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NON-STEROID ANTI-INFFLAMATORY DRUGS IN MUNICIPAL WASTEWATER AND SURFACE WATERS

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Abstract

Increased production and consumption of drugs influences the pollution pharmaceuticals. Recent years have seen a significant increase in the consumption of non-prescription medicines, among which, are a large group of non-steroidal anti-inflammatory drugs (NSAIDs). Research conducted in Poland and abroad showed the presence of NSAIDs, both in treated wastewater in surface waters and drinking waters. One of the most frequently detected drugs in the environment is diclofenac, belongs to NSAID. Its concentration in surface waters range from 9 to 3363 ng/L. Traditional wastewater treatment plants are not specialized enough in removing the pharmaceuticals and their metabolites, and with purified wastewater are introduced into surface waters. Diclofenac concentrations in treated wastewater range from 0.29 to 2.5 µg/L, the average removal efficiency is about 40%.

Keywords: pharmaceuticals pollution, NSAIDs, wastewater, surface waters

1. INTRODUCTION

The production and consumption of drugs used in medicine for the treatment, diagnostics and prophylaxis of diseases is constantly increasing, and as a consequence of this, the pharmaceutical industry is presently one of the most rapidly developing industries worldwide [12]. A strong increase in the consumption of the medicines available without a prescription has been observed, among which, a significant group includes non-steroid anti-inflammatory drugs (NSAIDs) [17]. According to data from IMS Heath, the

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most frequently prescribed NSAID is diclofenac, whose consumption on a global scale is at the level of 940 Mg annually [26]. Poland occupies second place in the European Union and third place in the world as far as the consumption of analgesics is concerned. According to data from the year 2013, the consumption of analgesics was 115,000000 packages, which cost PLN 1 200 000 000. Statistically, on average, every Pole takes 26 tablets of analgesics annually [8].

Awareness of the hazard which the presence of drugs in the environment entails appeared at the end of the 20th century when the results of tests of the monitoring of the condition of rivers, streams and wastewater on the territory of Germany were published. The report showed that the presence of, among others, analgesics, anti-inflammatory drugs, psychotropic drugs and hormones was found in the tested samples. Studies conducted in other countries of the world confirmed the German findings. The first Polish findings on this subject were published in the year 2001 [11,17].

In the directive of the European Parliament and of the Council of August 12th, 2013 (2013/39/EU) on priority substances in the field of water policy, the European Commission placed 3 pharmaceutical substances on the watchlist: diclofenac (CAS 15307- 79-6), 17 beta-estradiol (E2) (CAS 50-28-2) and 17 alpha-ethinyl estradiol (EE2) (CAS 57-63-6). In art. 8c of the Directive, the European Commission presents detailed regulations regarding the identification of the problem of water and soil pollution with the residues of pharmaceuticals [3].

2. SOURCES OF PHARMACEUTICALS IN THE ENVIRONMENT

The routes of the emission of pharmaceuticals and their metabolites into the environment are diverse. Drugs used in medicine must be separated from veterinary drugs.

In the case of pharmaceuticals consumed by humans, a significant load of medicines is present in municipal wastewater and hospital wastewater. Drugs after consumption are subject to metabolism in the organism, during which their molecules are changed chemically and structurally, which leads to the transformation of the slowly excreted, non-polar and liophilic molecule of the drug into the hydrophilic and polar one [19, 26]. The biotransformation of the drugs takes place mainly in the liver, but also in the blood, lungs and digestive tract. The drugs are not metabolised 100 percent, in which case both the metabolized form and the one which is free of drugs is excreted from the organism [19].

Some of the drugs, those past their expiry date or unused drugs, are flushed down toilets and yet others reach waste landfills. Veterinary pharmaceuticals are used in veterinary medicine and in livestock holdings e.g. as growth promoters. On top of this, the source of pharmaceuticals may include industrial wastewater (e.g. from the pharmaceutical industry) and wastewater from the illegal production of drugs. The aforementioned sources of substances of pharmaceutical origin and their metabolites constitute a direct hazard for surface waters, underground waters and soil [2]. The sources of pharmaceuticals and the routes of their emission into the environment have been presented in fig. 1.

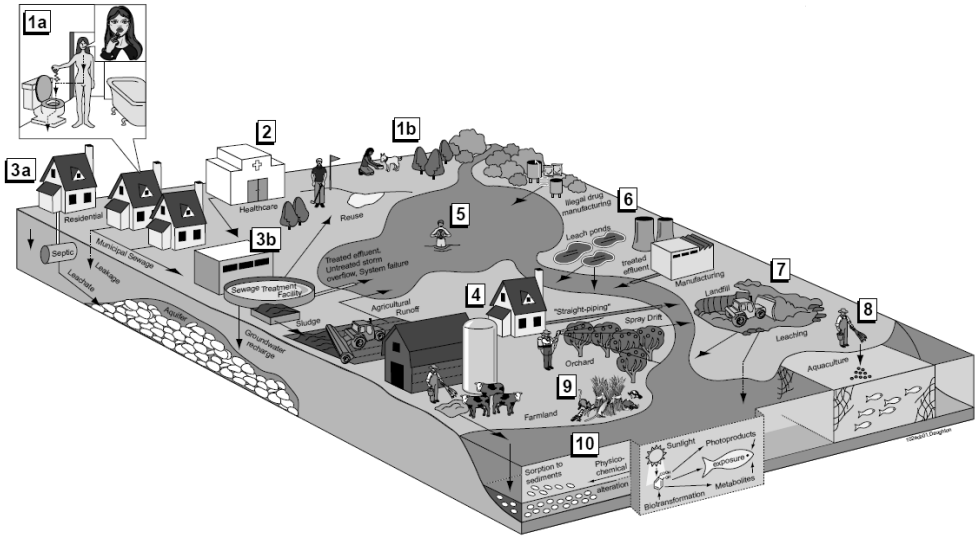

Fig. 1. Sources and routes of the emission of pharmaceuticals into the environment [2]

1. usage by individuals and pets: metabolic excretion (unmetabolized parent drug, parent-drug conjugates and bioactive metabolites), sweat and vomitus; excretion exacerbated by disease and slow-dissolving medications, - disposal and unused medication to sewage systems, - underground leakage from sewage systems.
2. release of treated/untreated hospital wastes to domestic sewage systems(weighted toward acutely toxic drugs and diagnosic agents, as opposed to long-term medications), also disposal by pharmacies, physicians, humanitarian drug surplus
3. release to private septic/leach fields, - treated effluent from domestic sewage treatment plants discharged to surface waters or re-injected into aquifers (recharge), - overflow of untreated sewage from storm events and system failures directly to surface waters.
4. transfer of sewage solids to land (e.g. soil amendment/fertilization), - “straight piping” from homes (untreated sewage discharged directly to surface waters), - release from agriculture: spray drift from tree crops (e.g. antibiotics), - dung from medicated domestic animals (e.g. feed) – CAFOs (confined animal feeding operations).

5. direct release to open waters via wasching/bathing/swimming.
6. discharge of regulated/controlled industrial manufacturing waste streams,- disposal/release from clandestine drug labs
7. disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes, - leaching from defective (poorly engineered) landfills.
8. release to open waters from aquaculture (medicated feed and resulting excreta).
9. release to drugs that serve double duty as pest control agents.
10. ultimate environmental fate: - most PPCPs eventually transported from terrestrial domain to aqueous domain, - phototransformation (both direct and indirect reactions via UV light), - physicochemical alteration, degradation and ultimate mineralization, - volatilization (mainly certain anesthetics, fragrances).

3. GENERAL CHARACTERISTICS OF NON-STEROID ANTI-INFLAMMATORY DRUGS

The non-steroid anti-inflammatory drugs belong to the most frequently prescribed drugs in the world. They include: diclofenac, naproxen, ketoprofen, salicylic acid and paracetamol. Every day they are taken by over 30,000,000 people, of whom 40% are more than 60 years old. The drugs are used in the treatment of acute and chronic pain occurring in the course of arthritis and other musculoskeletal disorders, as well as post-injury pains, migraines and, preventively, in primary and secondary coronary disease [15].
Taking into account the criterion of the drug sales volume, Poland is ranked among the first ten countries in the European Union[9]. The first data concerning the pollution of environment with pharmaceuticals in Poland were published in the year 2000 by scientists from the Silesian University of Technology.
The theoretical concentrations of the respective pharmaceuticals in municipal sewage were estimated taking into account:
- the data concerning the consumption of pharmaceuticals (according to the National Medicines Institute in Warsaw),
- metabolism of these substances in the human organism,
- and quantity of water in the given country.
The calculated concentrations were at a level of several µg/L. Comparison of the calculations with the real state determined by way of sewage monitoring tests at the wastewater treatment plant in Zabrze showed that the real concentrations of drugs are lower than the theoretical ones, but not so much as to ignore them [11].
It follows from the questionnaire surveys conducted by a group of over 2,500 physicians in Poland in the year 2011 that over 41% of respondents from almost as many as 670,000 people used or uses NSAIDs. Further studies, for which

almost 39,000 patients aged 45-66 were typified, confirm that the treatment time was longer than 5 years in the case of about 20% of them [15]. Fig. 2 presents the most frequently used non-steroid anti-inflammatory drugs on the basis of the data from a group of about 39,000 patients.

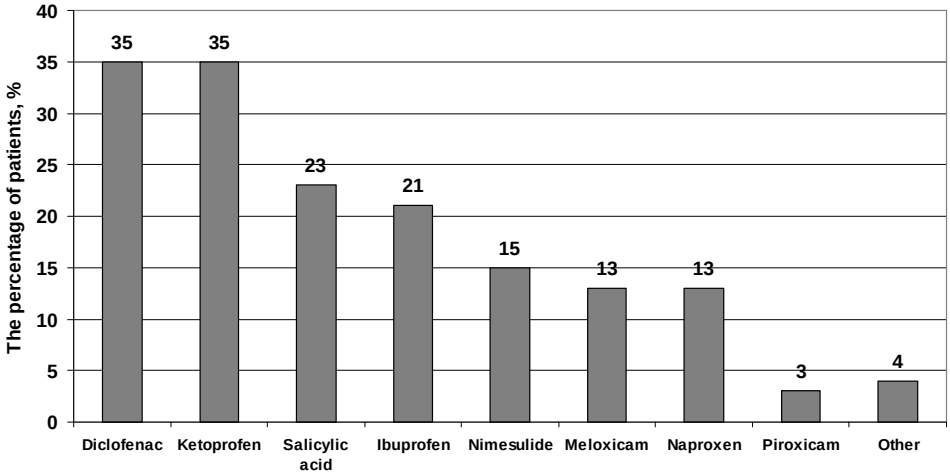

Fig. 2. The most frequently used non-steroid anti-inflammatory drugs (according to the data from a group of about 39,000 patients) [15]

Analysis of the data presented in fig. 2 shows that some of the patients used more than one drug, therefore the numbers do not add up to 100%.

4. NON- STEROID ANTI-INFLAMMATORY DRUGS IN MUNICIPAL WASTEWATER

The non-steroid anti-inflammatory drugs in living organisms are not subject to degradation, but are only subject to minor transformations. They reach the environment together with wastewater from the production of drugs, municipal wastewater, leachate from waste landfills or from the manure used for fertilisation purposes. At the wastewater treatment plants, the drugs and their metabolites may be subject to biodegradation to CO_2 and H_2O, biotransformation, or may remain in an unchanged form [4]. Table 1 presents the concentrations of selected NSAIDs in raw wastewater and treated wastewater.

Table 1. Concentration of non-steroid anti-inflammatory drugs in raw and treated wastewater [10,17,18]

Medicament	Concentration in the wastewater µg/L		Removal, %	Literature
	raw	treated		
Salicylic acid	3.2	0.6	81	22
	8.0361 – 0.4339	0.0472- 0.0252	94-99	18
	0.351-9.172	<0.115	67-99	10
Diclofenac	3.0	2.5	17	5
	1.0	0.29	71	16
	2.8	1.9	23-30	14
	n.d	<0.743- <2.478	n.d	10
Ibuprofen	9.5-14.7	0.01-0.02	99	23
	2.0-3.0	0.6-0.8	53-79	21
	5.7	0.18	97	14
	28.0	3.0	98	16
	<0.760-3.204	n.d.	n.d.	10
Paracetamol	6.9	0	100	16
Ketoprofen	0.41-0.52	0.008-0.02	98	23
	0.25-0.43	0.15-0.24	8-53	21

n.d.-no data

Tests aimed at the evaluation of the removal of drug residues in various technologies used for running the biological process of wastewater treatment, showed that these methods were not sufficient. It follows from the data presented in the table 1 that the effectiveness of the removal of NSAIDs in municipal wastewater treatment plants is diverse even with regards to the same drug. This may prove that conventional wastewater treatment plants are not specialised enough in removing the residues of pharmaceutical substances, and the process of the removal of the drugs takes place, so to speak, ”additionally”. The treatment efficiency for each medicinal substance is different. High treatment efficiency was confirmed for salicylic acid, ibuprofen and paracetamol. On the other hand, in the case of diclofenac, the efficiency of removal was at a low level.

The removal of pharmaceuticals from wastewater in wastewater treatment plants takes place mainly as a result of adsorption in primary and secondary sludge, biodegradation in the biological processes in the second degree of wastewater treatment, or removal via highly efficient processes such as advanced oxidization [17, 19, 20].

The adsorption of pharmaceutical substances in sewage sludge depends on the hydrophobic properties of the drug and the electrostatic impacts with solid particles and microorganisms. Acidic pharmaceuticals, i.e. salicylic acid, ibuprofen, ketoprofen or diclofenac present in ionic form in a neutral environment, practically do not undergo the sorption process in the sewage sludge and remain in the liquid phase. For alkaline and hydrophobic pharmaceuticals, which include, for instance antibiotics, the sorption processes take place to a greater extent [17]. The effectiveness of the removal of diclofenac and naproxen in the wastewater treatment processes has been presented in table 2.

Table 2. The effectiveness of the removal of diclofenac and naproxen from wastewater in different treatment processes [20]

Process	The removal efficiency, %	
	Diclofenac	Naproxen
Adsorption in activated sludge	21-40 %	50-80%
Biological degradation/ biodegradation	0-25%	n.d.
Photolysis	25-75%	99-100%
Ozonation / H_2O_2	98%	98%
Adsorption on activated carbon	n.d.	52%

n.d. –no data

While analysing the data included in table 2, the conclusion may be drawn that the typical technological system for the treatment of municipal wastewater, including a primary settling tank, active sludge chamber and secondary settling tank eliminates up to 40% of diclofenac concentration and up to 90% of naproxen from wastewater. The remaining part of these drugs is discharged into flowing waters which act as a receiving body for wastewater. It must also be remembered that a significant part of the non-steroid anti-inflammatory drugs reaching the municipal wastewater treatment plants remains in sewage sludge. The use of such sludge in agriculture creates the risk of pharmaceutical substances permeating to the soil or ground waters [26]. In order to eliminate the residues of pharmaceuticals from the wastewater, it is necessary to apply other, more advanced treatment methods.

5. NON-STEROID ANTI-INFLAMMATORY DRUGS IN WATER ENVIRONMENT

Pharmaceuticals reach the water environment together with the treated municipal wastewater. The quantity of drugs which is discharged into the water environment on a one-off basis is small, however, the continuity of discharge may contribute to the accumulation of these substances, and thus, an increase in their concentration in the water environment. Table 3 presents the NSAID concentrations in surface waters of Poland and Europe.

Table 3. NSAID concentrations in surface waters of Poland and Europe [19]

Medicament	Concentration, ng/L	The State	Literature
Salicylic acid	100	Germany	24
Triclosan	200-2400	Norway	13
Paracetamol	188-2813	Spain	25
Diclofenac	25-170	Sweden	1
	9-49	Slovenia	7
	17-486	Poland	6
	313-3363	Spain	25
Ibuprofen	13-87	Sweden	1
	12-76	Poland	6
	2234-16886	Spain	25
Naproxen	6-130	Sweden	1
	17-80	Slovenia	7
	25-87	Poland	6
	387-3140	Spain	25
Ketoprofen	10-163	Sweden	1
	6-47	Poland	6
	43-1567	Spain	25

Analysis of the results listed in the table 3 showed that diclofenac, ibuprofen and naproxen were present in the highest concentrations.

Drugs in water ecosystems may exert a directly negative impact on water organisms. There is also an indirect hazard for humans in view of the fact that the surface waters are a frequent source of water intended for the supply of humans in potable water. It was proven that the concentration of 1.8 mg/dm^3 of acetylsalicylic acid, which belongs to the non-steroid anti-inflammatory drugs, affects the reproduction of a daphnia species called *Daphna magna* and cladocera from the *Digesta longispina* species. Diclofenac, characterised by the highest toxicity among NSAIDs, is acutely toxic for phytoplankton (EC_{50} (96h) = 14.5 mg/L) and zooplankton (EC_{50} (96h) = 22.43 mg/L) and shows chronic

toxicity as well as pathological changes in the kidneys and bronchi of rainbow trout (*O. mykiss*). The toxic impact of naproxen amounts to 12.3 mg/L for green algae and 690 mg/L for the rainbow trout [19].

It must be emphasised that the drug toxicity tests are usually performed for a specific xenobiotic, whereas the data regarding the toxicity of drug mixture are scarce. One of the tests proved that the mixture of drugs from the group of NSAIDs which included diclofenac, ibuprofen, naproxen and acetylsalicylic acid caused toxic effects despite the fact that the concentration of each of the drugs separately did not have a negative impact [17,19].

6. SUMMARY

The non-steroid anti-inflammatory drugs and other groups of drugs are a chemically diverse groups of compounds, which impact living organisms causing specific pharmacological effects. Pharmaceuticals and their metabolites reach the wastewater treatment plants together with municipal wastewater. Unfortunately, the traditional technological treatment systems do not eliminate these polar compounds occurring in hardly traceable amounts and are discharged into the surface waters together with the treated wastewater.

Tests performed all over the world and in Poland demonstrated the presence of non-steroid anti-inflammatory drugs both in the treated wastewater and in surface waters. However, the presented results do not reflect the reality as the tests are performed randomly.

The presence of biologically active pharmaceuticals or their metabolites exerts an impact on water organisms, triggering adverse effects, i.e. genetic mutations or development of drug-resistant bacterial cultures.

In the directive of the European Parliament and of the Council of August 12th, 2013 (2013/39/EU) on priority substances in the field of water policy, the European Commission placed 3 pharmaceutical substances on the watchlist: diclofenac, 17 beta-estradiol and 17 alpha-ethinyl estradiol. However in the detailed legal provisions concerning the identification of the problem of pollution of water and soil with residues of pharmaceuticals, there are no limits for these substances.

In view of the continuously increasing production and consumption of pharmaceuticals and the lack of effective methods of the removal of a broad spectrum of drugs reaching the ecosystems, it is indispensable to determine the critical concentrations of drug substances, which will not cause changes in the functioning of the whole natural environment.

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NIESTEROIDOWE LEKI PRZECIWZAPLANE W ŚCIEKACH MIESKICH I WODACH POWIERZCHNIOWYCH

S t r e s z c z e n i e

Wzrost produkcji i spożycia leków wpływa na zanieczyszczenie środowiska farmaceutykami. W ostatnich latach zaobserwowano zdecydowany wzrost spożycia leków dostępnych bez recepty, wśród których znaczną grupę stanowią niesteroidowe leki przeciwzapalne (NLPZ). Badania prowadzone na świecie i w Polsce wykazały obecność niesteroidowych leków przeciwzapalnych zarówno w ściekach oczyszczonych, w wodach powierzchniowych oraz w wodach pitnych. Jednym z najczęściej wykrywanych leków w środowisku jest diklofenak należący NLPZ. Jego stężenia w wodach powierzchniowych wynoszą od 9 do 3633 ng/dm^3. Tradycyjne układy technologiczne oczyszczania nie eliminują zupełnie farmaceutyków i ich metabolitów i wraz ze ściekami oczyszczonymi są one wprowadzane do wód powierzchniowych. Stężenia diklofenaku w ściekach oczyszczonych wynoszą od 0,29 do 2,5 µg/dm^3, a średnia skuteczność usuwania jest na poziomie ok 40%. Należy zaznaczyć, że dane te nie odzwierciedlają stanu rzeczywistego, gdyż badania są prowadzone wyrywkowo.
W 2013 r. Komisja Europejska w dyrektywie Parlamentu Europejskiego i Rady (2013/39/EU) w zakresie substancji priorytetowych w dziedzinie polityki wodnej, umieściła na liście obserwacyjnej trzy substancje farmaceutyczne, wśród których wymieniany jest diklofenak. Ciągle jednak nie ustalono limitów dotyczących wprowadzania substancji farmaceutycznych do środowiska.

Słowa kluczowe: zanieczyszczenie farmaceutykami, niesteroidowe leki przeciwzapalne, ścieki miejskie, wody powierzchniowe

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