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The Problem of Health Risk Resulting from the Presence of Pharmaceuticals in Water Used for Drinking Purposes: A Review

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ABSTRACT

The article addresses the problem of the presence of selected pharmaceuticals in waters by determining the state of scientific knowledge. The sources of drug residues in the aquatic environment were characterized and the most important information was collected on the toxicity measures of the most commonly used drugs, including NLPZ: (1) non-steroidal analgesics and antipyretics (diclofenac, ibuprofen, phenazone, acetaminophen, propyphenazone, indomethacin, ketoprofen, pentoxifylline, and phenacetin), (2) pharmaceuticals used to reduce blood lipid levels (bezafibrate, fenofibrate, gemfibrozil), (3) drugs used in cardiac conditions, in particular those used to lower blood pressure and treat arrhythmia (atenolol, sotalol, metoprolol), (4) antibiotics (trimethoprim, clarithromycin, amoxicillin, sulfamethoxazole, piperacillin, erythromycin, sulfadimidine, dehydrate-erythromycin, 4N-Acetylsulfamethoxazol), (5)drugs used to treat rheumatoid arthritis (naproxen, fenoprofen), and (6) anticonvulsants, drugs used in neuropathic disorders and tranquilisers (carbamazepine, diazepam, primidone, oxazepam, temazepam). The authors reviewed research papers dealing with the indicated issue, taking into account: (1) research on the presence of pharmaceuticals in water, (2) studies on the health and environmental risk of drinking water for the presence of drug residues and their mixtures, (3) research on the effectiveness of water treatment in terms of pharmaceuticals. Gaps in scientific knowledge have been demonstrated, which are a hint for the directions of future research work.

Keywords: pharmaceuticals in water, non-steroidal anti-inflammatory drugs, surface water, health risk, OTC.

INTRODUCTION

Due to the advancing climate change and global environmental pollution, the world is facing increasing challenges with respect to the safety of water intended for human and animal consumption, both in terms of its quality and quantity (Carballa et al., 2008; Besse et al., 2008). The wide occurrence of xenobiotics, including pharmaceutical residues, in the aquatic environment is an increasing cause for concern among the scientific community and is associated with an alarming increase in antibiotic resistance, both in people and in animals. A new area of research has thus emerged dealing with the occurrence of pharmaceuticals in surface and ground waters (Pharmaceuticals In the Water Environment, PIWE). The increasing levels of micropollutants (MPs), including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics (ABs) and hormones (HMs), in the water environment is a growing problem worldwide in terms of the quality of water (Huang et al., 2020). The problem relates not only to strictly environmental issues. It also concerns public administration, legislative bodies and, consequently, water companies and consumers. It is to be expected that in the near future the managers of water and wastewater companies will have to face the problem of the occurrence and removal of MPs, ABs and HMs from water and sewage. Thus, the broadest possible thorough knowledge will be needed about the

spatial occurrence of pharmaceuticals in surface and ground waters and the removal rate of those substances in different technological systems, including water and sewage treatment plants. One extremely important issue that must be addressed today is the assessment of health risk (HR) to people and animals associated with long-term consumption of water containing low levels of particular pharmaceuticals and their metabolites (Huang, 2020). The problem of drug residues in water and the associated potential health risks to recipients has not yet been adequately examined. The documents published by EU management authorities indicate that there is a need for a strategic approach to contamination of water with non-specific pollutants, which undoubtedly include PIWE (Commission Communication, 2019). The existing laws and regulations do not impose an obligation on the suppliers of water to the general public to analyse the levels of the parameters concerned in raw and treated water. The "new" EU Directive (Directive of the European Parliament and of the Council (EU), 2020) on the quality of water intended for human consumption does not explicitly address the maximum permissible levels of particular hormonal substances and drugs (including NSAIDs) in surface, ground and treated waters. It does not provide a classification of substances and does not specify the research methods required for their collection and determination.The new watch list of selected parameters (Commission Implementing Decision (EU) 2022/679 of 19 January 2022) which make it possible to monitor emerging chemicals in water that are of concern for human health, such as nonylphenol and 17-beta estradiol (HM). The watch respond to communications, opinions from the Commission and the Committees of the Regions and resolutions such as the EU Strategic Approach to Pharmaceuticals in the Environment (Commission Communication, 2019), "Towards a more comprehensive EU framework on endocrine disruptors" (Commission Communication, 2018) and the European Parliament resolution on a chemicals strategy for sustainability of 10 July 2020 (2020/2531(RSP)) (European Parliament Resolution, 2020). The European Commission (EC) expressly states that it is necessary to fill gaps in knowledge of pharmaceuticals and their concentrations in the environment, in particular the aquatic environment, and assess the level of health risk associated with them (Commission Communication, 2019).

Sources of pharmaceuticals in the aquatic environment

The residues of non-steroidal drugs, including NSAIDs, in raw water (especially surface water) mainly come from wastewater discharged to the soil and aquatic environment from households, pharmaceutical industry, hospitals etc. While the residues discharged to water and soil from industrial installations may be residues of drugs subject to medical prescription, the vast majority of NSAIDs discharged to water from households are generally available over-the-counter (OTC) pharmaceuticals. Ibuprofen, ketoprofen, paracetamol and other NSAIDs are components of over-the-counter analgesic and anti-inflammatory drugs available in pharmacies, grocery stores, kiosks and petrol stations (Figure 1).

Those drugs are widely available and thus widely used. As a result, the demand for these substances is constantly increasing. The worrying trend relating to the use of OTC medications has been confirmed by worldwide statistics. The surveys carried out by the Public Opinion Research Centre (CBOS) in 2010 (on a random sample of 1041 adults) and 2016 (on a sample of 981 people) showed that a continuing significant proportion of people use over-the-counter drugs, including dietary supplements (CBOS, 2010, 2016). The survey conducted in 2010 showed that as many as 80% of respondents had used OTC medications in the 12 months preceding the survey, of whom 65% had used painkillers, 14% – over-the counter cardiac medicines and 14% – tranquilisers and sleeping pills. Seventy-two per cent of participants in the study reported that they had used prescription drugs.

However, as many as 61% of respondents reported that they had used both prescription and OTC drugs (CBOS, 2010). The study conducted in 2016 showed a continuing trend in terms of the use of OTC medications. In 2019, as many as 89% of respondents reported using over-the-counter drugs, an increase by 9% when compared to the 2010 study, 72% of respondents used prescription drugs and as many as 65% used both OTC and prescription drugs. The most commonly used OTC medications were painkillers and anti-inflammatory drugs (68%) as well as cold remedies (81%). It is alarming that as many as 28% of respondents reported that they used OTC drugs contrary to leaflet instructions, for instance by using a higher dose (CBOS, 2010).

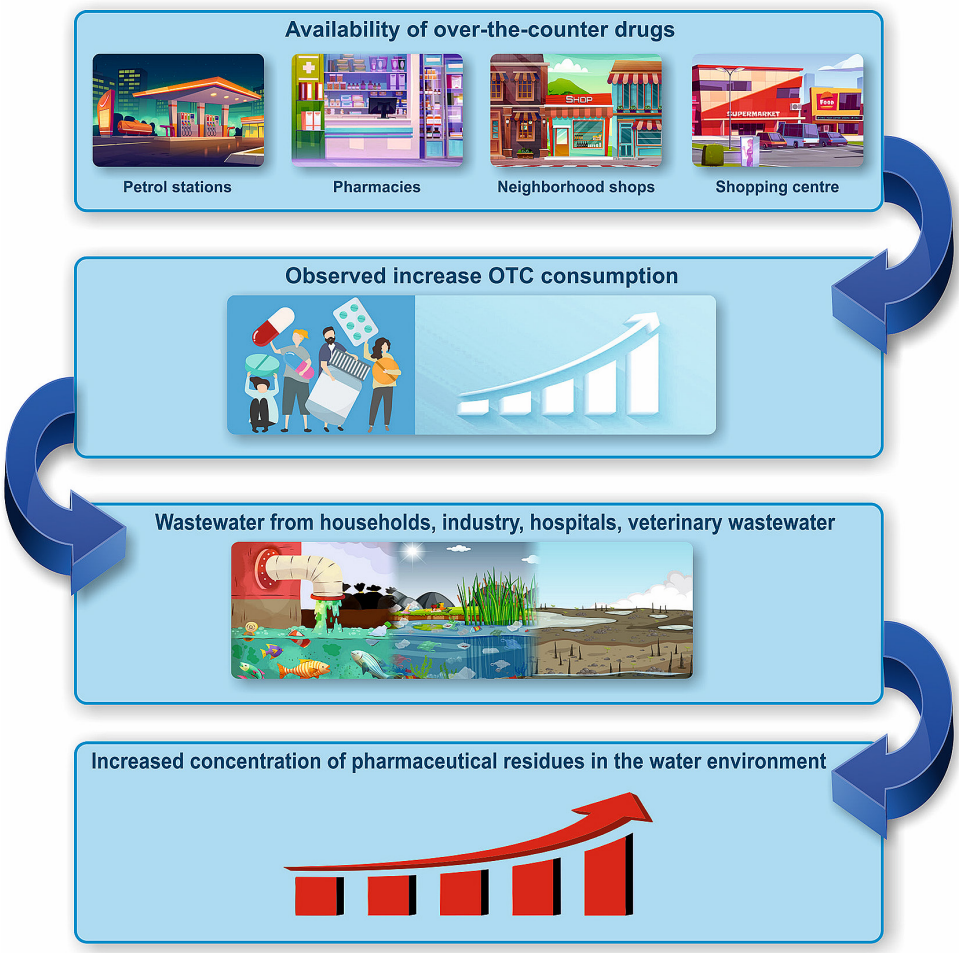

Figure 1. Scheme of sources of pharmaceuticals in the water and ground environment

Characteristics of selected pharmaceuticals

The work focused on 6 groups of the most commonly used pharmaceuticals have been selected. Their basic chemical and toxicological parameters are described below (Table 1). These groups are:

- non-steroidal analgesics and antipyretics – non-steroidal anti-inflammatory drugs: diclofenac, ibuprofen, phenazone, acetaminophen, propyphenazone, indomethacin, ketoprofen, pentoxifylline, and phenacetin (in combination with other substances);
- pharmaceuticals used to reduce blood lipid levels: bezafibrate, fenofibrate, gemfibrozil;
- drugs used in cardiac conditions, in particular those used to lower blood pressure and treat arrhythmia: atenolol, sotalol, metoprolol;
- antibiotics: trimethoprim, clarithromycin, amoxicillin, sulfamethoxazole, piperacillin, erythromycin, sulfadimidine, dehydrate-erythromycin, 4N-Acetylsulfamethoxazol;
- drugs used to treat rheumatoid arthritis: naproxen, fenoprofen;
- anticonvulsants, drugs used in neuropathic disorders and tranquilisers: carbamazepine, diazepam, primidone, oxazepam, temazepam.

REVIEW OF RESEARCH DATA

Research on the presence of pharmaceuticals in water

The issue of PIWE has been investigated by multiple research teams around the world (Boroń and Pawlas, 2015; Dhaka et al., 2019; Domaradzka et al., 2015; Gao et al., 2019; Huang et al., 2019; Huang et al., 2020; Khaleeq et al., 2020; Mansour et al., 2018; Murdoch, 2015). Much research interest is focused on NSAIDs, as these substances are widely used, largely stable in the aquatic environment, and minimally transformed in living organisms (Boroń et al., 2015). Khaleeq et al. (2020) also researched the content of analgesic and anti-depressant medication residues in water, confirming the presence

Table 1. Key information on the potential toxicity of selected pharmaceuticals

Name	Formula	Toxicological characteristics*
Diclofenac	$C_{14}H_{11}Cl_2NO$	Chronic toxicity value for humans - 72 mg/dm^3
Ibuprofen	$C_{13}H_{18}O_2$	NOAEL for oral exposure in monkeys = 100 mg/kg-day
Phenazone	$C_{11}H_{12}N_2O$	LD_{50} (determined in studies on rats) = 1,705 mg/kg for oral route of exposure
Propyphenazone	$C_{14}H_{18}N_2O$	LD_{50} is 860 mg/kg
Acetaminophen (Paracetamol)	$C_8H_9NO_2$	Minimum oral POD for acetaminophen was estimated at 30 mg/kg-day. According to the IARC database, a carcinogenicity warning for the chemical has been issued
Indomethacin	$C_{19}H_{16}ClNO_4$	Estimated average exposure rate for the U.S. population is 4.58E-8 mg/kg-bw/day for women and 2.38E-8 mg/kg-bw/day for men, with a 50% confidence that the exposure for the chemical is below the median estimate
Ketoprofen	$C_{16}H_{14}O_3$	LD_{50} for the oral route of exposure is only 62.4 mg/kg
Pentoxifylline	$C_{13}H_{18}N_4O_3$	LD_{50} was experimentally determined as 1,170 mg/kg
Phenacetin	$C_{10}H_{13}NO_2$	Minimum oral POD for the chemical was estimated at 50 mg/kg-day
Fenofibrate	$C_{20}H_{21}ClO_4$	Minimum oral POD was estimated at 5.9E+2 mg/kg-day; the NOAEL for the oral route of exposure in mice is 585.5 mg/kg-day
Gemfibrozil	$C_{15}H_{22}O_3$	The oral exposure rate was estimated at 1.46E-6 mg/kg-day
Atenolol	$C_{14}H_{22}N_2O_3$	LD_{50} = 2,000 mg/kg
Trimethoprim	$C_{14}H_{18}N_4O_3$	LD_{50} in rats = 530 mg/kg
Clarithromycin	$C_{38}H_{69}NO_{13}$	Estimated average exposure rate for the U.S. population is 5.02E-7 mg/kg-bw/day for women and 4.45E-7 mg/kg-bw/day for men, with a 50% confidence that the exposure for the chemical is below the median estimate
Amoxicillin	$C_{16}H_{19}N_3O_5S$	Average exposure rate for the U.S. population is 2.82E-7 mg/kg-bw/day for women and 2.25E-7 mg/kg-bw/day for men, with a 50% confidence that the exposure for the chemical is below the median estimate
Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	LD_{50} for oral exposure is 6,200 mg/kg
Erythromycin	$C_{37}H_{67}NO_{13}$	Minimum oral POD = 12 mg/kg-day
Roxithromycin	$C_{41}H_{76}N_2O_{15}$	Exposure rate for the chemical for the U.S. population is 9.38E-8 mg/kg-bw/day for women and 6.28E-8 mg/kg-bw/day for men, with a 50% confidence that the exposure for the chemical is below the median estimate
Sulfamethazine	$C_{12}H_{14}N_4O_2$	Exposure rate for the U.S. population was estimated at 3.38E-8 mg/kg-bw/day for women and 1.74-8 mg/kg-bw/day for men, with a 50% confidence that the exposure for the chemical is below the median estimate
Naproxen	$C_{14}H_{14}O_3$	LD_{50} = 248 mg/kg (classified as an acutely toxic chemical)
Diazepam	$C_{16}H_{13}ClN_2O$	NOAEL – 10 mg/kg-day
Primidone	$C_{12}H_{14}N_2O_2$	Minimum oral POD is 15.0 mg/kg-day
Oxazepam	$C_{15}H_{11}ClN_2O_2$	Minimum oral POD = 12 mg/kg-day
Temazepam	$C_{16}H_{13}ClN_2O_2$	Exposure rate for the U.S. population was estimated at 3.411E-8 mg/kg-bw/day for women and 2.59E-8 mg/kg-bw/day for men, with a 50% confidence that the exposure for the chemical is below the median estimate

Note: * According to the U.S. EPA (https://comptox.epa.gov, http://www.chemspider.com); NOAEL – no observed adverse effect level. It should be stressed that no reference doses with respect to water quality have been determined for the pharmaceuticals concerned (https://comptox.epa.gov).

of these substances in the water environment in South Asia. The authors pointed to gaps in pharmaceutical monitoring data and emphasized the need for large-scale studies in this area. In Poland, research on NSAID biotransformation and biodegradation has been undertaken, among others, by Domaradzka et al. (2015). A study on the presence of selected NSAIDs in raw water was also performed by Poland's Chief Inspectorate for Environment Protection in the years 2016–2019. The study focused on detection of diclofenac (highest concentrations), erythromycin, clarithromycin, azithromycin, and selected hormones in 15 measurement sites across the country (https://

www.wody.gov.pl). A significant threat to human health is the presence of antibiotics in the water and ground environment and their impact on the potential increase in bacterial resistance to pharmacological agents. Interesting research on this aspect was conducted in Poland by: Korzeniowska et al. (2013), Felis et al. (2020), Osińska et al. (2020), Harnisz et al. (2015, 2020) and Koniuszewska et al. (2020). In particular, the study addressed the issue of transfer of genes encoding antibiotic resistance by bacteria, both taking into account post-hospital sewage and municipal sewage at various stages of treatment and treated sewage directed to the recipient. As a result of the work, it was found that despite the high efficiency of wastewater treatment (99% effectiveness), genes encoding resistance are released into the environment. Research on the threat of antibiotic resistance of bacteria in the Polish river environment included, among others: teams Harnisz et al. (2015) and Koniuszewska et al. (2020). The work showed an increase in the diversity of resistance genes in rivers (Koniuszewska et al. 2020). Researchers emphasize the need to conduct long-term ecotoxicological studies focused on environmental risk.

Studies on the health and environmental risk of drinking water for the presence of drug residues and their mixtures

Health exposure assessment was developed by the US Environmental Protection Agency in the 1980s (US EPA 1989, 1991, 2012, 2018). It is a tool to assess the potential negative impact on human health caused by environmental factors. Research on the ocean health risk of water is conducted by many research teams from around the world, including Berner et al. (2004), Lopez et al. (2008). The health risk assessment of water related to the presence of potentially toxic elements was studied by, among others: Junhua et al. (2018), Yang et al. (2012) and Izquierdo et al. (2015), Kicińska and Wysowska (2019), Wysowska and Kicińska (2021, 2022), Ukić et al. (2019), Zwiener et al. (2002). Risk assessments carried out in many European Union member states are mainly based on individual pharmaceutical compounds, and not their mixtures, despite their ubiquity. Ukić et al. (2019) analyzed the toxicity of six selected pharmaceuticals: azithromycin (AZM), erythromycin (ERM), carbamazepine (CBA), oxytetracycline (OTC), dexamethasone (DXM), and diclofenac (DCF), both individually and in two-component mixtures (for a total of 45 mixtures). Mathematical models including concentration addition (CA) and independent action (IA) demonstrated synergism with respect to additive behavior (CA model) for the OTC-DCF, ORC-CBA, and DCF-CBA mixtures, while OTC-AZM, OTC-ERM, DCF-AZM, and DCF-ERM exhibited antagonistic behavior with respect to the CA model. The IA model was applicable to DCF-AZM, DCF-ERM, and OTC-AZM mixtures. Godoy et al. (2019) performed a toxicity study of metformin, bisoprolol, ranitidine, and sotalol individually and in binary mixtures, using the CA and IA mathematical models, with *Daphnia similis* and *Danio reio* as target organisms. They found that the environmental risk assessments should also include pharmaceutical mixture toxicity analyses, as results based on individual compounds only may result in underestimated risk.

Currently, the impact of these substances on living organisms' health is mainly evaluated based on their toxicity to fauna and flora. Very important biochemical tests involving the duckweed *Lemna minor* were performed by Markovic et al. (2020). They studied: 17-α-ethinylestradiol (synthetic estrogen), methotrexate (cancer drug), diclofenac (NSAID), and fluoxetine (antidepressant) and their two-component mixtures at concentrations of mg/L in a 7-day test on *Lemna minor*, using biochemical markers such as: chlorophyll a and b, carotenoids, oxidative stress enzymes, catalase, glutathione S-transferase, and glutathione reductase. All the studied pharmaceuticals (both individually and in binary mixtures) can be considered toxic or harmful to aquatic life, and methotrexate was found highly toxic. Synergy was found in mixtures of methotrexate and fluoxetine, and of methotrexate and 17-α-ethinylestradiol. Mixtures of diclofenac with fluoxetine, 17-α-ethinylestradiol, and methotrexate mostly showed additive behavior. All this leads to the general conclusion that surface waters may contain residues of medications that exhibit biological activity even at low concentrations. An interesting trend in toxicity studies involving pharmaceutical residues in drinking water are biological tests for cytotoxicity, endocrine dysregulation, and genotoxicity, among other factors as in the study by Barceló et al. (2020). Literature still lacks ecotoxicology data for invertebrates and fish. Such data would allow contribute to assessments of environmental risks associated with pharmaceutical residues in water.

Hong et al. (2020) studied levels of diclofenac (DF), sulpiride (SP), sulfamethoxazole (SMX), and sulfisomidine (SIM) in a landfill area. They found concentrations ranging between 0.85 and 11.57 μg/L. Subsequently, they studied the UV-Fenton degradation of these compounds and their transformation products in ultrapure water and in concentrate. DF, SP, SMX, and SIM were identified by HPLC-QTOF-MS. Cytotoxicity was determined using HepG2 cells. The method of eliminating the toxicity of refractory pharmaceuticals by the UV-Fenton procedure was effective. Another important aspect of PIWE detection and health risk assessment is the (simultaneous) measurement of other physico-chemical parameters in the water. Sun et al. (2020) were one of the few research teams investigating, in a laboratory setting, the impact of water pH changes (6.5–8.0) on the toxicity of enrofloxacin (AB) and triclosan, used in personal hygiene products, towards freshwater invertebrates: *ephemeroptera — Cloeon dipterum, amphipoda — Gammarus pulex*, and the freshwater snail *Physella acuta*. Their experiment demonstrated that a pH change of only 1.5 units may modify EC50–48 h and EC50–96 h test results by a factor of 1.4–2.7, which is why pH values should be considered in risk assessment for pharmaceutical residues. World literature lacks such data, or only includes temperature (Kołecka et al., 2019, Kot-Wasik et al., 2016) and pH (Sun et al., 2020) of aqueous solutions. The available research findings have not confirmed that pharmaceuticals in water have a direct demonstrable impact on human health. According to the WHO (2017), research so far has not confirmed that water containing pharmaceutical residues has direct health effects on the people who drink it, which is due to the low levels of the residues. However, the WHO draws attention to the unexplored issue of the health effects of long-term exposure to drug residues in water. This is all the more important as some pharmaceuticals are chemically or metabolically stable, which means that up to 90% of the active ingredient is excreted in its original form (Commission Communication, 2019). According to the literature, the average daily intake, per person, of ibuprofen (one of the most popular NSAIDs) ranges from 600÷1,200 mg/d for people suffering from short-term inflammation or pain to 2,400 mg/d for people suffering from long-term rheumatic inflammation and other serious musculoskeletal diseases (Zwiener and Glauner, 2002; Rainsford, 2009). This indicates that it is necessary to try to solve the problem of pharmaceuticals from a different point of view – in the context of the health safety of the users of water supplied through water supply facilities, which is subject to specific treatment processes. The proposed research project is a direct response to the problem concerned. The project is of great importance and is characterized by a particularly novel and innovative approach.According to scientific publications of the medical community, one of the main problems of the widespread use of NSAIDs (especially OTC) is the possibility of negative health effects resulting from their interaction (Kołtunowicz and Sierzysko, 2009). The residues of veterinary medicines administered to domestic animals which are released into the soil and aquatic environment also deserve attention.

Pharmaceuticals are also discharged into the environment with wastewater from production facilities and excreta from livestock. Animals treated with antibiotics excrete their active form. Pharmaceuticals get into the environment with sewage from production as well as with livestock manure. One other significant problem is hospital wastewater and improper storage or disposal of medicines. Pharmaceuticals, which are released into water mainly with municipal wastewater effluents, which are not 100% effectively treated in water treatment plants, may be present in sludge. The available research studies (Fent, 2008) showed that a mixture of acetylsalicylic acid, ibuprofen, naproxen and diclofenac is highly toxic for Daphnia species (*D. magna*) as compared with the individual toxicity of these pharmaceuticals. This is confirmed by, among others, studies by Rizzo et al. (2015), which showed that a mixture of ibuprofen, diclofenac, carbamazepine and caffeine was associated with 87–100% higher toxicity compared with the toxicity of these substances administered individually. The results of the analyses carried out by scientists from the Idaho State University showed that a mixture of three drugs, namely Prozac (fluoxetine), venlafaxine and carbamazepine, at environmentally safe concentrations may have negative effects on a developing foetus (Thomas et al., 2012). The lack of knowledge about the conversion of active pharmaceuticals in the water environment leading to the formation of new compounds, which are often even more toxic than the basic compounds, as stressed by, among others, Kot-Wasik et al. (2016) and Jakimska-Nagórska (2014) in their studies.

Research on the effectiveness of water treatment in terms of pharmaceuticals

The subject of the impact of technological processes of water treatment on their impact on human health was addressed by, among others: Gitis and Hankins (2018), Smith and Kamal (2009), Wacławek et al. (2017), Huang et al. (2020), Kairigo et al. (2020). Currently, researchers focus on the search for the most effective, low-cost technologies for removing pharmaceuticals from water and wastewater, including adsorption and application of porous materials such as: activated carbon, silicates, porous organic polymers, metal-organic frameworks, and coordination polymers (Dhaka et al., 2019, Huang et al., 2019, Huang et al., 2020, Mansour et al., 2018, Gao et al., 2019), as well as oxidation and catalysis processes. The effectiveness of removal of selected pharmaceutical groups from water was studied by Andrade et al. (2018).

The authors identified adsorption as one of the most promising methods for removing pharmaceuticals from water. It involves low electricity consumption, is well-understood, and simpler to use than other methods. The best-researched and most commonly used adsorbent for pharmaceuticals is activated carbon. Yu et al. (2016) reviewed a variety of unconventional adsorbents, including clays, biocarbons, chitosan, agricultural and industrial waste products, and metal-organic structures, none of which have yet been applied on an industrial scale. Additionally, they identified adsorption technology as a fast, efficient, and cost-effective method for removing antibiotics (Abs) from aqueous solutions, used in wastewater treatment and water treatment. Both traditional activated carbon and other materials such as graphene or carbon nanotubes are used and seen as highly effective for the removal of tetracycline, sulfonamide, macrolide, and chinolone antibiotics. Also Xu et al. (2017) reported that adsorption and high-efficiency oxidation methods are the most effective and most widely available of the current pharmaceutical removal technologies. The difficult task of evaluating the effectiveness of removing various low-concentration pharmaceuticals, which actually affect the conditions in water supply systems, was undertaken by Kanakaraju et al. (2018). Advanced oxidation processes (AOPs) were used to remove the PIWE, including the photo-Fenton reaction, sonolysis, electrochemical oxidation, UV radiation, and ozonation. These oxidation processes involve the creation of highly reactive radicals, including hydroxyl radicals, which gradually oxidize organic compounds to transform them into harmless reaction products. The reactions included a photocatalyst, i.e. TiO_2, which is highly effective in accelerating the decomposition of pharmaceutical residues. Also Soliu et al. (2015) studied a combination of membrane filtration with advanced oxidation techniques with a view to completely removing pharmaceutical residues from wastewater and water. The authors suggest that the combination offers a lot of advantages, e.g. eliminating the problem of membrane fouling through preliminary oxidation, which supports the removal of suspended matter and organic compounds. The application of hybrid initial and/or final AOP allows for contaminants to be separated and oxidized individually and/or simultaneously. In the study, the following AOP techniques were used: ozonation, peroxone (O_3/H_2O_2), UV/H_2O_2, photo-Fenton, photocatalysis, and electrochemical advanced oxidation processes (EAOP), in combination with membrane filtration. Similarly to previous teams, Pavithra et al. (2017) reviewed a variety of techniques for removing pharmaceuticals from water and wastewater. Nanotechnology, i.e. the use of membrane-based techniques, was found the most effective, when compared to conventional methods.

The latest research has focused on the search for specific photocatalysts – metallic nanoparticles showing great potential in terms of removing pharmaceuticals from aqueous solutions (Kumar et al., 2019, Sharma et al., 2018). Kumar et al. (2019) studied the photocatalytic properties of a previously synthesized $Ag_2BiPO_4/BiOBr/BiFeO_3$ nano-hetero-structure in the context of removing norfloxacin under visible light, UV light, near infrared, and natural sunlight. Sharma et al. (2018) synthesized nanoparticles made of three metals (LA/Cu/Zr) using microwaves, and used these particles as a nanophotocatalyst in removing ampicillin (AB) from water. Their findings indicate a considerable potential of this technique for removing (degrading) ampicillin in an aqueous solution (up to 86%). In turn, Abukhadra et al. (2020) synthesized a novel photocatalyst active in visible light, composed of kaolin nanotubes with zinc oxide (ZnO/KNT).

The photocatalyst allowed for rapid oxidation of levofloxacin residue in an aqueous solution, in the presence of light. Adsorption combined with oxidation processes and membrane filtration is well-known (Wiewiórska, 2023a, Wiewiórska,

2023b) but research to date has not yet led to clear conclusions regarding the possibility of removing pharmaceutical residues using strong oxidants, activated carbon, and membranes. Subsequent studies should focus on evaluating the currently used, well-understood technologies for removing pharmaceuticals from water and wastewater, as well as synthesizing new, highly effective, efficient, and cost-effective adsorbents and catalysts for pharmaceutical removal. The seasonality and spatial distribution of selected pharmaceuticals (including NSAIDs), such as carbamazepine, ibuprofen, paracetamol, naproxen, metformin, and diclofenac in wastewater treated at a conventional wastewater treatment plant (mechanical, biological, and chemical methods, and STRB) and in a water treatment plant was studied in Poland by Kołecka et al. (2019) and Kot-Wasik et al. (2016). The compounds most commonly detected in water samples were carbamazepine (100% of samples) and ibuprofen (98%). Metformin also reached high concentrations in water. Levels of PIWE (in particular NSAIDs) were higher in the winter due to less intense degradation, resulting from low temperature and less solar radiation (Kot-Wasik et al., 2016). (Kołecka et al., 2019) also studied ibuprofen, paracetamol, flurbiprofen, ketoprofen, naproxen, and diclofenac in wastewater samples. Standard wastewater treatment technology eliminated 100% of the ibuprofen and naproxen content, while diclofenac and its metabolites were the most difficult to remove and the most commonly detected. Many of the studies on PIWE performed to date concern ways of removing these contaminants from wastewater. This issue is extremely important and still requires more in-depth research. Active substances from medications are excreted from the human body with urine, and flow with wastewater to treatment plants which are not equipped to remove them using conventional methods (Behera et al., 2011). Reported findings indicate that most of the available technological solutions for municipal and industrial wastewater treatment, even the best ones, are not 100% effective in removing pharmaceuticals. Conventional wastewater treatment plants effectively remove suspended solids and certain trace elements but may mostly or even completely fail to remove micro-pollutants (Kosek et al., 2020). Oberoi et al. (2019) report that biological wastewater treatment systems are moderately effective in removing antibiotics (48–77%). Research to date demonstrates that the penetration of active ingredients from pharmaceuticals, and especially antibiotics, into water and their accumulation in aquatic sediments may be toxic to many aquatic organisms and contribute to the development of antibiotic resistance (Kairigo et al., 2020, Kanakaraju 2018). Kairigo et al. (2020) investigated levels of antibiotics in four sewage treatment plants and bodies of water. The concentrations of doxycycline, amoxicillin, sulfamethoxazole, trimethoprim, ciprofloxacin, and norfloxacin in treated water, surface waters, and river sediments were 0.2–49.3, 0.1–21.4, < 0.1, 56.6, respectively in μg/dm^3, and 1.8 and 47.4, respectively in μg/kg. The risk ratio for antibiotic resistance in bacteria in wastewater and surface waters (< 0.1–53) indicated moderate-to-high risk of resistance to the analyzed antibiotics, which makes the issue a priority in the studied area. The residues of veterinary medicines administered to domestic animals which are released into the soil and aquatic environment also deserve attention. Pharmaceuticals are also discharged into the environment with wastewater from production facilities and excreta from livestock, which is why their effective treatment is so important (Ciuła, 2022, Ciuła et al., 2019). Animals treated with antibiotics excrete their active form. One other significant problem is hospital wastewater and improper storage or disposal of medicines. Pharmaceuticals, which are released into water mainly with municipal wastewater effluents, which are not 100% effectively treated in water treatment plants, may be present in sludge.

CONCLUSIONS

The indicated knowledge gaps relate to, in particular:

1. The scientific analysis substrates (pharmaceutical residues) are important, potentially harmful xenobiotics. While the public is increasingly informed of the possible contamination of water (in particular surface waters) with the substances concerned, the problem of the use of such water for drinking has not yet been solved. It should be stressed that even the problem of monitoring water supplied to the general public for the parameters concerned has not been dealt with. The administrators of water intakes seek a response to those issues as well as clear guidelines to follow in the event of an exposure situation;
2. Most available papers are based on experimental

laboratory studies of selected NSAID levels. Authors have emphasized the lack of cross-sectional studies involving pharmaceutical (NSAID, AB) content monitoring and removal in surface waters and ground water at the consecutive technological stages of treatment, using strong oxidants such as ozone and chlorine gas, as well as activated carbon beds;

3. To date, no attempt has been made to determine the impact of strong chemical oxidants, i.e. ozone and chlorine gas, and UV radiation on the reduction of pharmaceutical residue levels in water, or to identify the relationship between the presence of pharmaceuticals in water and other continuously monitored physico-chemical parameters of water, such as temperature, color, turbidity, pH, specific electrical conductivity, absorbance at 254 nm and total organic carbon.
4. Literature also lacks information on the impact of treated effluent discharge into reservoirs, and most importantly, any attempts to calculate the environmental and health risks for humans and water organisms associated with the substances in scope: NSAIDs and ABs.e lack of clarity as to whether pharmaceutical emissions are sufficiently monitored;
5. Research shows that despite the high efficiency of wastewater treatment (99% effectiveness), genes encoding bacterial resistance to antibiotics are released into the environment;
6. The need to select specific pharmaceuticals for the purposes of the review of the surface and ground water watch list;
7. The lack of environmental risk assessment as part of the authorisation process for many pharmaceuticals put on the market several years ago;
8. Very limited monitoring of pharmaceuticals in the water environment, despite the fact that selected substances are monitored in surface and ground waters under the Water Framework Directive 2000/60/EC of the European Parliament and of the Council (2000);
9. The lack of sufficient understanding of the possible "cocktail" effects from the combined presence of many pharmaceuticals and other chemicals in the environment;
10. The lack of knowledge about the conversion of active pharmaceuticals in the water environment leading to the formation of new compounds, which are often even more toxic than the basic compounds, as stressed by, among others, Kot-Wasik et al. (2016) and Jakimska-Nagórska (2014) in their studies. Therefore, it is very important to identify pharmaceuticals and their conversion products;
11. The absence of information about the risk posed by particular pharmaceuticals through their individual presence on the basis of which efforts relating to the management of the overall risk can be targeted;
12. The need to improve environmental risk assessment and its review. Risk assessment should be coordinated and guidelines should be developed taking into account all relevant expertise;
13. The determination of the eco-toxicity and environmental fate of pharmaceuticals, in particular those not yet subject to environmental risk assessment;
14. The knowledge of the effects on humans of chronic exposure to low levels of pharmaceuticals via the environment, taking account of the potential for combined effects from multiple substances, and of vulnerable sub-populations;
15. The indication of cost-effective methods for reducing the presence of pharmaceuticals, including antimicrobials, in water.

The reported review of global literature shows how much is happening in the field of PIWE and how serious a problem they pose to the entire world. The transfer of pharmaceuticals to the aquatic environment must be curbed, and therefore, there is a need for continued monitoring of the levels of selected pharmaceutical substances and their effective removal at wastewater treatment plants and water treatment stations. Scientists are quickly coming up with new technologies for the removal of pharmaceuticals from wastewater and water, such as nanomaterials combined with catalysts, but these technologies have so far remained at the laboratory testing stage. Well-known technologies that have already been implemented on an industrial scale, such as chemical oxidation, activated carbon adsorption, and membrane filtration, are fundamental to current research on micro-pollutant removal.

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