REVIEW ARTICLE

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Endocrine disrupting micropollutants in water and their effects on human fertility and fecundity

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Abstract

Introduction and Objective. Micropollutants (MPs) are defined as persistent and biologically-active substances which occur in the environment in trace amounts, mainly as a result of industrial processes and human domestic activity. The published experimental data prove that, among other things, MPs present in the environment may also affect and disturb hormonal balance in humans, resulting in impairment of the reproductive function. In addition to the many MPs disrupting endocrine function described in literature and which exert an effect on human reproductive function, the study presents a review of current literature concerning the exposure to Bisphenol A, phthalates, organochlorine pesticides, and pyrethroids.

Review Methods. Two independent authors searched in PubMed and Google scholar (any date until September 2022) for studies concerning chosen endocrine-disrupting MPs in water and their effects on human fertility and fecundity.

Brief description of the state of knowledge. The review of the literature showed that EDMs present in the environment may create risk in the prenatal and postnatal development following premature birth, and exert a negative effect on fertility and reproductive functions in humans, especially during the perinatal period.

Summary. The presented review of literature indicates a negative effect of exposure to BPA, phthalates, OC and OP pesticides, as well as to pyrethroids, regarding human reproductive health. It also demonstrated considerable differences according to gender. Generally, there is a definitely stronger evidence for the presence of a cause-effect relationship between the discussed EDMs and a decreased fertility and fecundity in males. The negative effect of exposure to Bisphenol A, phthalates, selected organochlorine pesticides and pyrethroids appears to be quite well documented.

Key words

health effects, Endocrine disrupting micropollutants, human fertility and fecundity, reproductive functions

INTRODUCTION

Micropollutants (MPs) are defined as persistent and biologically-active substances which in trace amounts occur in the environment, mainly as a result of industrial processes and human domestic activity [1].

In the aquatic environment, MPs are present in trace concentrations of several microgames (μg) in one litre of water. Until quite recently, these ranges of concentrations of MPs have caused numerous technical and methodological problems with their detection and quantitative determination [2], and it was not until the 1980s that while analysing environmental samples attention was paid for the first time to micropollutants. From that time, the occurrence of MPs in the aquatic environment, problems with their elimination, as well as a negative effect of MPs on human health and life, have become an important problem dealt with in a constantly growing number of scientific publications [3].

MPs ingested with drinking water are mainly organic chemicals of anthropogenic origin from industrial and agricultural processes, and domestic human activities which, together with precipitation, runoff from farm fields, leaching from landfills, and industrial or municipal waste water, may penetrate untreated into the water system [4]. To this group belong various industrial chemicals, plant protection products (biocides), pharmaceutics, natural and synthetic hormones, personal hygiene products, etc.[4]. The descriptions of the risk of water pollution and hence the risk to human health are presented in numerous works, e.g. [5, 6, 7]. The Stockholm Convention of 2001 banned the production and use of persistent organic pollutants, which included pesticides, industrial chemicals and aldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene, PCBs, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans [8].

Due to high chemical diversity and very low concentration of these compounds, commonly used sewage treatment technologies are unable to cope with their total elimination. According to many environmental factors, MPs are removed to a varying degree with the use of advanced and modern treatment processes [3]. The treatment procedures used, security measures and monitoring of the levels of MPs before and after the process of elimination of contaminations, are not applied, or, at best, they are inappropriate. In consequence, many particular MPs, often in an unchanged quantity, may pass through wastewater treatment processes and return to the aquatic environment, thus increasing the risk for aquatic ecosystems and humans.

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The occurrence of MPs in drinking water and the environment is associated with factual, serious health effects for humans and water ecosystems; however, knowledge of this problem appears to be fairly limited [7]. A report published by the Government of Canada in 2022 indicated that even 80% of all diseases and deaths in the developing countries are caused by consumption of contaminated water [9]. Results of numerous preclinical and clinical studies concerning the exposure to MPs demonstrate their considerable toxic potential, especially with regard to their long-term action. This results from the properties of MPs, i.e. their easy bioaccumulation in aquatic species and human organs, considerable toxicity and persistence in the environment (resistance to degradation) [10]. The published experimental data prove that, among other things, MPs may be carcinogens, neurotoxins related to onset of e.g. neurodegenerative diseases, or a potential factor increasing multi-antibiotic resistance of microorganisms pathogenic for humans [9, 11, 12].

MPs present in the environment may also affect and disturb hormonal balance in humans, resulting in the impairment of the reproductive function. These are so-called Endocrine Disrupting Micropollutants (EDMs) [4, 13]. Among many MPs disrupting endocrine function described in literature and which exert an effect on human reproductive function, the current study is presents a review of extant literature concerning exposure to BPA, phthalates, DDE, organochlorine pesticides, and pyrethroids. These compounds, according to the authors, are the main danger to human fertility and fecundity. The International Programme on Chemical Safety (IPCS) classifies each compound which disturbs the endocrine function in the body, its offspring, or population in humans, as an Endocrine Disrupting Compound (EDC), a term introduced in early 1990s and concerned mainly the estrogenic effects of chemicals polluting the environment. EDCs were therefore initially called xenoestrogens and researchers focused primarily on the reproductive toxicity of EDCs, and reduced fertility and fecundity in both males and females [5]. Among these compounds one could mention natural EDMs: endogenous hormones and phytoestrogens, as well as many various anthropogenic EDMs, including: industrial chemicals, mainly: polycyclic aromatic hydrocarbons, halogen compounds (dioxins, furans, biphenyls), phthalates, phenolic compounds, pesticides, pharmaceuticals, synthetic hormones, etc. At present, approximately 1,500 compounds are characterized as EDMs [13]. They occur in items and articles of everyday use, such as plastic water containers, personal hygiene products, food products, and as a component of industrial and agricultural processes. Due to the widespread presence in the environment and washing-out of many various products, a serious threat to health human through exposure to EDMs via different absorption routes, is constant. However, coherent health consequences of exposure to EDMs in relation to their various routes of exposure, pace of their metabolism in humans, as well as the dose and duration of exposure, are difficult to specify [14].

Together, the animal model data and human evidence support the idea that exposure to EDCs during foetal development and puberty plays a role in the increased incidences of reproductive diseases [15, 16], endocrine-related cancers [17], neurological and behavioural disorders [18, 19] metabolic dysfunction and related disorders, which promote obesity and increase the risk of type 2 diabetes [20, 21, 22]. Some EDCs alter bone metabolism [23] and affect immune system function [24].

A new challenge for research is the immune and inflammatory effects of EDCs. Inflammation is associated with a wide range of chronic diseases, including obesity, cognitive deficits, cardiovascular disease, respiratory disorders, cancer, and even autism. The immune and endocrine systems often work together in responding to environmental challenges, and the convergence of their signaling pathways may underlie some of the inflammatory effects [24].

It is worth mentioning that Directive 2013/39/EU of the European Parliament and of the Council of 23 October 2000 established a framework for Community action in the field of water policy and a strategy for combating water pollution. This strategy includes the identification of priority substances among those that pose a significant risk to human via the aquatic environment. Therefore, Directive 2013/39/EU recommended the monitoring of chemicals from a watch list where EDCs include: estriol, 17-β-estradiol, 17-α-ethinylestradiol and nonylphenol and bisphenol A. These compounds were included in the first watch list for data collection monitoring to help identify appropriate measures to address the risk posed by these substances [25].

Normal endocrine signalling of the body covers negligible changes in the levels of hormones, but may result in considerable negative biological effects, due to which, chemical exposure, even at very low doses, may disturb the delicate hormonal system of the body and lead to diseases. EDMs, with regard to their structure and activities, may disturb these natural hormonal signals of the body:

1) by imitating natural hormone, EDM may block the receptor inside the cell and cause that the signal will be stronger or initiated an 'inappropriate' time, compared to the natural hormone;
2) may block the receptor inside the cell and cause that the signal will not occur, and the body will not respond normally;
3) may disturb or block the synthesis of receptors and the metabolism of endogenous hormones [26].

There is some evidence that by the deregulation of the hormonal system, EDMs may affect a wide range of health effects, including especially fertility and fecundity in humans [27, 28, 29, 30, 31].

Reproductive effects of endocrine disrupting chemicals. The effect of EDMs on reproduction results from their similarity to steroid hormones, and the consequential disruption of the signalling oestrogen, androgen and thyroid hormones pathways. In addition, EDMs may act with the participation of the central hypothalamic-pituitary-gonadal axis by modification of the secretion and/or response to the gonadotrophin releasing hormone (GnRH), and gonadotrophin [32] modulating reproduction in humans. Thanks to these properties, the effect of EDMs present in the environment may create risk in the prenatal and postnatal development following premature birth, and exert a negative effect on fertility and reproductive functions in humans, especially during the perinatal period [13].

Bisphenol A. Bisphenol A (BPA) is a high production volume chemical substance used, among others, in the

manufacturing of polycarbonate plastics, epoxy resins and thermal paper [33]. Due to the washing-out from numerous diverse products the exposure to BPA in the human life environment is relatively common [33]. Table 1 presents summing up of the latest research.

The results of studies shown above provide strong evidence for the unfavourable effect of BPA on the reproductive capabilities of males and females. Simultaneously, there is a need for prospective studies which would be helpful in understanding the severity of the effects of BPA, and the conditions of exposure in which they occur. Based on the same findings, males and females who would like to have an offspring should obviously minimize their exposure to BPA.

Phthalates. Phthalates are the salts and esters of phthalic acid commonly applied as so-called plasticisers for improvement of the functional properties of plastics. These are mainly phthalate diesters: di(2-ethylhexyl)phthalate (DEHP), dibutyl phthalate (DBP), and diethyl phthalate (DEP). In humans, it was common found in the blood and urine of more than 95% of examined people exposed to phthalates [43]. However, their monoester metabolites were responsible for fertility, mainly in males: mono(2-ethylhexyl) phthalate (MEHP), aminobutyl phthalate (MBP), monomethyl phthalate, and homobenzylic phthalate (MBzP) (Tab. 2).

It is worth noting that there are studies which did not confirm any relationships between the level of monoester metabolites in urine and the measurable sperm parameters in males [54]; there are also reports concerning the lack of the effect of phthalates and their metabolites on fertility and fecundity in humans [13].

Pesticides. Pesticides are mainly applied in agriculture for the control of pests which reduce crop yields, and may be divided into many categories, of which the best known are organochlorine compounds (OC), organophosphates (OP), and pyrethroids (PTD). The results of studies concerning the effects of pesticide on human fertility are equivocal [11]. This results from the methodology of research (lack of actual measurements of direct exposure; simultaneous exposure to many chemicals at various concentrations and for a different duration, including additional substances, with their own toxicity in commercial preparations), as well as the large number of compounds in a given category of pesticides and the resulting diverse mechanisms of action on many hormonal pathways [11]. Nevertheless, a documented effect of the hazardous effect of some compounds from this group on fertility may evidence the risk resulting from their use (Tab. 3).

Organochlorines (OC). Dichlorodiphenyltrichloroethane (DDT) and its metabolite – dichlorodiphenyldichloroethylene (DDE) are the best documented OCs exerting a negative effect on human fertility and fecundity [32, 55].

Table 1. Effects of bisphenol A on human reproductive system

Model / Study Population	Value of BPA in urine	Effects/Reference
BPA concentrations in infertile males according to infertility cause	BPA > 3 ng / ml	BPA (>3 ng/ml) was observed only in infertile men; azoospermia [34]
Cross-sectional study with young males	BPA 2,8 (0,16–11,5) ng / ml in urine	Decrease in serum luteinizing hormone and sperm concentration [35]
Case-control studies, urinary BPA levels in infertile patients	BPA 0.44 µg/g creatinine; BPA median values of 24.2µg/l; BPA 1.63 µg/ g creatinine all in urine	Reduced semen quality, decrease in both sperm concentration and motility, an increased percentage of immature sperm, decreased antioxidants levels [36, 37, 38]
A prospective cohort study among females undergoing *in vitro* fertilization	BPA concentrations range <0.4 – 25.5 microg/L (geometric mean 2.52 +/- SD 3.2) in urine	BPA were associated with the number of oocytes and serum levels of estradiol [39]
BPA concentrations in girls diagnosed with precocious puberty	BPA 8,7 (7,6) µg/g creatinine (+/- SD) in urine	Increase in serum testosterone, estradiol, and pregnenolone levels [40]
Case-control study	BPA 0.98±2.67µg/g creatinine in urine	increased risk of miscarriage [41]
A population-based prospective cohort study	BPA median values of 1.67 ng/ml in urine	decreased weight gain during pregnancy and low birth weight [42]

Table 2. Effects of phthalates on human reproductive system.

Model / Study Population	Phthalates	Effects/Reference
Males: large epidemiological and fertility centre studies	high DEHP or mono-ester metabolites (e.g. MBP and MEHP) exposure	decreased testosterone, oestradiol and increased sex hormone binding globulin (SHBG) [44, 45]
Males: meta-analyses	mono-ester phthalates; high concentrations in urine	poor sperm motility and quality [46, 47]
Males: cross-sectional study	phthalate mono-ester metabolites in urine	poor semen parameters: low sperm concentration, decreased volume, and morphology [44, 48]
Females: fertility treatment	mono-ester concentrations, especially DEHP metabolites in urine	decreased antral follicle counts, lowered oocyte yield [49, 50]
Females: females undergoing in vitro fertilization	specific DEHP metabolites, in urine	lower rate of clinical pregnancy and live birth [49, 51]
Females: women at reproductive age	phthalate metabolites (e.g. MEHP) in urine	higher occurrence of pregnancy loss [52]
Females: long-term effect on fertility parameters	high DEHP exposure	reduction in serum FSH and increase in serum SHBG [53]

Table 3. Effects of pesticides on human reproductive system

Model / Study Population	Pesticides	Effects/ Reference
Females, males: various studies	Organochlorines: DDT and its metabolite DDE	Strong correlations between DDT and DDE exposure and male and female fertility and fecundity[32]
Cohort study	Organochlorines: chlordane, hexachlorobenzene, heptachlor, mirex and toxaphene	Modulate endocrine hormone production in women [61]
Females: various studies	Organochlorines: lindane; lindane isomer high concentrations in blood samples.	Fertility disorders [62]: lower implantation rate [63]: low concentrations of gonadotrophins, oestradiol and IGF-I [64]
818 pregnant women from the West Indies	Organochlorines: Chlordecone	Decrease in gestational length; increased risk of pre-term birth [65]
Males: various studies	Organophosphates	Sperm concentration, count, volume and morphology, increased sperm aneuploidy [66]
Males: various studies	Organophosphates: diazinon	Reductions in testosterone and changes in gonadotrophin levels in plasma, and decreased activity of antioxidant enzymes [67]
Females: cross-sectional observational study	Organophosphates: urinary metabolite concentration	Longer time to pregnancy (TTP) and lower fertility [58]
Females: Cross-sectional observational study	Organophosphates: chlorpyrifos; diazinon follicular fluid	Reduced endometrial thickness, longer TTP, reduced oocyte numbers and implantation rates[63]
Males: 15 cross-sectional studies	Pyrethroids: urinary metabolite concentration	Negative associations with sperm parameters: chromatin and DNA quality, as well as aneuploidy rates[13].
Males: several studies	Pyrethroids: higher 3-PBA urine concentration	Lower sperm concentration [13]
Females: prospective cohort pstudy	Pyrethroids: higher 3-PBA urine concentration	Longer TTP and decreased fertility [58]
Females: 420 women from Limpopo, South Africa	Pyrethroids: indoor use of pyrethroids	Decreased plasma anti-Mullerian hormone concentration, poor reproductive outcomes [59]

In the 1970s, DDT was banned for use in the majority of countries; however, it is still used in the countries where malaria periodically occurs.

Other OCs which may affect reproductive processes in humans are: lindane, heptachlor, toxaphene, methoxychlor, mirex, chlordane, chlordecone and dieldrin. Data from a small number of studies indicate that the exposure of males to these pesticides did not result in any great consequences for the quality of sperm and semen [32]. On the contrary,however, in females, studies confirm the negative effect of various OCs on fertility (Tab. 3).

Organophosphates (OP). Contemporary studies show that although a considerable reduction in the use of OP was achieved due to rigorous legal regulations, the risk in the context of human fertility and fecundity in the general population has not changed [55]. The majority of data confirming the effect of OP on fertility comes from the studies of males exposed to Ops, which have provided evidence for the negative effect of OPs on the basic semen and sperm parameters, although the majority of them concerned only a small group of males. Thus, the data pertaining to the relationship between occupational exposure of males to some OP pesticides and fertility are basically coherent, and indicate a negative effect on various semen parameters, although there is a lack of comprehensive, cross-sectional studies of this problem. In females, the exposure to OPs is also associated with fertility disorders, especially with regard to the longer time to pregnancy (TTP) used as an indicator of fertility (Tab. 3).

Pyrethroids (PTD). In the last decades, along with the withdrawal from use of increasing amounts of particular OC and OP pesticides, the application of pyrethroids has become common in households and agricultural crops [56]. The effect of PTDs on human fertility has been examined to a limited degree, and concerns mostly the effects in males. Due to different methodology, the results of these studies and their interpretation are frequently equivocal and fairly difficult to assess. In addition, the frequency of the exposure to PTDs was determined based on self-reported occupational cases. However, regarding available data it may be concluded that exposure to PTDs in males may be associated with a negative effect on reproduction, affecting the quality and concentration of sperm DNA. In females, the small number of studies additionally hinder unequivocal conclusions, but a constant presence of PTDs metabolites in urine [57] and unfavourable data from studies in males, indicate an urgent need for carrying out some definitive research. Nevertheless, the results of several studies demonstrate a negative effect of PTDs on fertility in females through, e.g. a longer TTP [58], and a decrease in anti-Mullerian hormone concentration – a marker of ovarian reserve, in plasma [59], which results in reduced fertility (Tab. 3).

Importantly, there is some conflicting evidence that the mechanism of action of PTDs is associated with the modulation of estrogen pathways [60], which may call into question the potential of TPDs as compounds disrupting the human endocrine system (Tab. 3).

CONCLUSIONS

The presented review of literature indicates the negative effect of exposure to BPA, phthalates, OC and OP pesticides, and pyrethroids, regarding human reproductive health, and demonstrates the considerable differences according to gender. Generally, there is definitely stronger evidence

for the presence of a cause-effect relationship between the discussed PTDs and decreased fertility and fecundity in males. The negative effect of exposure to BPA, phthalates, DDE, selected organochlorine pesticides and pyrethroids, appears to be quite well documented.

In females, due to a limited number of studies, different methodology, and a small amount of data for analysis, the relationship between exposure to TPDs and female fertility is poorly documented, which should encourage researchers to deal with this scope of problems. Based on scientific evidence, such a relationship may be assumed for BPA and organochlorine pesticides, including DDE, and within a limited scope for OP pesticides and pyrethroids.

Generally, there is an urgent need for studies on individual PTDs using a unified methodology with regard to which the effect on human fertility is uncertain or the collected experimental data are incomplete, to draw definite, final conclusions. This is justified by the results of studies indicating that in both males and females with reduced fertility parameters there occurred elevated concentrations of PTDs or their metabolites in blood, plasma, and tissues, which unequivocally indicates relationships between exposure to PTDs and fertility disorders.

There is also the need for a critical review of the legal regulations concerning chemical purity of the environment of human life, as well as systems of purification of water designed for consumption from the aspect of micropollutants, especially environmental toxins reducing human reproductive capabilities.

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