminate pests. However, some are biologically potent and can bioaccumulate. They can also contaminate crops consumed by humans (Pathak et al., 2022). The representatives of this group are OCPs - organochlorine pesticides, which have the ability to bind to estrogen receptors (Kumar et al., 2022). In the case of insecticides, the example is set by OPs - organophosphates. Although their use is associated with an increased risk of breast cancer, they are still one of the most frequently used insecticides. Not only the unconscious consumption of these EDCs is a serious concern - there is some proof that persistent exposure during work in the agriculture
sector might lead to the development of different diseases such as non-Hodgkin lymphoma or hormone-related cancers (Table 2) (Yang et al., 2020).

Table 2. Synthetic Xenoestrogens: Biological Activities and Sources

Synthetic Xenoestrogens	Activities	Sources
Bisphenol A	Alteration endocrine system Associated with hormone-related cancers Increases intracellular levels of ROS Changes in the expression of histone-modifying enzymes Increases sperm DNA fragmentation index Changes in genes associated with metabolic and reproductive processes Associated with miscarriages	Found in personal care products, pharmaceuticals, metal can coatings, plastic bottles, thermal paper, and as contaminants in foodstuff, fruits and vegetables.
Phtalates	Changes in genes associated with metabolic and reproductive processes Associated with males' infertility Negatively affects pregnancy and development	Used as plasticizers. Found in food contact materials, medical devices, personal care products, toys, and as contaminants in foodstuff, fruits and vegetables.
Parabens	Estrogenic activity Ability to accumulate Associated with hormone-related cancers (e.g. breast cancer)	Personal care products
Organochlorine pesticides	Ability to accumulate Estrogenic activity Associated with hormone-related cancers Negatively affects pregnancy and development	Used as pesticides. Found in fruits and vegetables.
Organophosphates	Associated with hormone-related cancer (e.g. breast cancer)	Used as insecticides.

3. Interactions with estrogen receptors

Owing to their chemical structure, xenoestrogens can affect natural estrogen receptors, and by binding to them, they might act as agonists, antagonists, or modulators of estrogen receptors (Wang et al., 2021). It has been proven that these substances show affinity not only

to these receptors but also to progesterone, androgen, thyroid and corticosteroid receptors. The effects on the receptors may be both direct and indirect. An example of their indirect action is the blockade of thyroid receptors, which are connected to estrogen receptors. Through an uncertain mechanism, they affect them and can cause various effects (Waring et al., 2005).

There are two types of estrogen receptors. We differ in ERα and ERβ, both of which belong to the type of nuclear receptors called steroid hormone receptors. (Mal et al., 2020). One of the main differences between them is their distribution in the tissues. ERα is expressed in the mammary gland, ovary, uterus, testes, epididymis, prostate, bone, adipose tissue, and the liver. Meanwhile, ERβ is located in the ovaries, testes, prostate gland, bladder, and lungs (Heldring et al., 2007). Both ERα and ERβ also appear in the central nervous and cardiovascular systems (Dębska et al., 2010). Likewise, the function is the aspect that distinguishes these two subtypes of estrogen receptors. While the alpha subtype primarily affects the uterus and mammary glands, playing a role in metabolic regulation and maintaining skeletal homeostasis, ERβ is involved in regulating programmed cell death, modulating antioxidant gene expression, adjusting immune responses, influencing the risk of heart failure, and modulating anxiety-driven behavior (Koehler et al., 2005). It is also worth mentioning that ERα supports cell proliferation, while subtype β has an opposing effect (Heldring et al., 2007). Even though they have some differences, both subtypes of estrogen receptors participate in the formation and function of the ovaries, as well as preservation of the cardiovascular system (Heldring et al., 2007; Dębska et al., 2010).

Estrogens typically exert their steroidal influence on target tissues through two cellular pathways: via the nucleus and plasma membrane. In the nuclear mechanism, estrogen compounds can bind as ligands to both subtypes of estrogen receptors, causing their translocation to the nucleus. Inside the nucleus, the estrogen – receptor complex binds to specific transcription elements, defined as estrogen response elements (ERE), initiating the transcription of target genes (Heldring et al., 2007). The proteins encoded by these genes participate in cell survival, proliferation, and tumor growth (Dębska et al., 2010).

Among the most crucial compounds facilitated by the activation of these receptors are insulin-like growth factor receptor 1, cyclin D1, anti-apoptotic protein BCL-2, vascular endothelial growth factor, HER and its ligands, transforming growth factor alpha (TGF-α), and amphiregulin (Dębska et al., 2010). The second pathway is the membrane-mediated pathway, which is independent of the cell nucleus. A small fraction of estrogen receptors are located near the cytoplasmic membrane. The interaction between the ligand and membrane-bound ER or G-protein-coupled E2 receptors triggers the activation of a signaling cascade. This cascade affects cell metabolism through secondary messengers (Wnuk et al., 2023).

4. Endocrine mechanisms and their effects on hormonal homeostasis.

Xenoestrogens not only affect various receptors but also disrupt hormonal homeostasis at multiple levels. Despite their similarity to endogenous estrogens, these endocrine disruptors can do more than mimic natural hormones. They may counteract natural hormones, interfere with hormone synthesis, metabolism, and transport, and disrupt hormone receptor formation (Maniradhan et al., 2023).

Cholesterol is the precursor of steroid hormones, such as estrogens, which are synthesized through modifications involving cytochrome P450 isoforms. Recent studies have shown that xenoestrogens influence steroid production by modulating the cytochrome activity. Estrogens and their precursor, dehydroepiandrosterone (DHEA), are transported in the bloodstream as sulfate esters, which prevent cell entry until hydrolysis by sulfatases. Xenoestrogens can alter estrogen availability by interfering with sulfation or desulfation enzymes, potentially increasing or decreasing the estrogen levels, respectively. Additionally, xenoestrogens may disrupt estrogen inactivation through sulfation, thereby increasing the level of active endogenous estrogens. They also negatively affect the neuroendocrine system by affecting the thyroid gland. It has been shown that these substances not only obstruct the attachment of thyroxine to thyroxine-binding globulin (TBG), but they can also bind to the thyroid receptor due to their structural similarity to thyroid hormones. The outcomes arising from the mechanisms of action of xenoestrogens outlined above disrupt endocrine homeostasis, leading to obesity, fatty liver disease, insulin resistance, polycystic ovary syndrome (PCOS), neurotoxicity, and carcinogenesis in certain hormone-sensitive tissues, etc. (Waring et al., 2005; Maniradhan et al., 2023).

5. Genotoxic and epigenetic effects

Xenoestrogens influence gene expression by exerting genotoxic or epigenetic effects. The genotoxic effects of estrogenic compounds are primarily caused by chromosomal aberrations or DNA damage (Amir et al., 2021).

5.1 Chromosomal aberration

Chromosomal aberrations are among the most dangerous cellular changes. Among them, we distinguished chromosomal aneuploidies, which signify any changes in the structure or number of chromosomes. Endogenous estrogens play an important role during meiosis because of their influence on chromosomal segregation and microtubule assembly. Xenoestrogens interfere with the estrogenic pathway, causing defects in chromosome synapsis during meiosis. Additionally, they interfere with the mechanisms responsible for repairing

double-stranded breaks during cellular division (Allard et al., 2010). All these factors have an impact on the reproductive system and lead to the formation of faulty gametes with chromosomal aneuploidies, often resulting in infertility and miscarriages as well as developmental defects and sterility in newborns (Hodes-Wertz et al., 2012).

5.2 DNA damage

Estrogens play a crucial role in shielding cells from oxidative stress by inhibiting their production, thereby preventing DNA damage. Xenoestrogens oppose this function of estrogens, thereby increasing the susceptibility of cells to DNA impairment (Amir et al., 2021). It has been proven that BPA increases intracellular levels of reactive oxygen species (ROS), and through this mechanism, causes damage to DNA. Sperm cells are particularly prone to DNA damage; therefore, xenoestrogens can lead to deterioration of semen quality and induce developmental abnormalities in offspring conceived by malfunctioning sperm (Chauhan et al., 2023).

5.3 Epigenetic effect

Xenoestrogens can also affect organisms by altering gene expression and function, without permanently changing the DNA sequence. These modifications are referred to as epigenetic alterations, serving as mediators between the environment and genes. The most important epigenetic modifications include methylation, histone modification, and non-coding RNAs. These changes appear to be heritable and can exert both positive and negative effects on the offspring (Manikkam et al., 2013).

5.4 Histone modifications

The most common histone modifications include ubiquitination, acetylation, phosphorylation, and methylation (Alaskhar Alhamwe et al., 2018). Estrogenic compounds can disrupt the histone code by inducing these modifications, leading to abnormal gene expression. For instance, women exposed to BPA showed altered expression of histone-modifying enzymes, potentially contributing to ovarian dysfunction (Rutkowska et al., 2014).

5.5 Methylation

Methylation is a key epigenetic mechanism involved in DNA regulation, where methyl groups attach to nucleotide bases, primarily cytosine. During lifetime, due to specific conditions, DNA methylation patterns can change, leading to the establishment of specialized methylation patterns in cells that regulate the transcription of tissue-specific genes (Kiselev et al., 2022).

Xenoestrogens are known for exerting influence on the methylation pattern in animals. By altering the methylation signature, they contribute to the development of heritable disorders (Dumasia et al., 2017). Many estrogenic compounds affect the expression of methyltransferase enzymes, and as a result can cause either hypermethylation or hypomethylation in various

tissues (Sklias et al., 2021). Alterations in the methylation pattern can not only have a negative impact on the female and male reproductive systems but also on other systems of the organism (Amir et al., 2021; Dumasia et al., 2017). These chemicals exert a detrimental influence on adipogenesis and embryonic development, among other processes, by interfering with the conversion of androgen to estrogen in gonads (Bjune et al., 2022).

5.6 Micro RNAs damage

MicroRNAs (miRNAs) are a group of non-coding, single-stranded RNAs. This type of RNA has a wide variety of functions and affects genes at the post-transcriptional level, cell cycle regulation, cell specialization, stress response, programmed cell death, inflammation, and mRNA firmness disruption (Budakoti et al., 2021).

Recently, it was suggested that miRNAs play a significant role in ontogenesis, as an altered miRNA profile may cause defects in the development of the genital system in both sexes. Due to their similar chemical structure to endogenous estrogens, xenoestrogens affect both miRNA expression and activity. These chemicals can suppress and/or increase the expression of various miRNAs. By altering miRNA expression, xenoestrogens lead to impaired spermatogenesis, infertility, and a higher susceptibility to the toxic effects of harmful agents in human placental cells, etc. (Avissar-Whiting et al., 2010; Sabry et al., 2019).

6. The influence of xenoestrogens on reproductive health and recent Research in this field

Owing to their structural resemblance to estrogens, xenoestrogens can affect the reproductive system of both males and females. Moreover, they can accumulate in the placenta and disrupt fetal development, thereby influencing their subsequent health (Avissar-Whiting et al., 2010). Xenoestrogens known to affect reproductive health include BPA, OCPs, polychlorinated biphenyls (PCBs), perfluoroalkylated substances (PFAS), and phthalate esters (PEs) (Table 2) (Manikkam et al., 2013; Rutkowska et al., 2014; Winstanley et al., 2024; Iribarne-Durán et al., 2024).

6.1 The influence of xenoestrogens on males' reproductive health

In men, xenoestrogens may lead to decreased fertility; however, the literature does not conclusively confirm their negative impact on fertility (Toppari et al., 1996). In a study conducted by Rozati et al., the levels of xenoestrogens (PCBs and PEs) in the semen of fertile and infertile men were compared. PCBs were not detected in fertile men, but were present in infertile men. Additionally, infertile men exhibited significantly higher concentrations of PEs in their sperms. Elevated levels of xenoestrogens in infertile patients correlated with significantly reduced semen parameters (decreased ejaculate volume, sperm count, rapid and

total progressive motility, normal morphology, vitality, sperm osmoregulatory capacity, nuclear chromatin decondensation, and sperm nuclear chromatin integrity) (Rozati et al., 2002). Recent research by Kiwitt-Cárdenas et al. (2021) also identified a probable association between high BPA concentrations in urine and a significantly increased sperm DNA fragmentation index (SDF) (Kiwitt-Cárdenas et al., 2021). This suggests that xenoestrogens may be one of the causes of reduced sperm quality and the consequent infertility (Table 2).

In male individuals exposed to xenoestrogens during fetal life, disruptions in the differentiation and development of reproductive organs as well as sexual behavior disorders in adult life may occur (Chauhan et al., 2023; Manikkam et al., 2013). Studies on rats have shown that fetal exposure to BPA, diethylhexyl phthalate (DEHP), and dibutyl phthalate (DBP) resulted in changes in genes associated with metabolic and reproductive processes, including genes regulating male sexual behaviors (Manikkam et al., 2013). Additionally, data suggest that rats perinatally exposed to butylbenzyl phthalate had reduced testicular size and decreased daily sperm production (Toppari et al., 1996).

6.2 The influence of xenoestrogens on females' reproductive health

Xenoestrogens can affect the reproductive health of pregnant women. Studies have shown that, similar to men, exposure of the female fetus to xenoestrogens can influence the differentiation of reproductive organs. Research on mice has revealed the impact of diethylstilbestrol (DES) on the expression of HOX genes responsible for the development of the Müllerian duct into reproductive organs. Mice exposed to DES during fetal life exhibited mutations in HOXA10 or HOXA11 genes, leading to uterine factor infertility (Taylor et al., 2008).

In addition to influencing the development of the reproductive systems of male and female fetuses, xenoestrogens may interfere with other organ systems in the developing fetuses. Studies have documented the passage of xenoestrogens from the maternal blood to fetal tissues, such as adipose tissue, liver, heart, lung, and brain, as well as their accumulation in the placenta. This may have further health consequences on the offspring and may be associated with miscarriages (Iribarne-Durán et al., 2024).

In women with a history of miscarriage, significantly higher levels of BPA are detected in the blood compared to women who have not experienced miscarriage. Furthermore, in some women with elevated BPA levels in the blood, neutrophil extracellular traps (NETs) and proinflammatory proteins (MCP-1, TNF-α, NOX1, and NCF2) are also present. This suggests that BPA may participate in the pathogenesis of miscarriage by promoting NET formation (Omeljaniuk et al., 2022). BPA may also adversely affect pregnancy outcomes by acting on the endocannabinoid system (Zbucka-Kretowska et al., 2018).

7. The mechanisms and impact of xenoestrogens on hormone-dependent tumors and recent research in this field

Xenoestrogens can influence the initiation and progression of various tumors – both classical hormone-dependent tumors and non-classical hormone-dependent tumors. This can be achieved through various mechanisms. One of them is binding to human sex hormone-binding globulin (hSHBG) and modulating the bioavailability of endogenous estrogens. By binding to hSHBG, endogenous testosterone and estradiol (E2) are displaced from their binding sites, increasing the levels of the free forms of these hormones in the blood. In addition, hSHBG can transport xenoestrogens to target tissues and cells. Studies have also demonstrated that xenoestrogens can stimulate steroidogenesis by enhancing aromatase expression, resulting in elevated E2 levels (Wang et al., 2021).

E2 activates ERα, which plays a significant role in the regulation of hormone-dependent tumors (Wang et al., 2021). Activation of ER-related signaling pathways is closely associated with the progression of many tumors, as it is linked to the regulation of downstream genes. Activation of ERα has been shown to have a pro-carcinogenic effect, whereas activation of ERβ is associated with an anti-carcinogenic effect (Song et al., 2022). Most xenoestrogens, including polybrominated diphenyl ether (PBDE) congeners, act as agonists of both ERα and ERβ, influencing cell proliferation, apoptosis, and migration (Arowolo et al., 2022). However, phytoestrogens, such as GEN, DAI, and coumestrol (COU), have a significantly greater affinity for ERβ, thus exhibiting anti-tumor effects (Wang et al., 2021).

Xenoestrogens can act on both healthy cells and tumor cells by generating reactive oxygen species (ROS). Oxidative stress, generated in part by xenoestrogens, such as BPA, is likely associated with estrogen-dependent breast cancer carcinogenesis. On the other hand, oxidative stress is essential for combating tumor cells. For this reason, the phytoestrogen COU is considered a potential chemotherapeutic agent for breast cancer (Wang et al., 2021).

7.1 The impact of xenoestrogens on breast cancer development

Breast cancer is one of the tumors most strongly associated with estrogen. Given the similarity between xenoestrogens and estrogens, several studies have been conducted on the impact of xenoestrogens on breast cancer (Table 2).

A study conducted in rodents sought to establish a link between BPA exposure and the development of breast cancer. The results suggest that BPA activates p53 and stimulates breast cancer cell proliferation. Other studies have found that BPA inhibits the expression of tumor suppressor genes. It has also been observed that BPA reduces the effectiveness of tamoxifen (TAM), used in breast cancer therapy, by preventing TAM from binding to the estrogen-related

receptor gamma (ERRγ) (Wang et al., 2021). Moreover, another xenoestrogen, flavonoid-genistein, has been found to reverse the therapeutic effects of TAM at low doses (Boszkiewicz et al., 2020).

A study was conducted to examine the impact of reducing the use of personal care products (PCPs) containing xenoestrogens (parabens and phthalates) on xenoestrogen levels in breast tissue (Reduced xenoestrogens intervention, REDUXE). Participants excluded PCPs containing xenoestrogens from their daily lives. The study results showed that REDUXE led to reduced excretion of xenoestrogens and their metabolites, and contributed to a decrease in the expression of pro-oncogenic genes present in breast tissue cells prior to the study (Dairkee et al., 2023).

7.2 The impact of xenoestrogens on the development of other tumors

Xenoestrogens may also influence the development of tumors other than breast cancer (Tables 1 and 2). A study conducted in patients with endometrial cancer demonstrated a positive correlation between the total effective xenoestrogen burden in serum samples (TEXB) and the risk of this cancer (Costas et al., 2024). Additionally, the ability of xenoestrogen benzophenone-1 (BP-1) to induce proliferation and metastasis of ovarian cancer cells through the activation of the ERα and Wnt/β-catenin signaling pathways has been observed. It has also been demonstrated that patients with meningiomas and gliomas exhibit higher levels of free and bound BPA than the healthy population. This suggests a connection between xenoestrogens and these tumors (Liu et al., 2022).

8. Current state of research on the impact of xenoestrogens on health

Due to the significant prevalence of xenoestrogens in the environment and their comprehensive impact on organisms, the area requiring research and widening of knowledge regarding their impact on disease progression and treatment methods continues to expand.

The correlation between the progression of hormone-dependent breast cancer and the effectiveness of chemotherapy depending on the concentration of xenoestrogens requires further investigation. Current knowledge suggests that phytoestrogens found in food products may reduce the effectiveness of standard therapies and promote disease progression. Clinical studies and a more detailed analysis of the impact of patients' diets on therapeutic effectiveness would enable the creation of dietary recommendations that enhance its efficacy (Boszkiewicz et al., 2020). To effectively monitor and assess exposure levels to xenoestrogens in food, it is essential to conduct precise analyses of the content of these compounds in the individual ingredients. Additionally, ensuring compositional control of patient meals is crucial.

Developing a reliable and validated method for exposure assessment is imperative for accurate evaluation.

Studies on the impact of xenoestrogens other than phytoestrogens on hormone-dependent breast cancer are needed. Their frequent presence in a patient's environment has been observed, yet a wide variety of exposure levels exists. Statistical studies have indicated a significant relationship between the presence of dichlorodiphenyltrichloroethane (DDT) in the environment and breast cancer risk, particularly when exposure occurs before the age of 14 years (Cohn et al., 2019). Given the carcinogenic potential of metalloestrogens, pesticides, and industrial chemicals, it is conceivable that they may adversely affect breast cancer treatment outcomes (Boszkiewicz et al., 2020). Developing methods that enable reliable estimation of exposure to this class of compounds presents a challenge. The prospect of enhancing the response to breast cancer treatment introduces a new approach to disease management, potentially increasing the likelihood of successful treatment.

The association between the incidence of male cancers and exposure to environmental xenoestrogens has been documented. Studies have indicated a higher likelihood of testicular dysfunction, a significant risk factor for testicular cancer, due to the influence of pesticides. While the impact of pesticides on prostate cancer development has not been definitively established, important studies have suggested implications (Kumar et al., 2022). Further research in these areas is necessary to establish appropriate preventive recommendations for men.

An area requiring further study regarding xenoestrogens is the male reproductive system. In addition to cancer risks, excessive levels of estrogens may lead to defects such as testicular maldescent or a decrease in the number of sperm cells in ejaculation. It is important to accurately measure exposure to these contaminants, especially during fetal life, identify hazardous doses, and assess their potential to cause adverse effects on the male reproductive system. Developing rapid tests capable of detecting estrogenic structures in chemicals and determining their degree of harmfulness is also essential (Toppari et al., 1996).

There is a correlation between the progression of colorectal cancer and exposure to xenoestrogens like BPA, diethylstilbestrol which is influenced by the presence of a specific type of receptor, G protein–coupled estrogen receptor 1 (GPER1) on colorectal cancer cells. However, the exact role of these substances remains unclear and requires further investigation (Bühler et al., 2022). Additionally, comprehensive research is needed to understand the overall influence of xenoestrogens on the colon and the entire gastrointestinal tract.

9. Summary

Xenoestrogens are an increasing concern in the modern world and may contribute to the rising incidence of endocrine-related cancers. The level of exposure and the resulting impact vary depending on the type of xenoestrogen. However, given their prevalence, exposure to these compounds is virtually unavoidable. Therefore, it is crucial to conduct research on lesser-known groups of xenoestrogens, such as metalloestrogens, as this could yield significant insights (Boszkiewicz et al., 2020).

Their environmental impact is linked to various factors, including water pollution and agricultural activities, particularly the use of pesticides and insecticides (Pathak et al., 2022; Yang et al., 2020; Iribarne-Durán et al. 2024). Further research and the implementation of environmental regulations are needed. Xenoestrogens significantly affect many areas of human health, including the progression and treatment of diseases. The reproductive systems of both males (Toppari et al., 1996) and females (Taylor et al., 2008) and certain types of cancer are particularly susceptible to these compounds. Considering the current prevalence of cancer, the impact of xenoestrogens in this domain is of significant importance and warrants comprehensive analysis.

The association between xenoestrogens and tumors in many tissues requires thorough analysis and testing. Incidences of non-classical hormone-related tumors including lung cancer, colorectal cancer and gastric cancer appear to be linked to xenoestrogen exposure (Wang et al., 2021), either due to the presence of ER receptors on cancer cells or their impact on chemical reaction pathways. The current understanding in this field is limited and needs to be expanded. Advancing knowledge about the influence of environmental factors on the mechanisms underlying tumor occurrence and development would enable the establishment of more up-to-date health recommendations and enhance effective prevention strategies.

The use of current knowledge, as well as its expansion regarding the occurrence of xenoestrogens, their impact on the environment, and human health, will allow for the establishment of the most sustainable approach to the problem of using these compounds.

References

1. Alaskhar Alhamwe B., Khalaila R., Wolf J., et al., 2018, Histone Modifications and Their Role in Epigenetics of Atopy and Allergic Diseases, Allergy, Asthma & Clinical Immunology, 14:39, doi: 10.1186/s13223-018-0259-4.
2. Allard P., Colaiácovo M. P., 2010, Bisphenol A Impairs the Double-Strand Break Repair Machinery in the Germline and Causes Chromosome Abnormalities, Proceedings of the National Academy of Sciences of the United States of America, 107(47):20405-20410, doi: 10.1073/pnas.1010386107.

3. Amir S., Shah S. T. A., Mamoulakis C., et al., 2021, Endocrine Disruptors Acting on Estrogen and Androgen Pathways Cause Reproductive Disorders through Multiple Mechanisms: A Review, International Journal of Environmental Research and Public Health, 18(4):1464, doi: 10.3390/ijerph18041464.
4. Arowolo O., Pilsner J. R., Sergeyev O., et al., 2022, Mechanisms of Male Reproductive Toxicity of Polybrominated Diphenyl Ethers, International Journal of Molecular Sciences, 23(22):14229, doi: 10.3390/ijms232214229.
5. Avissar-Whiting M., Veiga K. R., Uhl K. M., et al., 2010, Bisphenol A exposure leads to specific microRNA alterations in placental cells, Reproductive Toxicology, 29(4):401-406, doi: 10.1016/j.reprotox.2010.04.004.
6. Bjune J. I., Strømland P. P., Jersin R. Å., et al., 2022, Metabolic and Epigenetic Regulation by Estrogen in Adipocytes, Frontiers in Endocrinology (Lausanne), 13:828780, doi: 10.3389/fendo.2022.828780.
7. Boszkiewicz K., Sawicka E., Piwowar A., 2020, The impact of xenoestrogens on effectiveness of treatment for hormone-dependent breast cancer - current state of knowledge and perspectives for research, Annals of Agricultural and Environmental Medicine, 27(4):526-534, doi: 10.26444/aaem/124165.
8. Budakoti M., Panwar A. S., Molpa D., et al., 2021, Micro-RNA: The darkhorse of cancer, Cell Signaling, 83:109995, doi: 10.1016/j.cellsig.2021.109995.
9. Bühler M., Fahrländer J., Sauter A., et al., 2022, GPER1 links estrogens to centrosome amplification and chromosomal instability in human colon cells, Life Sciences Alliance, 6(1):e202201499, doi: 10.26508/lsa.202201499.
10. Chauhan R., Archibong A. E., Ramesh A., 2023, Imprinting and Reproductive Health: A Toxicological Perspective, International Journal of Molecular Sciences, 24(23):16559, doi: 10.3390/ijms242316559.
11. Cohn B. A., Cirillo P. M., Terry M. B., 2019, DDT and Breast Cancer: Prospective Study of Induction Time and Susceptibility Windows, Journal of the National Cancer Institute, 111(8):803-810, doi: 10.1093/jnci/djy198.
12. Costas L., Frias-Gomez J., Peinado F. M., et al., 2024, Total Effective Xenoestrogen Burden in Serum Samples and Risk of Endometrial Cancer in the Spanish Screenwide Case-Control Study, Environmental Health Perspectives, 132(2):27012, doi: 10.1289/EHP13202.
13. Dairkee S. H., Moore D. H., Luciani M. G., et al., 2023, Reduction of Daily-Use Parabens and Phthalates Reverses Accumulation of Cancer-Associated Phenotypes

within Disease-Free Breast Tissue of Study Subjects, Chemosphere, 322:138014, doi: 10.1016/j.chemosphere.2023.138014.

14. Dębska S., Potemski P., 2010, Structure and Function of Hormone Receptors and Their Crosstalk with Growth Factor Receptors, Contemporary Oncology, 14(6):347-354, doi: 10.5114/wo.2010.19149.
15. Dumasia K., Kumar A., Deshpande S., et al., 2017, Estrogen signaling, through estrogen receptor β, regulates DNA methylation and its machinery in male germ line in adult rats, Epigenetics, 12(6):476-483, doi: 10.1080/15592294.2017.1309489.
16. Heldring N., Pike A., Andersson S., et al., 2007, Estrogen Receptors: How Do They Signal and What Are Their Targets, Physiological Reviews, 87(3):905-931, doi: 10.1152/physrev.00026.2006.
17. Hodes-Wertz B., Grifo J., Ghadir S., et al., 2012, Idiopathic Recurrent Miscarriage Is Caused Mostly by Aneuploid Embryos, Fertility and Sterility, 98(3):675-680, doi: 10.1016/j.fertnstert.2012.05.025.
18. Iribarne-Durán L. M., Castillero-Rosales I., Peinado F. M., et al., 2024, Placental concentrations of xenoestrogenic organochlorine pesticides and polychlorinated biphenyls and assessment of their xenoestrogenicity in the PA-MAMI mother-child cohort, Environmental Research, 241:117622, doi: 10.1016/j.envres.2023.117622.
19. Kiselev A., 2022, Environmental Pollution: Impacts on Human Health and Future Directions, Reviews on Environmental Health, 37(3):309-319, doi: 10.1515/reveh-2021-0071.
20. Kiwitt-Cárdenas J., Adoamnei E., Arense-Gonzalo J. J., et al., 2021, Associations Between Urinary Concentrations of Bisphenol A and Sperm DNA Fragmentation in Young Men, Environmental Research, 199:111289, doi: 10.1016/j.envres.2021.111289.
21. Koehler K. F., Helguero L. A., Haldosén L. A., et al., 2005, Reflections on the Discovery and Significance of Estrogen Receptor Beta, Endocrine Reviews, 26(3):465-478, doi: 10.1210/er.2004-0027.
22. Komarowska M., Chrzanowski R., Tylicka M., et al., 2022, Plasma Concentration of Bisphenol A and Leptin in Patients with Meningioma and Glioma: A Pilot Study, Advances in Medical Sciences, 67(2):229-233, doi: 10.1016/j.advms.2022.04.002.
23. Křížová L., Dadáková K., Kašparovská J., et al., 2019, Isoflavones, Molecules, 24(6):1076, doi: 10.3390/molecules24061076.
24. Kumar V., Yadav C. S., Banerjee B. D., 2022, Xeno-Estrogenic Pesticides and the Risk of Related Human Cancers, Journal of Xenobiotics, 12(4):344-355, doi: 10.3390/jox12040024.

25. Liu X., Zhan T., Gao Y., et al., 2022, Benzophenone-1 induced aberrant proliferation and metastasis of ovarian cancer cells via activated ERα and Wnt/β-catenin signaling pathways, Environmental Pollution, 292(Pt B):118370, doi: 10.1016/j.envpol.2021.118370.
26. Mal R., Magner A., David J., et al., 2020, Estrogen Receptor Beta (ERβ): A Ligand Activated Tumor Suppressor, Frontiers in Oncology, 10:587386, doi: 10.3389/fonc.2020.587386.
27. Manikkam M., Tracey R., Guerrero-Bosagna C., et al., 2013, Plastics Derived Endocrine Disruptors (BPA, DEHP and DBP) Induce Epigenetic Transgenerational Inheritance of Obesity, Reproductive Disease and Sperm Epimutations, PLOS One, 8(1):e55387, doi: 10.1371/journal.pone.0055387.
28. Maniradhan M., Calivarathan L., 2023, Bisphenol A-Induced Endocrine Dysfunction and Its Associated Metabolic Disorders, Endocrine, Metabolic & Immune Disorders-Drug Targets, 23(4):515-529, doi: 10.2174/1871530322666220928144043.
29. Omeljaniuk W. J., Charkiewicz A. E., Garley M., et al., 2022, Bisphenol A: Potential Factor of Miscarriage in Women in the Context of the Phenomenon of Neutrophil Extracellular Traps, Archives of Immunology and Therapy Experimental (Warsaw), 70(1):24, doi: 10.1007/s00005-022-00661-w.
30. Paterni I., Granchi C., Minutolo F., 2017, Risks and Benefits Related to Alimentary Exposure to Xenoestrogens, Critical Reviews in Food Science and Nutrition, 57(16):3384-3404, doi: 10.1080/10408398.2015.1126547.
31. Pathak V. M., Verma V. K., Rawat B. S., et al., 2022, Current Status of Pesticide Effects on Environment, Human Health and Its Eco-Friendly Management as Bioremediation: A Comprehensive Review, Frontiers in Microbiology, 13:962619, doi: 10.3389/fmicb.2022.962619.
32. Rozati R., Reddy P. P., Reddanna P., et al., 2002, Role of environmental estrogens in the deterioration of male factor fertility, Fertility and Sterility, 78(6):1187-1194, doi: 10.1016/s0015-0282(02)04389-3.
33. Rutkowska A., Rachoń D., 2014, Bisphenol A (BPA) and Its Potential Role in the Pathogenesis of the Polycystic Ovary Syndrome (PCOS), Gynecological Endocrinology, 30(4):260-265, doi: 10.3109/09513590.2013.871517.
34. Sabry R., Yamate J., Favetta L., et al., 2019, MicroRNAs: potential targets and agents of endocrine disruption in female reproduction, Journal of Toxicologic Pathology, 32(4):213-221, doi: 10.1293/tox.2019-0054.

35. Sklias A., Halaburkova A., Vanzan L., et al., 2021, Epigenetic remodelling of enhancers in response to estrogen deprivation and re-stimulation, Nucleic Acids Research, 49(17):9738-9754, doi: 10.1093/nar/gkab697.
36. Song D., He H., Indukuri R., et al., 2022, ERα and ERβ Homodimers in the Same Cellular Context Regulate Distinct Transcriptomes and Functions, Frontiers in Endocrinology (Lausanne), 13:930227, doi: 10.3389/fendo.2022.930227.
37. Taylor H. S., 2008, Endocrine disruptors affect developmental programming of HOX gene expression, Fertility and Sterility, 89(2 Suppl):e57-58, doi: 10.1016/j.fertnstert.2007.12.030.
38. Toppari J., Larsen J. C., Christiansen P., et al., 1996, Male reproductive health and environmental xenoestrogens, Environmental Health Perspectives, 104(Suppl 4):741-803, doi: 10.1289/ehp.96104s4741.
39. Tumu K., Vorst K., Curtzwiler G., 2023, Endocrine Modulating Chemicals in Food Packaging: A Review of Phthalates and Bisphenols, Comprehensive Reviews in Food Science and Food Safety, 22(2):1337-1359, doi: 10.1111/1541-4337.13113.
40. U.S. Environmental Protection Agency, 2017, America's Children and the Environment. 3rd ed. Phthalates. Available from: https://www.epa.gov/sites/production/files/2017-08/documents/phthalates_updates_live_file_508_0.pdf (dostęp: 2024.05.05).
41. Wang L. H., Chen L. R., Chen K. H., 2021, In Vitro and Vivo Identification, Metabolism and Action of Xenoestrogens: An Overview, International Journal of Molecular Sciences, 22(8):4013, doi: 10.3390/ijms22084013.
42. Wang X., Ha D., Yoshitake R., et al., 2021, Exploring the Biological Activity and Mechanism of Xenoestrogens and Phytoestrogens in Cancers: Emerging Methods and Concepts, International Journal of Molecular Sciences, 22(16):8798, doi: 10.3390/ijms22168798.
43. Waring R. H., Harris R. M., 2005, Endocrine Disrupters: A Human Risk?, Molecular and Cellular Endocrinology, 244(1-2):2-9, doi: 10.1016/j.mce.2005.02.007.
44. Winstanley Y. E., Gonzalez M. B., Andreas E., et al., 2024, Drinking water quality impacts oocyte viability and embryo development, Frontiers in Reproductive Health, 6:1394099, doi: 10.3389/frph.2024.1394099.
45. Wnuk A., Przepiórska K., Pietrzak B. A., et al., 2023, Emerging Evidence on Membrane Estrogen Receptors as Novel Therapeutic Targets for Central Nervous System Pathologies, International Journal of Molecular Sciences, 24(4):4043, doi: 10.3390/ijms24044043.

46. Yang K. J., Lee J., Park H. L., 2020, Organophosphate Pesticide Exposure and Breast Cancer Risk: A Rapid Review of Human, Animal, and Cell-Based Studies, International Journal of Environmental Research and Public Health, 17(14):5030, doi: 10.3390/ijerph17145030.
47. Zbucka-Kretowska M., Zbucki R., Parfieniuk E., et al., 2018, Evaluation of Bisphenol A Influence on Endocannabinoid System in Pregnant Women, Chemosphere, 203:387-392, doi: 10.1016/j.chemosphere.2018.03.195.