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The influence of endocrine disrupting chemicals

Bartosz Pawłowski, Michał Sienkiewicz, Magdalena Kłusek, Dorota Zatłoka-Mazur, Monika Żybowska-Męczyńska, Filip Klimas, Bartłomiej Sienkiewicz, Kacper Rusiński, Adriana Potoczek

Bartosz Pawłowski
University Clinical Hospital No. 4 in Lublin Doktora Kazimierza Jaczewskiego Street 8, 20-954 Lublin
Email: bartek4245@gmail.com
ORCID: https://orcid.org/0009-0009-3515-1777

Michał Sienkiewicz
Regional Specialist Hospital in Biała Podlaska Terebelska Street 57/65, 21-500 Biała Podlaska
Email: michal.sienkiewicz09@gmail.com
ORCID: https://orcid.org/0009-0001-0427-9198

Magdalena Kłusek
University Clinical Hospital No 4 in Lublin, Doktora Kazimierza Jaczewskiego Street 8, 20-954 Lublin
Email: magdalenaklusek1@gmail.com
ORCID: https://orcid.org/0009-0001-8055-6054

Dorota Zatłoka-Mazur
Tytus Chałubiński Regional Hospital in Zakopane, Kamieniec 10 street, 34-500 Zakopane
Email: zdorota811@gmail.com
ORCID: https://orcid.org/0009-0003-3663-1891

Monika Żybowska-Męczyńska
St. John Paul II Mazovian Provincial Hospital in Siedlce, Poland, Księcia Józefa Poniatowskiego 26, 08-110 Siedlce, Poland,
Email: zybowska.m@gmail.com
ORCID: https://orcid.org/0000-0002-3885-5907

Filip Klimas
SP ZOZ MSWiA Hospital in Kraków, Kronikarza Galla 25 Street, 30-053 Kraków
Email: e1filipklimas@gmail.com
ORCID: https://orcid.org/0009-0000-5266-8676

Bartłomiej Sienkiewicz
Medical University of Białystok Jana Kilińskiego Street 1, 15-089 Białystok
Email: bsienkiewicz78@gmail.com
ORCID: https://orcid.org/0009-0003-2695-5542

Kacper Rusiński
University Clinical Hospital in Poznan, Przybyszewskiego Street 49, 60-355 Poznań
E-mail: kacper.rusinski1@gmail.com
ORCID: https://orcid.org/0009-0005-4002-9267

Adriana Potoczek
University Clinical Hospital in Katowice, Medyków 14 street, 40-752 Katowice
e-mail: adriana.potoczek@interia.pl
ORCID: https://orcid.org/0009-0002-3981-3490

Abstract

On a daily basis, everyone is exposed to many chemical compounds that have been classified as endocrine disrupting chemicals (EDCs). These are natural and artificially produced substances that are widely available in the environment today. The aim of the study is to determine the effect of endocrine disrupting chemicals on hormonal processes occurring in the human body and to determine their mechanisms of action. The research method used was a literature review on the Pubmed platform.

Studies show that EDCs affect prenatal growth, thyroid function, glucose metabolism, obesity development, and puberty and fertility processes by mimicking hormones naturally occurring in the human body, which very often leads to disorders in the hormonal axis at various levels. Recent research reports say that EDCs interact through epigenetic mechanisms.

These substances are considered safe individually, but the subject of research remains the "cocktail effect", which consists in exposing several EDCs to the body at the same time. The key here is to limit human contact with these substances as much as possible. Studies have so far proven the negativin effects of many of them on our body, but many of the long-term effects have yet to be studied. Fortunately, more and more countries are introducing restrictions on the use of these substances and are looking for methods to replace them with less harmful substitutes.

Further research is needed to understand the effects of these substances on humans, which will further enable the development of appropriate regulation of EDCs.

Keywords: endocrine disrupting chemicals, cocktail effect, epigenetics, metabolic disorders.

1. EDC – Introduction

Endocrine disrupting chemicals (EDCs) are exogenous substances of natural or artificially produced origin that can cause a number of side effects on health by affecting the endocrine system and metabolism. These substances can disrupt hormonal processes even at low concentrations.

Most of them are lipophilic and accumulate in adipose tissue, which is why they have a long half-life. It is difficult to determine their direct impact on humans due to the usually late manifestations of the effects of exposure (1). In recent years, there has been a growing interest in EDCs among researchers, including major international health organizations. Thanks to our research, we know that EDCs are able to block specific metabolic pathways at the most important moments for development, which can further lead to many disorders. These substances are widely available in the environment. Some of them are exposed due to the circulation of water and air, and others due to the use of everyday objects (2) (3) (4). The increase in the incidence of the full spectrum of diseases due to exposure to EDCs also generates significant costs and burdens for health care. EDCs affect not only personal and population health, but also the economy, making them a significant threat to society and the environment (5).

2. Mechanisms of action

EDCs, by mimicking hormone molecules naturally occurring in the human body, are able to disrupt entire hormonal and metabolic pathways. Despite their lower affinity for receptors than real hormone molecules, they are also able to antagonize them. Thanks to their properties, the synthesis, transport and action of hormones, and consequently hormone-dependent metabolic processes, are disrupted. These substances can interact through nuclear and non-nuclear receptors, receptors for hormones, indirectly through steroid hormones. Currently, great emphasis is placed on epigenetic mechanisms (6). The first contact with substances of this type usually takes place in critical phases of life, which include pregnancy and lactation, which can result in damage to peripheral and central tissues, followed by programming disorders at various stages of life (7).

3. **The most common examples of EDC**

Plastics and plasticizers, this group includes bisphenol A and phthalates. These are substances that people are exposed to in connection with their use in the production process. For example, bisphenol A is used in protective coatings, varnishes for coating metal products, including water pipes. As such, it can potentially be present in tap water. Phthalates, on the other hand, are used in lids for glass containers, cling film or cardboard packaging (7). Due to the negative effects of phthalates on health, their use has been minimized by restrictions in state laws. Despite this, they can still be present in the environment. They affect the expression of microRNAs in placenta, Sertoli, and breast cancer cell lines.

Another group are **pesticides,** in the context of which a number of studies have been carried out in the context of

pregnant women. The most important is the CHARGE test. The aim of this study was to demonstrate the relationship between the exposure of pregnant women to agricultural pesticides and the occurrence of ASD, i.e. autism spectrum disorders or developmental delay in their children. The results showed that maternal exposure to these substances increased the risk of these disorders in children. The risk was particularly increased if the exposure occurred during the 2nd or 3rd trimester of pregnancy (8). A very popular pesticide used to be atrazine, which was used in agriculture as a weed killer. It was banned in the EU in 2004 due to its persistence in the environment and therefore its potential high human exposure. Substances from the group of chlorinated herbicides triazine, which also includes the above-mentioned atrazine, showed in studies in mice an increase in estrogen synthesis in males, which was manifested by a decrease in testosterone concentration and an increase in circulating estrogens.

PFAS, or perfluoroalkyl and polyfluoroalkyl substances Thanks to their hydrophobic, lipophobic and long-lasting properties, they are used in extinguishing agents, non-stick pans, paper and textiles (9). Their long-term effects on the human body have not yet been fully understood, but it is already known that these substances are eliminated from the body for a very long time. It appears that substances from this group may affect the nuclear receptor binding to the estrogen receptor, and the non-steroidal receptor as an agonist of the peroxisome proliferator-activated receptor alpha (PPARα).

EDC with a wide range of applications is also **brominated flame retardants** – these are substances used to reduce the risk of catching fire on specific objects. People are exposed to them every day. These substances are added primarily to plastics, but also to wood or fabrics in order to delay their combustion. They have been shown to significantly affect the steroidogenesis pathway, exert an anti-estrogenic effect and act antagonistically on the glucocorticoid receptor. Their effect is further enhanced by the fact that when using these substances, they do not bind to the objects in which they are used and thus can easily get into the environment.

Dioxins and dioxin-like polychlorinated biphenyls are substances produced as a result of industrial processes and combustion. They are absorbed into the human body mainly through the gastrointestinal tract, then accumulate in adipose tissue. When released, they remain in the environment for a very long time, are resistant to degradation, which is why they have been classified as persistent organic pollutants. Some of them are able to interfere with the process of adipogenesis.

Heavy metals such as lead (Pb) and mercury (Hg). Pb can mainly affect the hypothalamic-pituitary-adrenal axis and cause oxidative stress. In the past, it was used very widely in the production of gasoline. At the moment, it has been banned for use and the fuels are now lead-free. Hg is very often found in fish and seafood that live in water bodies contaminated with this heavy metal. It works by lowering progesterone levels, increasing estrogen levels and disrupting the steroidogenesis pathway. Human foetuses and people who are occupationally exposed to this element are particularly vulnerable to Hg (10).

4. Negative impact on the development and functioning of the body

4.1. Thyroid gland

Thyroid cells are very sensitive to the effects of EDCs, keeping in mind the ~~incredibly~~ significant impact of the thyroid gland on the functioning of the body, including metabolism, disorders of this organ can lead to a strong dysregulation of homeostasis. Due to the thyroid gland's need for iodine, a state of iodine deficiency may increase the potential for EDC to act on the thyroid gland (11).

Dysregulation of the level of these hormones can significantly affect the development and functioning of the body. The work of the thyroid gland can be disturbed, among other things, in the subpituitary-pituitary-thyroid axis, the transport of thyroid hormones and their metabolism. (12) An example of an EDC that strongly affects thyroid function is perchlorate. It reduces thyroid function by blocking the sodium-iodine symporter (13). There is more and more talk about the potential impact of EDC on the thyroid gland of pregnant women. This is of particular importance because, as we know, maternal thyroid hormones are essential for the proper development of the fetus (14).

4.2. Female reproductive system

The balance of the endocrine system in women is extremely important because the cycle menstrual and fertility are particularly sensitive to fluctuations in hormone levels.

A relationship has been noted between exposure to these substances and accelerated ovarian aging. The primary ovarian reserve is reduced, folliculogenesis and steroidogenesis are disrupted, which ultimately leads to irregularities in the menstrual cycle and reduced fertility (15)(16). A higher risk of polycystic ovary syndrome, uterine smooth fibroids and endometriosis is also observed (17). A growing number of epidemiological studies indicate the potential for EDC to affect the development or progression of breast cancer, which in the long term may lead to negative health consequences, especially when exposed early in life (18).

4.3. Male reproductive system

EDCs can lower testosterone levels and increase estrogen levels.

Studies have shown that EDCs increase the risk of cryptorchidism in children, affect the tubular part of the testicle, disrupting its development, which is at risk of cancer development in the next stage. They also disrupt hormonal processes in the testicles, which is manifested by reduced testosterone levels. Studies in humans have shown that exposure to EDC caused a temporary decrease in sperm quality and quantity in semen (19).

In the occupational group of farmers exposed to pesticides, an increased risk of sperm morphological abnormalities was observed. Some pesticides, such as parathion and methyl parathion, have the ability to damage the seminiferous epithelium, resulting in a decrease in sperm volume and sperm concentration(20).

4.4. **Metabolic diseases**

Within metabolic diseases, we distinguish: obesity, insulin resistance and diabetes. EDCs stimulate adipogenesis, which leads to an increase in the number and volume of adipocytes and an increase in the likelihood of obesity. At the same time, many EDCs accumulate in adipose tissue.

These substances disrupt cell morphology and biochemistry, increase the number of adipocytes, stimulate inflammatory and oncogenic processes, and increase the accumulation of triglycerides (21)(22).

The data show that EDCs (phthalates, bisphenol compounds) have the ability to modify anthropometric parameters depending on the dose and sex of the person exposed to these substances. Phthalates and bisphenol compounds increase waist circumference, body mass index and the sum of skin fold thickness only in women. On the other hand, the opposite is true for exposure to low doses of persistent organic pollutants, as they lead to an increase in the body mass index in men and a decrease in it in women(23).

Substances belonging to EDCs can be classified as risk factors for insulin resistance and type 2 diabetes. They interfere with the synthesis and secretion of insulin, and are able to abolish glucose homeostasis in the body.

The etiopathogenesis of type 1 diabetes is complex. It consists of genetic factors, but in the case of autoimmunity against pancreatic beta cells, environmental factors are also important. These include EDCs. They interact on their own as well as in the form of mixtures that have a much stronger effect. Their effect is mainly based on stimulating the immune system and weakening the protection of pancreatic beta cells against autoimmunity. A lot of epidemiological and experimental research is still being conducted in this area (24).

4.5 **Skeletal system**

EDCs also have a negative impact on the skeletal system. This occurs in connection with altered bone modeling and remodeling by altering paracrine hormone synthesis, the release of systemic hormones, cytokines, chemokines, and growth factors, and influencing stem cell fate, as well as the differentiation of bone marrow mesenchymal stem cells (25) (26).

4.6 **Immune system**

The immunotoxicity of EDCs involves, among other things, altering the expression of genes that are dependent on the activation of nuclear receptors, such as the aryl hydrocarbon receptor (AHR) or the peroxisome proliferator-activated receptor (PPAR), which can also cause skin and intestinal disorders.

Environmental pollutants, which include polycyclic aromatic hydrocarbons, heavy metals or pesticides, affect the body's immune response, leading to its deficiency or hyperactivation, i.e. allergies or even autoimmune diseases. (27) (28).

Phytoestrogens should also be mentioned here, which, through immediate or late steroid effects, can affect the incidence and course of autoimmune diseases. One of the most common sources of dietary phytoestrogens is soy (29).

4.7 **Hypertension**

Recent studies on perfluoroalkyl substances belonging to EDCs, the presence of which has been noticed in drinking water, have shown that they are capable of increasing the secretion of aldosterone by the adrenal cortex. This information is important in relation to the potential exposure to excess Na+, which is also classified as an EDC and leads to hypertension in conditions of excessive aldosterone secretion (30).

5. **„Cocktail effect"**

This concept was created due to the fact that EDCs are very rarely found individually in the environment. Most often, the human body is affected by several or even a dozen of them. The impact of the EDC mixture was exposed due to its stronger impact on humans than individual substances from this group. Their effect consists in creating hormone-receptor connections by resembling the hormone molecule, causing an agonist effect or blocking receptors, an antagonistic effect, and disrupting the work of hormone-transporting proteins (31).

A team of researchers from Paris has discovered another phenomenon called the "reverse cocktail effect". Chlorpyrifos, found in lavender essential oil, which is a mixture of EDCs, reduced its negative effects on endocrine disorders. This was the opposite observation to most EDCs, which amplify their toxicity in a mixture (32) (33).

6. **Summary**

The problem of the negative impact of EDC on humans is indisputable. Knowledge in this area is deepening, but unfortunately it does not allow to fully eliminate the risk of contact with EDC and its further health consequences. The difficulty in understanding the mechanisms of action of these substances is due to their long-term effects on the body and the manifestation of its effect at a late age. Usually, the effects of exposure appear in adulthood or even old age. Evidence for prenatal and postnatal exposure is also limited. Further research seems important, as well as the introduction of appropriate legal regulations limiting the use of EDC. This will make it possible to reduce the population's contact with these substances, as well as negative health effects, including hormonal disorders.

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Author's contribution:
All authors contributed to the article.
Conceptualization: Pawłowski B, Sienkiewicz M, Kłusek M;
Methodology: Sienkiewicz M, Zatłoka-Mazur D, Potoczek A, Żybowska-Męczyńska M, Kłusek M;
Software: Pawłowski B, Zatłoka-Mazur D, Rusiński K, Żybowska-Męczyńska M, Klimas F;
Formal analysis: Sienkiewicz M, Zatłoka-Mazur D, Pawłowski B;
Investigation: Pawłowski B, Kłusek M, Zatłoka-Mazur D, Rusiński K;
Resources: Pawłowski B, Sienkiewicz M, Rusiński K, Żybowska-Męczyńska M, Kłusek M;
Data curation: Sienkiewicz M, Sienkiewicz B, Żybowska-Męczyńska M, Kłusek M;
Writing - rough preparation: Pawłowski B, Sienkiewicz B, Sienkiewicz M, Klimas F;
Writing - review and editing: Żybowska-Męczyńska M, Sienkiewicz B, Zatłoka-Mazur D, Potoczek A, Sienkiewicz M;
Visualization: Pawłowski B, Sienkiewicz M, Zatłoka-Mazur D, Potoczek A, Rusiński K, Klimas F;
Supervision: Pawłowski B, Sienkiewicz M, Sienkiewicz B, Rusiński K, Potoczek A, Klimas F;
Project administration: Pawłowski B, Zatłoka-Mazur D, Kłusek M, Żybowska-Męczyńska M, Klimas F;

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