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Occurrence of pharmaceuticals in aquatic environment–a review

Barbara Gworek, Marta Kijeńska*, Magdalena Zaborowska, Justyna Wrzosek, Lidia Tokarz, Jarosław Chmielewski

Institute of Environmental Protection–National Research Institute, Warsaw, Poland, Tel. +48 (22) 37 50 548, email: marta.kijenska@ios.edu.pl (M. Kijeńska), Tel. +48 (22) 37 50 503; email: barbara.gworek@ios.edu.pl (B. Gworek), Tel. +48 (22) 37 50 513; email: m.zaborowska@ios.edu.pl (M. Zaborowska), Tel. +48 (22) 37 50 539; email: justyna.wrzosek@ios.edu.pl (J. Wrzosek), Tel. +48 (22) 37 50 572; email: lidia.tokarz@ios.edu.pl (L. Tokarz), Tel. +48 (22) 37 50 503; email: jaroslaw.chmielewski@ios.home.pl (J. Chmielewski)

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ABSTRACT

Pharmaceuticals are long-lasting, biologically active substances that, when discharged into the natural environment, affect ecosystem stability. The presence of increasing amounts of pharmaceuticals and their transformation products in the environment has been a subject of growing interest due to their impact on living organisms, including human health. The incidence of pharmaceuticals and their transformation products has been so far recorded in surface and ground waters, drinking water, bottom sediments, soils, wastewater, and sewage sludge, as well as in animal organisms. A wide range of pharmaceuticals, including analgesics, antibiotics, and stimulant drugs are found in water resources. The pharmaceuticals commonly present in the environment are pharmaceuticals such as diclofenac, ibuprofen, ketoprofen, paracetamol, carbamazepine, fluoxetine, gemfibrozil, clofibric acid and caffeine. The article presents issues related to the presence of pharmaceuticals in the aquatic environment and their content in waters.

Keywords: Pharmaceuticals; Aquatic environment; Antibiotics; Steroidal sex hormones; Wastewater

1. Introduction

It was estimated, that more than 3,000 active substances of pharmaceuticals are registered and sold in the European Union [1]. The occurrence of pharmaceuticals and their transformation products in the environment has become a subject of growing interest due to their impact on living organisms, including human health, as well as the increasing amounts of these compounds that are introduced into the environment [2–7]. The presence of pharmaceuticals and their transformation products was observed in surface and ground waters, drinking water, bottom sediments, soils, wastewater and sewage sludge, as well as in animals (e.g. fish) and edible plants [4,6,8–10].

Further research is needed regarding the fate and behavior of pharmaceuticals in the environment [11]. It is estimated that over 4,000 pharmaceuticals are used in the treatment/prevention of humans and animals, and their metabolites (transformation products) are distributed in the environment in various ways [4,12,13].

The sources of pharmaceutical discharge into the environment are primarily: the pharmaceutical industry, landfills (e.g. with dumped expired drugs), as well as wastewater and sewage sludge (drug residues and their metabolites excreted mainly by humans) [14].

A wide range of pharmaceuticals, including analgesics, antibiotics and stimulant drugs has been observed in water and soil resources. Active substances such as diclofenac, ibuprofen, ketoprofen, paracetamol, carbamazepine, fluoxetine, gemfibrozil, clofibric acid and caffeine are regularly reported as being present in the environment [6]. Other

* Corresponding author.

important reported pharmaceutical classes are antibiotics and recently monitored illegal substances, such as amphetamine or heroin [15–19]. The presence of many widely available pharmaceuticals has been detected in treated wastewater, as well as in surface and underground waters-in the concentrations up to mg/L. Chronic exposure to even trace levels of pharmaceuticals can cause a potential hazard to the aquatic environment and to human health with possible effects such as antibiotic resistance and endocrine disruptive conditions [20]. According to Cunningham et al. [21], trace concentrations of pharmaceutical compounds in the aquatic environment, their dispersion in drinking water reservoirs and accumulation in fish tissues, do not pose any significant threat to human health.

Li [22] describes point and dispersed sources as significant pharmaceutical pathways in the environment (Table 1 [22–30]). Residue concentrations of active substances in the soil, drinking water sources and groundwater showed that residue concentrations in the environment were generally lower compared to the effluents from wastewater treatment plants. Natural processes occurring in the environment, such as biotransformation, photolysis and sorption reduce the impact of pharmaceuticals on living organisms. However, pharmaceuticals that do not degrade or dilute during natural processes or as a result of human activity, can accumulate in the environment and have potentially adverse effects on many organisms including humans. Some sources indicate that wastewater treatment plants are the main sources of pharmaceuticals in the environment [31]. Li [22] suggests that it is necessary to improve the wastewater treatment process (e.g. by introducing the third stage of treatment), towards reducing the concentration of pharmaceuticals released into the environment, thus eliminating the potential impact on nature. The author claims that it is necessary for the government to develop regulations and standards regarding the presence of pharmaceuticals in the environment in order to recognize its potential toxicity.

Standard methods of wastewater treatment cannot fully remove pharmaceuticals [32], therefore new effective methods for wastewater treatment and water purification should be sought. Currently, research on methods such as membrane processes, photocatalytic oxidation and adsorption dominate. Unfortunately, currently used technologies effectively remove only pharmaceuticals of certain classes. It is also important to carefully analyze the occurrence of active pharmaceutical substances in sewage sludge, so as to eliminate the migration of these compounds to the soil [33].

2. State-of-the-art

2.1. Occurrence of pharmaceuticals in the aquatic environment

2.1.1. Antibiotics

The three identified risks arising from excessive use of antibiotics in the treatment of environmental pollution are: original materials or byproducts, the secondary health effects through resilient microorganisms and direct biological injury [34]

The discharge of hospital wastewater into the municipal sewage network contributes to the overall pollution of the aquatic environment due to pharmaceutical residues. More persistent substances are bioaccumulation, which leads to an increased risk of accumulation in living organisms and the food chain in concentrations that can reach toxic levels. Therefore, a study was carried out which showed that it was possible to perform a preliminary ecotoxicological assessment of risks associated with pharmaceuticals released by hospitals – accumulating in the aquatic environment [35]. Hospital wastewater contains large amounts of hazardous contaminants that are discharged into the environment with or without treatment. Antibiotics belong to the group of pharmaceuticals considered to be a potential source of hazard to the health of humans and other living beings.

In the city of Ho Chi Minh (Vietnam), Vo et al. [36] conducted a wastewater analysis at 39 healthcare facilities to assess the real environmental risk of antibiotics in Vietnam. In the analyzed wastewater, sulfamethoxazole, norfloxacin, ciprofloxacin, ofloxacin, trimethoprim, erythromycin, and tetracycline were detected in high concentrations (up to 23 μg/L). The occurrence of antibiotics in the aquatic environment is associated with their potential impact on the quality of drinking water. Stackelberg et al. [37] state that pharmaceuticals and other organic compounds present in wastewater infiltrate drinking water and operate in this environment. As micro-pollutants, antibiotics can be introduced into water reservoirs, since they are detected there, although in very low concentrations [38].

Fluoroquinolones are one of the most important classes of antimicrobial chemotherapeutic agents used in human and veterinary medicine. A high prevalence of fluoroquinolones in medical procedures carries the risk of environmental pollution. Along with hospital and municipal wastewater, these pharmaceuticals and their metabolites get into water reservoirs [39,40]. Those that enter the aquatic environment are only slightly decomposed by microorganisms living in

Table 1
Examples of sources of pharmaceuticals in soil and water [22]

Type of source	Example	Reference
Point source	Municipal, hospital and industrial wastewater	[23–26]
	Septic tank	[27]
Dispersed source	Sewage sludge applied to the land surface	[28,29]
	Artificial recharge of aquifers with the use of water taken from the lake, river or other surface water	[30]
	Exchange of the surface water and the groundwater by the runoff and the downward migration due to attenuation mechanism in the soil and unsaturated zone	[22,30]

aquatic ecosystems, they can persist in surface waters for a long time and adversely affect aquatic organisms. Even with trace concentrations of fluoroquinolone in aquatic organisms, it has a gradual effect due to continuous exposure to these substances, because they cause invisible changes in aquatic organisms, with cumulative effects from generation to generation. This can lead to permanent and irreversible changes that will exceed the adaptability of species inhabiting streams, lakes, and rivers.

In Hanoi (Vietnam), wastewaters from the 6 largest local hospitals were tested for fluoroquinolone content. The focus was on five most commonly used: ciprofloxacin, norfloxacin, levofloxacin, ofloxacin, and lomefloxacin. Of the six hospitals examined, only one treated sewage before discharge. Duong et al. [41] showed only two of the five examined pharmaceuticals in untreated wastewater. Although the three remaining pharmaceuticals analyzed were used in large quantities in hospitals, the authors did not find any traces of these substances in untreated sewage. Detected ciprofloxacin concentrations ranged from 1.1 to 44 μg/L, and norfloxacin concentrations ranged from 0.9 to 17 μg/L. These results were compared with the values obtained in relevant studies carried out in Sweden, Switzerland and Germany. It was noted that the highest concentrations of fluoroquinolones were detected in wastewater from hospitals with large surgical departments, where the daily intake of norfloxacin and ciprofloxacin per one patient is 7.5 to 30.7 mg and 7.6 to 34.3 mg, respectively.

In the research of Hirsch et al. [42], the content of antibiotics was analyzed in groundwater collected in agricultural areas. Many test samples showed very high nitrogen concentrations (200 mg/L). Sulfonamide residues were also detected: in the samples from areas fertilized with sewage sludge-sulfamethoxazole (in concentrations reaching up to 0.47 μg/L in some samples) and sulfamethazine (0.16 μg/L). Erythromycin hydrate, clarithromycin, roxithromycin, and trimethoprim were detected in surface water samples at concentrations ranging from 0.20 (trimethoprim) to 1.70 (erythromycin) μg/L [38].

Total concentrations of various antibiotics are detected in the wastewater effluent and natural waters at concentrations ranging from ng/L to μg/L. For example, Watkinson et al. [43] determined antibiotic concentrations in sewage (concentrations of macrolides, quinolones and sulfonamide antibiotics in the load entering the wastewater treatment plant-up to 64 μg/L, and in the wastewater effluent-3.4 μg/L) and rivers (up to 2 μg/L in the surface waters). Hospital wastewater is a significant source of antibiotic residues that enter the treatment plant. Watkinson et al. [43] detected β-lactam, quinoline, lincosamides, macrolides and sulfonamides in hospital wastewater. In municipal sewage, human consumption of antibiotics constitutes the source of antibiotics, and in industrial sewage this may be for example, wastewater coming from meat processing plants [43]. In the influence of the municipal wastewater treatment plant, amoxicillin, erythromycin, penicillin, doxycycline, sulfasalazine, sulfamethoxazole were detected (the average concentration of the latter reported in various studies was: 0.243, 0.3, and 1.00 μg/L). Trimethoprim was detected in wastewater at the concentrations from 0.18 to 1 μg/L (median 0.43 μg/L). In the wastewater treatment process, quinolones and β-lactams undergo thermal degradation, however, minor concentrations of these substances were detected in the effluent. The situation is different with sulfonamides and trimethoprim, which showed high concentrations in the effluent, even though these pharmaceuticals are also degraded (incompletely) during the treatment process [43].

The results of Watkinson et al. [43] demonstrated the presence of, among others, trimethoprim, sulfamethoxazole, lincomycin and norfloxacin in the surface waters. The maximum concentrations of these compounds were: 0.042 μg/L (norfloxacin), 0.08 μg/L (ciprofloxacin), 0.027 μg/L (cefalexin). These data indicate incomplete removal of antibiotics studied during wastewater treatment. Only 80% of these compounds were found to be removed during the wastewater treatment process.

Karthikeyan and Meyer [44] detected antibiotics in the wastewater influent and effluent, in the vicinity of groundwater monitoring wells and in samples from wastewater treatment systems (Wisconsin, USA). There were detected: tetracyclines, trimethoprim (80% of all detected antibiotics), sulfamethoxazole (70%), hydrated erythromycin (45%), ciprofloxacin (40%) and sulfamethazine (10%).

The study conducted by Ye et al. [38] on the surface waters, showed significant concentrations of such antibiotics as fluoroquinolones, sulfonamides, lincomycins, tetracyclines, and macrolides. The most frequently detected compounds are also those that are regularly found in the effluent obtained in the wastewater treatment plant.

2.1.2. Steroid sex hormones

Steroid sex hormones constitute a separate class of pharmaceuticals detected in the aquatic environment, in which monitoring is required due to their increasing amounts and biological activity [45]. The fate and behavior of steroid hormones in the environment are not fully understood, although these compounds have been repeatedly detected in waters, soils and sediments. The dispersion of steroid sex hormones depends on their physico-chemical properties and the conditions in which they are found in individual components of the environment [46]. These pharmaceuticals get into the environment as a result of animal waste and municipal sewage disposal. Their presence in the aquatic environment has a significant impact on human and animal organisms [47]. Natural steroids: estrogen, estrone, 17β-estradiol and estriol, and synthetic steroids: 17α-ethinylestradiol and mestranol have a relatively low binding capacity in sediments and are rapidly degraded in water and soil. Estrogenic steroids have been detected in wastewater effluents at the concentrations up to 70 ng/L (estrone), 64 ng/L (17β-estradiol), 18 ng/L (estriol) and 42 ng/L (17α-ethinylestradiol).

The average concentration of 17β-estradiol in the rivers of Japan, Germany, Italy, and the Netherlands was up to 27 ng/L. High levels of this hormone were also detected in karstic groundwater reservoirs in Alaska (6–66 ng/L), as a result of the use of poultry and cattle manure [46]. Estrogenic steroids have been found in the wastewater influents and effluents in various countries. The average concentration of estrone, 17β-estradiol, estriol and ethinylestradiol in the influent wastewater of 6 treatment plants in Italy was 52, 12, 80 and 3 ng/L, respectively. Similarly, in

the wastewater influents in a wastewater treatment plant in Brazil, the same substances were detected at the concentrations: 21 ng/L (17β-estradiol), 40 ng/L (estrone) and 6 ng/L (ethinylestradiol).

Up to 48 ng/L of 17β-estradiol, 11–140 ng/L of estrone and <0.2–8.8 ng/L of ethinylestradiol have been reported in Dutch wastewater. In Japan, the concentrations of 17β-estradiol measured in the influent ranged from 30–90 ng/L (autumn) and 20–94 ng/L (summer). In the effluent, the average content of 17β-estradiol was up to 64 ng/L, that of estrone-up to 82 ng/L, estriol-from 0.43 to 18 ng/L and ethinylestradiol-up to 42 ng/L [42]. In surface waters, steroid hormones were found in the rivers of Japan (1.8–2.3 ng/L) and in coastal waters, estuaries and water reservoirs of the Netherlands (estrone-median 0.3 ng/L). In Germany, the concentrations of steroids in drinking water samples were on average 0.4, 0.7 and 0.35 ng/L. In the wastewater treatment process, 17α-ethinylestradiol (synthetic estrogen) is removed almost completely during the primary treatment, however, this stage has little effect on estrogen removal from wastewater. The latter is effectively removed in the process of the secondary treatment, with the use of activated sludge systems, membrane bioreactors or fixed-bed reactor systems. Membrane reactors are a promising method for removing synthetic estrogens from wastewater, due to the more complex degradation process compared to natural compounds [47].

Wastes from animal husbandry are a source of steroid hormones in the environment. The content of steroid hormones in animal husbandry waste is from 14 to 533 ng/g dry matter, on average 44 ng/g of 17β-estradiol. In manure from cattle that received doses of hormones TBA and MGA (trenbolone acetate and melengestrol acetate), 75 ng/g TBOH (trenbolone-17 beta) and 0.3–8 ng/g MGA were reported (46). As a result of the use of manure as a fertilizer, trenbolone and melengestrol enter the soil solution, where they show mobility and high affinity to the soil organic fraction [47]. The use of manure fertilizers also results in the discharge of steroid hormones into groundwater. 17β-estradiol is a mobile compound that was detected in surface runoff from lands fertilized with manure (at a rate of 5 Mg/ha, the average concentration of 17β-estradiol was 3,500 ng/L) [46]. Significant ecotoxic effects of hormonal substances on living organisms have been reported. Substances such as 17β-estradiol, estrone or 17α-ethynylstradiol cause, among others, an estrogenic effect, leading to disorders of secondary sexual characteristics and reproduction [48].

2.1.3. Residues of nonsteroidal anti-inflammatory and other pharmaceuticals in water

Increasing the production and consumption of pharmaceuticals may contribute to the problem of the presence of pharmaceuticals in aquatic ecosystems, and this particularly applies to over-the-counter (OTC) medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) [3,49]. In most cases, in waters, there are observed minor concentrations of pharmaceuticals [43]. The potential stability of pharmaceutical compounds and their derivatives in waters is, however, associated with exposure to unknown effects of chronic toxicity of these substances at low concentrations [5,7,13,38,43,50]. The introduction of unchanged pharmaceuticals or their metabolites into ecosystems poses a risk of accumulation of their residues in living organisms [48]. Drug resistance of microorganisms, which can be transferred to other strains (horizontal gene transfer), associated with the presence of antibiotics in the aquatic environment, has become a significant problem [4,42,51,49–53].

In Germany, in drinking water, there were found: diclofenac at a concentration of l6–35 ng/L, ibuprofen-3 ng/L, bezafibrate-27 ng/L, paracetamol-210 ng/L and clofibric acid-20–270 ng/L. In the studies of Zuccato et al. [54], diazepam (19.6–23.5 ng/L), tylosin (0.6–1.7 ng/L) and clofibric acid (3.2–5.3 ng/L) were detected in drinking water samples from various locations in Italy.

In the study by Ternes [25], concerning the occurrence of pharmaceutical substances in wastewater and rivers in Germany, carbamazepine (6.3 μg/L) was detected in wastewater effluent and bezafibrate-in river waters (up to 3.1 μg/L).

In the paper by Rodríguez-Navas et al. [55], the authors point out the discharges from wastewater treatment plants as the main source of pharmaceutical pollution of the aquatic environment of Majorca. The presented data indicate that the use of treated domestic wastewater for irrigation (which accounts for approx. 30% of the total water demand in Majorca) contributes to groundwater contamination. In addition, leaching of contaminants from landfills is identified as the second but less possible source of pharmaceuticals introduction into aquifers. Finally, the effluent from wastewater treatment plants reaches the Mediterranean Sea, with highly urbanized coastal areas, and causes the formation of pharmaceutical residues in marine waters.

The widespread occurrence of contaminants such as pharmaceuticals, hormones and steroids in the surface waters, draws attention to the impact of discharged wastewater-treated or untreated-on water quality along with fragile coastal ecosystems. Therefore, the occurrence and prevalence of steroids, hormones and selected pharmaceuticals in the coastal area of southern Florida were examined by Singh et al. [56]. The following substances were found in water samples: cholesterol, caffeine, estrone, N,N-diethyl-m-toluamide (DEET-insect repellent), bisphenol A (BPA), 17-β-estradiol and triclosan. Detected estrone and 17-β-estradiol concentrations were 5.2 and 1.8 ng/L, respectively. When compared to steroids, caffeine and DEET concentrations were higher and more widespread. Overall, the results indicate that water samples taken in inland canals, with limited water circulation, in the vicinity of densely populated areas, were characterized by high concentrations of steroids, pharmaceuticals and personal care products, while samples taken in open bay waters were largely free of target substances [56]. The average concentration of various pharmaceuticals in water treated sewage and sediments is shown in Table 2.

Lucero et al. [57] point out that the concentration of many pharmaceuticals, for example, naproxen, is often higher in sediments than that in the surface waters, but so far little research has been done on the presence of pharmaceuticals in bottom sediments. Camacho-Muñoz et al. [58] studied the occurrence of 16 pharmaceuticals in river sediments in the Doñana National Park, Spain. The highest sediment concentrations were recorded for diclofenac (52.1 μg/kg), salicylic acid (27.2 μg/kg) and caffeine (25.4 μg/kg). Other compounds detected in the analyzed sediments

Table 2
Occurrence of drug residues in sewage treatment plant effluents, surface waters and sediments [51]

Therapy class of drugs	Drugs	Sewage treatment plant effluents (ng/L)		Surface water (ng/L)		Sediments (ng/L)	
		Range of concentration	Average	Range of concentration	Average	Range of concentration	Average
Antibiotics	Trimethoprim	–	154	–	–	–	–
	Sulfamethoxazole	–	128	–	50	–	–
	Erythromycin	–	886	–	34	–	–
	Roxithromycin	–	680	–	–	–	–
	Tylosin	128–886	–	2–50	2.2	3–578	–
	Ofloxacin	–	–	–	–	–	3
	Chlortetracycline	–	–	–	–	–	73
	Flumequine	–	–	–	–	–	578
	Oxytetracycline	–	–	–	–	–	246
Analgesics and anti-inflammatories	Diclofenac	273–2,134	1,274	–	225	–	–
	Ibuprofen	–	2,134	–	226	–	–
	Naproxen	–	1,847	–	266	–	–
	Ketoprofen	–	733	–	–	–	–
	Mefenamic acid	–	–	–	68	–	–
Lipid regulator agents	Bezafibrate	–	2,353	270–1,100	–	–	–
	Fenofibrate	110–2,353	–	–	–	–	–
	Gemfibrozil	–	2,366	–	–	–	–
	Clofibric acid	–	361	–	270	–	–
β-Blockers	Propranolol	–	676	–	25	–	–
	Betaxolol	–	190	–	28	–	–
	Bisoprolol	190–777	–	25–2,000	–	–	–
	Atenolol	–	–	–	145	–	–
	Metoprolol	–	777	–	2,200	–	–
Antiepileptics	Carbamazepine	–	1,625	–	460	–	–
Steroid hormones	17-α-Ethinyl estradiol	–	7	–	2.4	28–51	–
	Diethylstilbestrol	18–20	–	2.4–7.5	–	–	–
	Diethylstilbestrol acetate	–	18	–	7.5	–	–

were naproxen, carbamazepine, propranolol, 17β-estradiol and estriol. Risk assessment revealed the possibility of long-term and acute threat to the ecosystem related to the presence of pharmaceuticals in the sediment [58].

Liquid chromatography (LC) (in many of its forms) is a preparative and analytical technique used to separate, identify, and quantify components in a mixture. It can be used to separate compound mixtures into two immiscible phases. Ultra or high-performance liquid chromatography (U/HPLC) has been widely used as a suitable technique in the analysis of large, polar, ionic, thermally unstable and non-volatile chemicals. As presented in Table 3, it has been proven that the above-mentioned methods, also in combination with mass spectrometry (MS), can be efficiently used in the determination of pharmaceuticals in aquatic environments [59–62].

2.1.4. Wastewater as a source for monitoring pharmaceuticals use

Pharmaceutical content research can be a powerful tool for monitoring levels and profiles of some pharmaceuticals, especially illicit drugs, consumed by the local community [17]. The examples of differentiation of antibiotics content in influents and effluents of wastewater treatment plants in various European countries are presented in Table 4 [89].

Various studies show that the commonly used of water treatments such as coagulation, flocculation, sedimentation, sand filtration, and disinfection with chlorine and wastewater treatment is not effective for removal of all pharmaceuticals present in raw water and wastewater [90], that is why new methods, such as ultrasonic degradation [91] or advanced oxidation processes [92] are developed. Until they become common and effective, the content of pharmaceuticals in wastewater can provide us with important information.

Table 3
Concentration of selected pharmaceuticals in various water environments

Drug	Range of concentration	Unit	Source of sampling	Country	Analytical method	Reference
Caffeine	1.11–621	ng/L	Danube surface water	Serbia	Solid-phase extraction LC-MS/MS	[11]
Carbamazepine	0.06–22.9					
Diazepam	<LOD–0.92					
Desmethyldiazepam	<LOD–0.68					
Sulfamethoxazole	<LOD–0.22					
Ibuprofen	<LOD–60.1					
Sotalol	<LOD–1,621.3	ng/L	3 samples – Ebro river 14 samples – wastewater from 6 sewage treatment plants	Spain	Solid-phase extraction Ultra-performance liquid chromatography/ (quatrupole time-of-flight)-MS	[59]
Trimethoprim	<LOD–748.6					
Ranitidine	<LOD–1,239.1					
Atenolol	<LOD–1,195					
Metoprolol	<LOD–21.3					
Sulfamethoxazole	<LOD–638.6					
Ofloxacin	<LOD–2,536.2					
Famotidine	<LOD					
Ibuprofen	<LOD–14,666.8					
Mefenamic acid	<LOD					
Gemfibrozil	<LOD–1,523					
Diclofenac	<LOD–989.2					
Indometacin	<LOD–178.3					
Bezafibrate	<LOD–350.2					
Clofibric acid	<LOD					
Naproxen	<LOD–1,998.2					
Ketoprofen	<LOD–550.7					
Propranolol	22–54	ng/L	Mouth of the Douro river	Portugal	Solid-phase extraction HPLC-DA (diode array detector)	[62]
Carbamazepine	21.3–32.7					
Acetaminophen	1.89	μg/L	Groundwater (median depth 61 m)-one of the sources of drinking water in California	USA	Solid-phase extraction HPLC-MS	[60]
Caffeine	0.29					
Carbamazepine	0.42					
Codeine	0.214					
Xanthine	0.12					
Sulfamethoxazole	0.17					
Trimethoprim	0.018					
Ibuprofen	<LOD–414 ± 13	ng/L	Mankyung river	South Korea	Solid-phase extraction HPLC-MS	[61]
Mefenamic acid	<LOD–326 ± 21					
Indometacin	<LOD–33.5 ± 8					
Carbamazepine	<LOD–595 ± 14					
Propranolol	<LOD–40.1 ± 3					
Atenolol	<LOD–690 ± 26					
Disopyramide	<LOD					
Ifenprodil	<LOD–35.4 ± 16					
Fluconazole	<LOD–111 ± 13					
Erythromycin	<LOD–137 ± 15					
Clarithromycin	<LOD–443 ± 14					
Levofloxacin	<LOD–87.4 ± 13					
Triclosan	<LOD					

LOD–Limit of detection

Table 4
Occurrence of antibiotics residues in European countries in wastewater treatment plant influents and effluents [63]

Country	Reference	Concentration in wastewater treatment plant influent (ng/L)	Concentration in wastewater treatment plant effluent (ng/L)
Belgium	[64]	Trimethoprim 111	Trimethoprim 34
		Metronidazole 24	Metronidazole ND
		Ciprofloxacin 342	Ciprofloxacin 45
		Levofloxacin 413	Levofloxacin 45
		Moxifloxacin 317	Moxifloxacin 281
		Sulfamethoxazole ND	Sulfamethoxazole 54
		Tetracycline 1,371	Tetracycline ND
Croatia	[65]	Trimethoprim 35–3,442	Trimethoprim 924–1,352
		Azithromycin 77–1,129	Azithromycin 38–784
		Clarithromycin 112–300	Clarithromycin 25–113
		Erythromycin 24–420	Erythromycin 15–163
		Roxithromycin ND-50	Roxithromycin ND
		Ciprofloxacin ND-2,610	Ciprofloxacin 11–201
		Enrofloxacin ND-16	Enrofloxacin 7–12
		Norfloxacin ND-2,937	Norfloxacin 24–1,185
		Sulfadiazine 2–132	Sulfadiazine 1–18
		Sulfamethoxazole 210–11,555	Sulfamethoxazole 119–1,207
		Sulfamethazine 2–175	Sulfamethazine ND
		Sulfapyridine 80–931	Sulfapyridine 48–784
Czech Republic	[66]	Trimethoprim 120–530	Trimethoprim 83–440
		Azithromycin 14–510	Azithromycin 8–220
		Clarithromycin 310–3,090	Clarithromycin 210–2,310
		Erythromycin 20–300	Erythromycin 30–350
		Ciprofloxacin 80–860	Ciprofloxacin 8–190
		Levofloxacin 5–69	Levofloxacin 4–18
		Norfloxacin 130–1,330	Norfloxacin 20–250
		Sulfamethoxazole 43–490	Sulfamethoxazole 31–230
		Sulfapyridine 18–660	Sulfapyridine 14–200
	[67]	Clindamycin ND-150.7	Clindamycin ND-102.1
		Lincomycin ND-32.7	Lincomycin ND-46.4
		Clarithromycin 79–1,287	Clarithromycin 61–794.2
		Erythromycin ND-248.6	Erythromycin ND-204.2
		Ciprofloxacin ND-640.6	Ciprofloxacin ND-133.6
		Norfloxacin ND-377.4	Norfloxacin 24.2–63
		Ofloxacin ND-485	Ofloxacin ND-283
		Sulfadimidine ND-177.1	Sulfadimidine ND
		Sulfamethoxazole ND-796.2	Sulfamethoxazole ND-681.1
France	[68]	Erythromycin 150–200	Erythromycin 100–200
		Ofloxacin 300–600	Ofloxacin 100–500
Germany	[69]	ND	Clarithromycin 110–460
	[70]	ND	Sulfamethoxazole 380–510
	[71]	Cefuroxime 49–6,196	Cefuroxime ND-1,957
		Cefotaxime ND-492	Cefotaxime ND-217
		Amoxicillin ND-1,270	Amoxicillin ND-187
		Penicillin V ND-252	Penicillin V ND
		Piperacillin ND-2,603	Piperacillin ND-1,205
		Trimethoprim 22–372	Trimethoprim 25–554
		Vancomycin ND-664	Vancomycin ND-348
		Clindamycin 11–163	Clindamycin 20–882
		Azithromycin 50–946	Azithromycin ND-956
		Clarithromycin 42–1,525	Clarithromycin 18–1,800
		Roxithromycin ND-771	Roxithromycin ND-181

Table 4 (*continued*)

Country	Reference	Concentration in wastewater treatment plant influent (ng/L)	Concentration in wastewater treatment plant effluent (ng/L)
Greece	[72]	Ampicillin ND-1,805	Ampicillin ND-498
		Trimethoprim <LOQ-200	Trimethoprim ND-95.8
		Lincomycin ND-281	Lincomycin ND-<LOQ
		Erythromycin ND-320	Erythromycin ND
		Roxithromycin ND-<LOQ	Roxithromycin ND
		Metronidazole ND-64.7	Metronidazole ND-35.2
		Ciprofloxacin ND-591	Ciprofloxacin ND-591
		Moxifloxacin ND-773	Moxifloxacin ND-298
		Sulfadiazine ND-846	Sulfadiazine ND-194
		Sulfamethoxazole ND-507	Sulfamethoxazole ND-80
	[73]	Trimethoprim ND-1,866.2	Trimethoprim ND-533.2
		Sulfamethoxazole ND-2,626.3	Sulfamethoxazole ND-481.3
Ireland	[74]	ND	Trimethoprim 60–1,200
Italy	[75]	Sulfamethoxazole 104.5	Sulfamethoxazole 53.4
	[76]	Trimethoprim 59	Trimethoprim 40
		Azithromycin 120	Azithromycin 130
		Clarithromycin 200	Clarithromycin 280
		Erythromycin 46	Erythromycin 15
		Roxithromycin 65	Roxithromycin 290
		Metronidazole 42	Roxithromycin 28
		Ciprofloxacin 2,200	Ciprofloxacin 630
		Norfloxacin 210	Norfloxacin 150
		Ofloxacin 980	Ofloxacin 400
	[77]	ND	Trimethoprim ND-27
			Azithromycin 44–175
			Clarithromycin 102–283
			Metronidazole 16–19
			Ciprofloxacin 25–284
			Sulfamethoxazole 91–97
	[78]	Chloramphenicol 13–24	Chloramphenicol ND
		Trimethoprim 39–72	Trimethoprim 36–51
		Azithromycin 10–330	Azithromycin 70–180
		Clarithromycin 110–780	Clarithromycin 260–310
		Erythromycin 26,573	Erythromycin 12,328
		Josamycin ND-7	Josamycin ND
		Roxithromycin ND-140	Roxithromycin 13–53
		Spiramycin ND-150	Spiramycin 19–53
		Tilmicosin 21–460	Tilmicosin ND-81
		Metronidazole 28–56	Metronidazole 13–41
		Ciprofloxacin 1,100–3,700	Ciprofloxacin 290–1,100
		Enoxacin 81–130	Enoxacin 30–100
		Norfloxacin 150–310	Norfloxacin 140–170
		Ofloxacin 450–2,200	Ofloxacin 220–520
		Sulfadiazine 13–26	Sulfadiazine 10–21
		Sulfamethazine 10–33	Sulfamethazine 10–15
		Sulfamethoxazole 280–740	Sulfamethoxazole 170–240

Table 4 (*continued*)

Country	Reference	Concentration in wastewater treatment plant influent (ng/L)	Concentration in wastewater treatment plant effluent (ng/L)
Portugal	[79]	Azithromycin ND-719.3	Azithromycin ND
		Ciprofloxacin ND-17,500	Ciprofloxacin ND-9,800
	[80]	Trimethoprim ND-360	Trimethoprim 66.6–299
		Azithromycin 79.7–295	Azithromycin 93.7–297
		Clarithromycin ND-52.3	Clarithromycin 12–40
		Erythromycin 9.64–220	Erythromycin 20.4–134
		Metronidazole <LOQ-113	Metronidazole 19.4–83.5
		Ciprofloxacin 107–330	Ciprofloxacin 127–1,396
		Ofloxacin 51.9–4,986	Ofloxacin 110–366
		Sulfamethoxazole 529–1,662	Sulfamethoxazole 340–1,679
		Tetracycline <LOQ-32.3	Tetracycline <LOQ-22.8
Romania	[81]	Ceftriaxone ND-334,000	Ceftriaxone ND
		Doxycycline ND-110,000	Doxycycline ND
		Tetracycline ND-146,000	Tetracycline ND
Slovakia	[82]	Trimethoprim 99–187	Trimethoprim 86–88
		Clindamycin 44–70	Clindamycin 35–69
		Azithromycin 276–1,360	Azithromycin 266–1,220
		Clarithromycin 771–2,520	Clarithromycin 624–1,890
		Erythromycin 79–118	Erythromycin 12–20
		Ciprofloxacin 484–2,710	Ciprofloxacin 96–338
		Norfloxacin 46–404	Norfloxacin 13–33
		Sulfamethoxypyridazine 28–57	Sulfamethoxypyridazine <LOQ
		Sulfamethoxazole 51–320	Sulfamethoxazole 9.2–108
		Sulfapyridine 137–419	Sulfapyridine 15–120
		Sulfasalazine 26–124	Sulfasalazine 7.5–124
		Doxycycline 12–48	Doxycycline <LOQ-8
		Tetracycline <LOQ-22	Tetracycline <LOQ-3.1
Spain	[83]	Ciprofloxacin 1,172–1,558	Ciprofloxacin 36–104
	[84]	Trimethoprim 54	Trimethoprim 7
		Azithromycin 129	Azithromycin 143
		Clarithromycin 100	Clarithromycin 99
		Erythromycin 15	Erythromycin 18
		Ciprofloxacin 392	Ciprofloxacin 176
		Ofloxacin 128	Ofloxacin 118
		Sulfamethoxazole 70	Sulfamethoxazole 10
	[85]	Trimethoprim 11–204	Trimethoprim ND-100
		Azithromycin 44–205	Azithromycin 20–170
		Clarithromycin 55–459	Clarithromycin <LOQ-192
		Erythromycin 35–63	Erythromycin <LOQ-17
		Ciprofloxacin 230–252	Ciprofloxacin 87–245
		Ofloxacin 202–309	Ofloxacin 169–191
		Sulfamethoxazole ND-768	Sulfamethoxazole ND-222
	[86]	Trimethoprim 60–160	Trimethoprim 60–100
		Clindamycin ND	Clindamycin 10–20
		Lincomycin 100–880	Lincomycin 10–160
		Clarithromycin 130–620	Clarithromycin 10–60
		Erythromycin ND	Erythromycin 50–120
		Ciprofloxacin 1,210–3,850	Ciprofloxacin 520–1,080
		Norfloxacin 290–1,070	Norfloxacin 90–150
		Ofloxacin 290–960	Ofloxacin 330–500
		Pipemidic acid <LOQ-540	Pipemidic acid <LOQ-120
		Sulfamethoxazole 220–640	Sulfamethoxazole 40–60
		Sulfathiazole 60–70	Sulfathiazole ND

Table 4 (*continued*)

Country	Reference	Concentration in wastewater treatment plant influent (ng/L)	Concentration in wastewater treatment plant effluent (ng/L)
Sweden	[87]	ND	Trimethoprim 27–101 Clindamycin <LOQ-154 Clarithromycin 14–78 Ciprofloxacin <LOQ-10.5 Norfloxacin <LOQ-10.6
Switzerland	[88]	ND	Trimethoprim 6.8–169 Clindamycin ND-23.5 Metronidazole ND-3,809.8 Ciprofloxacin 97.65–4,186.1 Norfloxacin <LOQ-1,283.8 Ofloxacin 10.9–1,865.3

It is very difficult to determine the rate of drug use in the community. Conventional methods include surveys, toxicological and overdose reports and crime statistics [89,93]. Sewage epidemiology is an approach of determining drug consumption by determining the concentration of target pharmaceuticals and their metabolites in wastewater influent. This method can provide a real-time and cost-effective measurement of drug abuse and, contrary to the conventional methods of drug use estimation, can be used on a rapid timescale, even including day to day variations [93]. Foppe et al. [89] conducted research focused on the comparison of illicit drug consumption in Western Kentucky during special events like Independence Day or solar eclipse and a typical week.

3. Conclusions

The scale of production and consumption of pharmaceuticals by humans and animals is becoming a serious threat to the environment. Sources of pharmaceutical discharge into the environment are pharmaceutical industry, landfills (with disposed of pharmaceuticals), as well as wastewater and sewage sludge (due to ingestion and following excretion by humans). Commonly occurring in the environment pharmaceuticals are diclofenac, ibuprofen, ketoprofen. paracetamol, carbamazepine, fluoxetine, gemfibrozil, clofibric acid and caffeine. Already at the end of the 1990s, more than 40 pharmaceutical substances were detected in treated wastewater and surface waters; in a range from pg/L to μg/L. Significantly, higher concentrations of pharmaceuticals are detected in inland waterways and reservoirs with limited water circulation, especially in the vicinity of densely populated areas as compared to flowing waters (rivers).

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