Sources of Pharmaceuticals in Water

Roberto Parra-Saldivar, Carlos Castillo-Zacarías, Muhammad Bilal, Hafiz M. N. Iqbal, and Damiá Barceló

Contents

Abstract This chapter focuses on the increasing environmental apprehensions and persistence of numerous organic contaminants so-called emerging contaminants (ECs), including biologically active elements from pharmaceutical source industries. Several types of diverse pharmaceutical-related compounds are being detected in environmental matrices and wastewater treatment units. Owing to this broader occurrence, transformation, and detection of pharmaceutical-related compounds in water matrices, people and legislative authorities are now more concerned about potential sources and ecological consequences of ECs. This is mainly because the free movement of ECs in water matrices is posing noteworthy adverse effects on human, aquatic animals, and naturally occurring plants, even at minimal

R. Parra-Saldivar, C. Castillo-Zacarías, and H. M. N. Iqbal (✉)
Tecnologico de Monterrey, School of Engineering and Sciences, Monterrey, NL, Mexico
e-mail: hafiz.iqbal@tec.mx

M. Bilal
School of Life Science and Food Engineering, Huaiyin Institute of Technology, Huaian, 223003, China

D. Barceló
Water and Soil Quality Research Group, Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Spain

Catalan Institute for Water Research (ICRA), Girona, Spain

College of Environmental and Resources Sciences, Zhejiang A&F University, Hangzhou, China

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concentrations. So far, several detection and treatment processes have been proposed and exploited against numerous pharmaceutical-related ECs. The useful and side effects of pharmaceutical-related compounds have been extensively inspected. Owing to this substantial research gap, the sources and environmental persistence of pharmaceutical-related ECs and their direct/indirect adverse effects have now been the topic of intensive studies. From the surface water perspective, wastewater treatment plants (WWTPs) are the major source of pharmaceutical-related ECs. The current chapter spotlights the widespread occurrence, numerous sources, and transportation fate of pharmaceutical-related ECs in water matrices.

Keywords Aquatic environment, Biological risks, Emerging contaminants, Hazardous compounds, Pharmaceuticals, Sources, Toxicity, Transmission fate, Wastewater treatment

1 Introduction: Problem Statement and Opportunities

In recent years, the term "emerging contaminants (ECs)" has raised the ecological concerns and public attention to the presence of toxic entities in the aquatic environment. Such harmful entities, with particular reference to the occurrence of pharmaceutical-related ECs, are mainly introduced in our water matrices through various industrial and domestic practices. A constant rise in the global population and urbanization and their associated increase in the consumption of pharmaceuticals have redirected the researches' attention. In addition, wide-ranging water contamination by pharmaceutical compounds has become a growing worldwide concern [1, 2]. The concentrations of persistent organic pollutants, such as pharmaceuticals and their metabolites, are continuously rising in the natural environment due to human activities [3–6]. The most practiced pharmaceuticals include analgesics/anti-inflammatories and synthetic antibiotic compounds. Some of them are β-lactams (amoxicillin and penicillin), cardiovascular pharmaceuticals (β-blockers/diuretics), estrogens and hormonal compounds (estriol, estradiol, estrone, and 17α-ethinylestradiol), and antiepileptic drugs (carbamazepine) [7]. AU2

The major source of pharmaceutical-related ECs is the treated/untreated effluents of WWTPs. WWTPs are not designed to eliminate environmental pollutants completely, and thus they can percolate through WWTPs and incorporated into the aquatic systems (streams and rivers) [8]. For example, the contents of diclofenac (an anti-inflammatory drug) and carbamazepine reached 0.99 and 0.95 μg/L, respectively, in WWTP effluents [9]. Particularly, a detectable level of diclofenac has been identified in drinking, surface, and groundwaters in the range of ng/L to μg/L in Sweden, Spain, Switzerland, and the Baltic region [10–12]. Apart from this, other pharmaceuticals, including tramadol, carbamazepine, ibuprofen, oxazepam, and naproxen, have also recently been detected in drinking water supplies in some countries. These concentrations of pharmaceuticals can induce serious environmental threats such as congenital disorders, physical abnormalities, impairments of the endocrine and reproductive system, and feminization of some fish species [13, 14]. Due to the capability of micro-pollutants and pharmaceutically active compounds to cause adverse effects to the ecosystem and human health, they have attracted the principal research focus in recent days. Some notable adverse effects of numerous ECs are shown in Fig. 1 [14].

This chapter focuses on the widespread occurrence, and numerous sources, such as domestic, medical, agricultural, and industrial sectors that discharge pharmaceutical-related ECs into water matrices. The focus is also given to the fate of pharmaceutical-related ECs in the aquatic environment. The later part of the chapter discusses risk management issues to advance the existing knowledge further to improve the sewage WWTPs and increase public consciousness of the concentration of pharmaceutical-related ECs and biologically active residues in the water matrices.

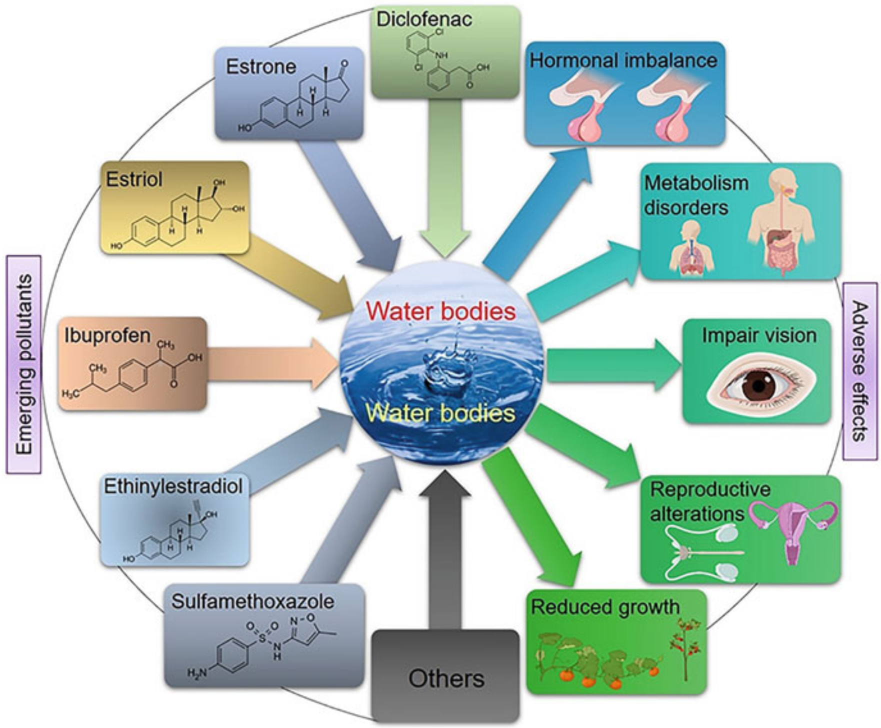

Fig. 1 A schematic illustration of considerable adverse effects of abundant ECs. Reprinted from Morsi et al. [14] Laccases and peroxidases: The smart, greener and futuristic biocatalytic tools to mitigate recalcitrant emerging pollutants. Science of The Total Environment, 714, 136572, © 2020 Elsevier B.V., with permission from Elsevier

2 Sources of Pharmaceuticals

Broadly speaking, the sources of pharmaceuticals can be categorized in two ways, i.e., (1) point-based pharmaceutical-related ECs and (2) diffuse-based pharmaceutical-related ECs. The former type is further considered as a single identifiable source that initiates from various location-based sources, such as domestic sewage sources, domestic solid waste, pharmaceutical-related industrial sector waste effluents, biomedical (hospital) wastes (effluents and solid wastes), and WWTPs. Such point-based sources are easy to identify and quantify from the specific location hotspots and can be calculated via mathematical modeling [7, 15]. Moreover, the wastewater effluent-based point sources are the main cause of environmental pollution and soil zone and water matrix contamination. Unlike point-based source pollution, the exact source location of the second category, i.e., diffuse-based source pollution, is hard to identify, which generally occurs over a broader geographical scale [15]. Some main examples of diffuse-based source pollution are the agricultural soil erosion/runoff, urban runoff, and unrecognized leakage of waste from wastewater treatment systems and plants [7, 16]. As it can be seen from Fig. 2, it shows the possible routes of antibiotics, one type of pharmaceuticals, that how such polluting agents are discharged from their sources and found their way to the receptor locations, such as ground and surface water bodies [1]. In addition to this, the receptor locations/ hotspots, which are directly or indirectly influenced by the pharmaceutical-related

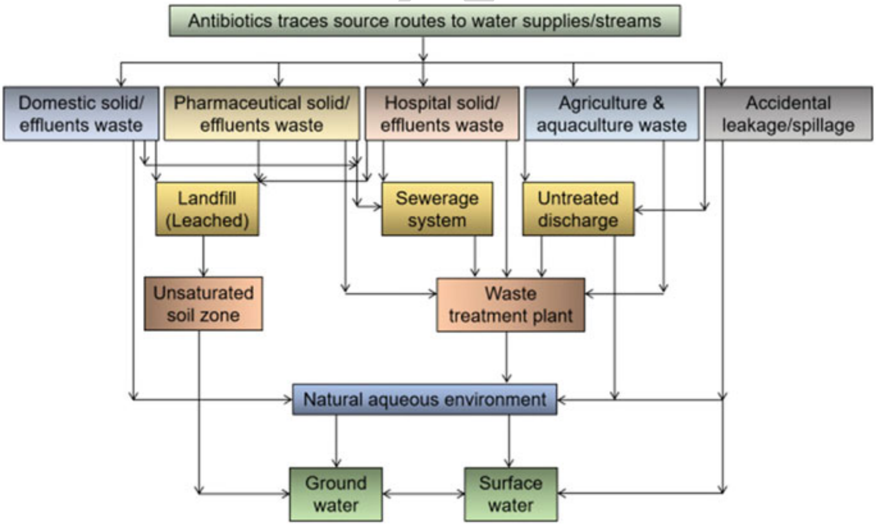

Fig. 2 Major point and nonpoint-based sources of antibiotics pollution and their possible transmission routes to groundwater and surface water bodies. Reprinted from Bilal et al. [1] Biocatalytic degradation/redefining "removal" fate of pharmaceutically active compounds and antibiotics in the aquatic environment. Science of The Total Environment, 691, 1190–1211, © 2019 Elsevier B.V., with permission from Elsevier

ECs, can be categorized into three main spots, i.e., (1) unsaturated soil zone, (2) groundwater, and (3) surface water. Plentiful aspects such as the type and class of antibiotics, concentration, unwarranted dosage, acquaintance time, persistence duration, removal pattern, reception hotspots, i.e., soil, water, or air. Moreover, the occurrences of multi-antibiotics along with other biologically active pollutants as a complex mixture pointedly affect their conceivable transmission into the aquatic environment. Consequently, a diverse spectrum of biologically active constituents of antibiotics has been found as micro-contaminants in soil and water matrices, in the past two decades [17, 18].

In addition, besides their broader occurrence, the concentration is disturbingly growing in an uncontrolled manner. The hefty usage of numerous antibiotics, regardless of types and classes, is being practiced around the globe in a controlled or uncontrolled fashion [1]. Main examples of heavily consumed antibiotics include active members from the class penicillins (under the category of amoxicillin, ampicillin, and dicloxacillin), active members from the class cephalosporins (under the category of cephalexin, cefaclor, cefotaxime, and ceftazidime), active members from the class macrolides (under the category of erythromycin, clarithromycin, and azithromycin), active members from the class quinolones (under the category of ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin), active members from the class sulfonamides (under the category of sulfasalazine and trimethoprim), active members from the class tetracyclines (under the category of minocycline, eravacycline, demeclocycline, and doxycycline), active members from the class glycopeptides (under the category of dalbavancin, oritavancin, telavancin, and vancomycin), active members from the class aminoglycosides (under the category of gentamicin, tobramycin, and amikacin), and active members from the class carbapenems (under the category of meropenem, doripenem, ertapenem, imipenem, and cilastatin) (Fig. 3) [1]. AU4

In a modern medicine practice, several types of antibiotics as mentioned above are among the most recurrently prescribed medications. According to one study, in the USA alone, out of 61 million US women with reproductive age, i.e., 15–44 years, around 99% used at least one contraceptive-based medicine, whereas other 60% regularly use contraceptive-based medicine [19–21]. More specifically, out of all those who used contraceptive-based medicine, approximately 72% practice nonpermanent methods, i.e., primarily hormonal methods (i.e., the pill, patch, implant, injectable, and vaginal ring) [21, 22]. Ultimately, upon excretion in the AU5 domestic sewage of poorly metabolized active residues of the used contraceptives find their way into the aquatic environment [17], even after passing through a partial or inadequate treatment at of the swage waste at the WWTPs. Similarly, other pharmaceuticals, such as ibuprofen, naproxen, acetaminophen, acetylsalicylic acid, and carbamazepine, have been considered high-use and/or overuse antibiotics in Canada [23]. Despite the excessive consumption of pharmaceuticals by humans, several other pharmaceutically active constituents, such as antibacterials, antifungals, and parasiticides, are tremendously employed in the aquaculture, veterinary, agriculture, and animal care settings. In the USA alone, about 92,500 and 196,400 kg antibacterials/year are used for aquaculture-based applications. Moreover, around 8.5 and 11.2 million kg antibacterials are employed in the agricultural setting, annually [24, 25]. Regardless of their usefulness in the respective sectors, the heavily

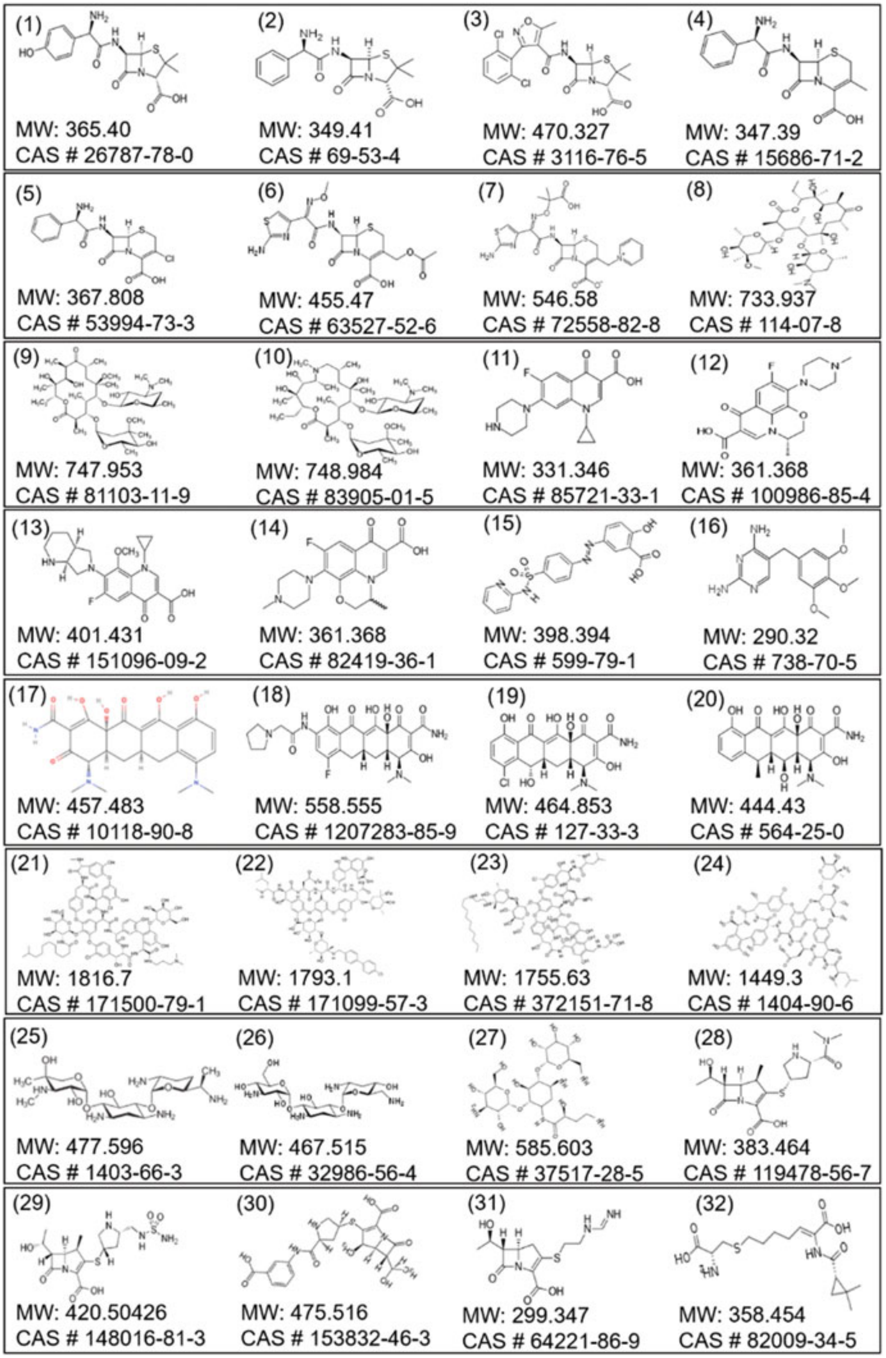

Fig. 3 Illustration of selected antibiotics. Structural, molecular, and CAS details for each represented antibiotic are also given accordingly. (1) Amoxicillin, (2) ampicillin, (3) dicloxacillin, (4) cephalexin, (5) cefaclor, (6) cefotaxime, (7) ceftazidime, (8) erythromycin, (9) clarithromycin, (10) azithromycin, (11) ciprofloxacin, (12) levofloxacin, (13) moxifloxacin, (14) ofloxacin,

exploited antibiotics end up their transmission fate to the soil, groundwater reservoirs, and surface waters, directly or indirectly, through runoff or drain-off [26]. Such a controlled or uncontrolled transmission of antibiotics residues massively stress the ecosystem that should be dealt with care for their effective mitigation prior to release into water matrices. Other potential sources of pharmaceuticals in our water bodies include the unrestrained spillage or improper dumping of expired drugs in the landfill site. Besides, drainage/sewage system and waste effluent streams are also the points of significant contamination [27, 28].

3 Case Studies of Point-Based Source Pollution

As mentioned earlier, WWTPs are considered one of the significant and imperative point-based sources of pharmaceutical-related ECs in water matrices [29–31]. The existing literature evidently shows that a diverse range of around 16 to 54 types of pharmaceuticals is found in wastewater effluents. For instance, He et al. [31] performed a scale-based approximation of pharmaceutical concentrations and associated environmental risk in the Japanese wastewater system. It was recorded that 36 pharmaceuticals, majority of them were antibiotics and analgesics, had high predicted environmental concentrations in influent with pranlukast, a receptor antagonist which has the highest concentration in wastewater influent at 257.0 μg/L. Moreover, among all tested pharmaceuticals, the occurrence concentrations of 26 were relatively higher than 1.0 μg/L, while the predicted environmental concentrations of 6 other pharmaceutical-related compounds were extremely higher than 10.0 μg/L. Such existence or occurrence of pharmaceuticals at extreme/higher level possibly attributes to excessive consumption rates by consumers and poor removal rates in WWTPs. From a consumers-based source view, partially or incompletely metabolized pharmaceutical excretion into the domestic sewage stream is the main cause of pharmaceuticals to the aquatic environment [32]. Among several reported pharmaceutical compounds, analgesics/anti-inflammatories (i.e., acetaminophen, salicylic acid, and salicylamide) are abundant in wastewater influent (>100 ng/L) in Japan [33, 34]. Likewise, the occurrence of pharmaceuticals in wastewater stream/influents in the USA, the UK, Spain, Italy, India, and China has been reported [35–40]. To avoid literature redundancy, Table 1 summarizes various studies that report the notable occurrence of pharmaceuticals in environmental matrices.

AU6 AU7

Fig. 3 (continued) (15) sulfasalazine, (16) trimethoprim, (17) minocycline, (18) eravacycline, (19) demeclocycline, (20) doxycycline, (21) dalbavancin, (22) oritavancin, (23) telavancin, (24) vancomycin, (25) gentamicin, (26) tobramycin, (27) amikacin, (28) meropenem, (29) doripenem, (30) ertapenem, (31) imipenem, and (32) cilastatin. MW: molecular weight (g/mol). See CAS # for further details. Reprinted from Bilal et al. [1] Biocatalytic degradation/redefining "removal" fate of pharmaceutically active compounds and antibiotics in the aquatic environment. Science of The Total Environment, 691, 1190–1211, © 2019 Elsevier B.V., with permission from Elsevier t1.1 **Table 1** Various studies that report the notable occurrence of pharmaceuticals in the environmental matrices

	Reference	Pharmaceuticals	Remarks/highlights
t1.2			
t1.3	He et al. [31]	Acetaminophen, salicylic acid, salicylamide, ibuprofen, naproxen, ketoprofen, clarithromycin, trimethoprim, roxithromycin, azithromycin, sulfamethoxazole, sulpiride, thiamphenicol, atenolol, diphenhydramine, and pirenzepine	Thirty-six pharmaceuticals, majority of them were antibiotics and analgesics, had high predicted environmental concentrations in influent. Nine pharmaceuticals in the effluent showed high toxicity based on predicted environmental concentrations/predicted no effect concentration ratio
t1.4	Felis et al. [41]	Aminoglycosides, β-lactams, glycopeptides, macrolides, fluoroquinolones, sulfonamides and trimethoprim, tetracyclines	Occurrence and environmental implications of antimicrobial pharmaceuticals in the aquatic environment WWTPs are indeed the main source responsible for the prevalence of these factors in the aquatic environment
t1.5	Nantaba et al. [42]	Trimethoprim, azithromycin, sulfamethoxazole, diclofenac, ibuprofen, sulfamethazine, enoxacin, sulfacetamide, atenolol, oxytetracycline, metoprolol, tetracycline, erythromycin, roxithromycin, bezafibrate, ciprofloxacin, levofloxacin, norfloxacin, sparfloxacin, metronidazole, diazepam, acetaminophen, carbamazepine, and fluoxetine	Occurrence of pharmaceutical residues in Africa's largest freshwater lake Twenty-four pharmaceuticals were detected in water from Lake Victoria, Uganda
t1.6	Su et al. [43]	Caffeine, carbamazepine, azithromycin, bezafibrate, metoprolol, sulfadiazine, sulfamethoxazole, clarithromycin, erythromycin, roxithromycin, and trimethoprim	Spatiotemporal distribution of 27 pharmaceuticals in the Chaobai River Agriculture area presented the highest pharmaceutical concentrations The acute toxic pressure in the river was mainly driven by caffeine
t1.7	Stroski et al. [6]	Atenolol, carbamazepine, metoprolol, naproxen, sulfapyridine, sulfamethoxazole, and trimethoprim	Seven pharmaceuticals were detected in Canadian Arctic wastewater Abundances of pharmaceuticals varied between communities and treatment methods
t1.8	Reis et al. [44]	Phenazone, ibuprofen, ketoprofen, phenylbutazone, betamethasone, ranitidine, loratadine, cimetidine, clarithromycin, erythromycin, paroxetine, scopolamine, omeprazole, trimetroprim, atenolol, fenofibrate, gemfibrozil, atorvastatin, fluconazole, prednisone, metformin, amoxicillin, ampicillin, caffeine, and enoxacin	Trace levels of pharmaceuticals were detected in superficial and drinking water Conventional drinking water treatment plants were not able to remove the pharmaceuticals completely Drier periods were related to the highest concentration of the pharmaceuticals Drinking water treatment plants' removal efficiency shows a great variation over the year
	Greenham et al. [45]	Acetaminophen, caffeine, atorvastatin, lorazepam, cotinine, metformin,	Twelve of top-used pharmaceuticals and 2 metabolites were assessed

(continued)

Table 1 (continued) t1.10

Reference	Pharmaceuticals	Remarks/highlights	t1.11
	metoprolol, paraxanthine, naproxen, quetiapine, ramipril, salbutamol, venlafaxine, and warfarin	Primary treatment was significantly less efficient than other technologies Removal efficiencies of pharmaceuticals with 9 different treatment technologies were tested	t1.9
Kleywegt et al. [46]	Paroxetine, sertraline, carbamazepine, penicillin, acetaminophen, codeine, ibuprofen, naproxen, oxycodone, atorvastatin, metoprolol, amlodipine, diltiazem, furosemide, and verapamil	Direct discharges from pharmaceutical facilities are a crucial source of pollution to receiving sewer sheds Elevated concentrations of pharmaceuticals are detected in effluents from manufacturers The manufacturer facilities may be discharging several kilograms of lost products directly to the sewers daily	t1.10
Kołecka et al. [47]	Ibuprofen, paracetamol, flurbiprofen, naproxen, diclofenac and its metabolites	Pharmaceuticals' distribution in wastewater treatment plant plus sludge treatment reed beds differs between season and chemical type Ibuprofen, naproxen, and paracetamol were eliminated by the conventional wastewater treatment plant	t1.11
Hanamoto et al. [34]	Caffeine, theophylline, acetaminophen, lincomycin, sulfamonomethoxine, metoprolol, ofloxacin, ketoprofen, bezafibrate, and roxithromycin	In-stream attenuation of pharmaceuticals was observed by a mass balance approach Source was estimated based on populations for pharmaceuticals conservative in the river Three pharmaceuticals were substantially affected by household septic tanks	t1.12
Afonso-Olivares et al. [48]	Trimethoprim, ofloxacin, metronidazole, ciprofloxacin, sulfamethoxazole, atenolol erythromycin, propanolol, ranitidine, omeprazole, fluoxetine, carbamazepine, metamizole, ketoprofen, naproxen, ibuprofen, diclofenac, bezafibrate, gemfibrozil, clofibric acid, nicotine, paraxanthine, caffeine, atenolol d7, sulfamethoxazole d4, ibuprofen d3	Twenty-three pharmaceuticals were monitored in sewage from wastewater treatment plants in Gran Canaria (Spain) Removal efficiencies of pharmaceuticals from two different wastewater treatment plants were evaluated Environmental risk assessment of pharmaceuticals was determined	t1.13
Liu et al. [49]	Amoxicillin, erythromycin, clarithromycin, ofloxacin, roxithromycin, norfloxacin, levofloxacin, lincomycin, sulfamethoxazole, ibuprofen, trimethoprim, flumequine, metronidazole, metoprolol, caffeine, chlortetracycline, clofibric acid, diclofenac, salicylic acid, and carbamazepine	Caffeine showed the highest influent concentration than other pharmaceuticals Wastewater treatment plants in north China had a higher influent level of total pharmaceuticals Several high-risk pharmaceuticals to the environment were identified	t1.14

4 Case Studies of Diffuse-Based Source Pollution

The unidentified movement of several organic contaminants that include active pharmaceutical compounds enters the soil zone and aquatic environments by numerous direct or indirect routes, with bioactive sludge being one of the furthermost essential diffuse sources [7, 50]. The excessive utilization of bioactive sludge, as a biofertilizer, in the agricultural settings is a dominant diffuse-based source of the pharmaceuticals which can then run off to the ground and enters the groundwater and freshwater resources [15]. Generally, bioactive sludge, also termed as biosolid which is commonly used as a biofertilizer, is a type of active residue obtained from the leftovers of the wastewater treatment plants. Such sewage sludge, as a biofertilizer, is typically used for soil amendment. For instance, it has been estimated that around 8 × 106 dry tons of sludge are produced, and 50% of the obtained sewage sludge is applied to the agricultural land in America. However, the maximum concentration of the pharmaceuticals found in the biosolid, i.e., thiabendazole, is 5,000 μg/kg, and other varieties of pharmaceuticals, e.g., caffeine and carbamazepine, can also be found in the sewage sludge. Owing to this high concentration of active pharmaceutical compounds and high solubility of halogenated hydrocarbon in sewage sludge, it leads to groundwater pollution from the application of biosolid to soil and surface runoff of the biosolid containing soil [15]. The controlled or uncontrolled excessive consumption of biologically active compounds in the agricultural settings is the foremost contributor, through activities such as agricultural runoff, the application of fertilizers and pesticides, tillage practices, habitat alteration, animal waste, and soil erosion. Thus, far more complex challenges are being posed by the diffuse-based source of the pharmaceuticals, which is also known as nonpoint source pollution. Considering the complexity, the diffuse-based source or nonpoint source pollution is a leading water quality problem, in recent times, as compared to the point-based source pollution. Moreover, the diffuse-based source or nonpoint source pollution from agriculture and the urban periphery is a most intractable dimension [51, 52], which is progressively being recognized by policymakers and regulatory authorities. According to the European Union Article 11(3)(h), the Water Framework Directive sets out lowest compliance requirements, i.e., “for diffuse sources liable to cause pollution, measures to prevent or control the input of pollutants. Controls may take the form of a prerequisite for prior regulation, e.g., a proscription on the entry of pollutants into water matrices, prior authorization based on general binding rules where such a prerequisite is not otherwise provided for under Community legislation” [53].

5 Pharmaceuticals’ Fate in the Environment

Owing to the complications of diffuse-based source or nonpoint source pollution, the real information on the fate of various pharmaceuticals in the environment is limited [54–56]. Another possible reason behind this vague fate of pharmaceuticals in the environment could be the low-level volatility of pharmaceuticals. Therefore, the main distribution/transportation of pharmaceuticals in the environment majorly occurs by aqueous transport via a point-based source route. The occurrence of pharmaceutical-related ECs in the environment is low but consistent/persistent. However, pharmaceutical-related ECs are ubiquitous in aqueous matrices. Such consistency/persistence of pharmaceuticals in the aquatic environment is mainly because the release rate is higher than the transformation rate [56, 57]. From the persistence viewpoint, sulfonamides and fluoroquinolones are the most persistent and then macrolides, tetracyclines, aminoglycosides, and β-lactam antibiotics. Among them, sulfonamides and fluoroquinolones are easier to adsorb than macrolides, sulfonamides, aminoglycosides, and β-lactams by the soils and sediments, which make them the most persistent [58].

The major transformation fate of biologically active pharmaceuticals occurs in WWTPs to soils via sludge usage as biofertilizer. However, such WWTP-based transformation significantly depends on the overall sewage composition, treatment conditions, and the design and operational factors of the wastewater treatment process [59]. The ultimate fate of pharmaceutical-related ECs and/or their active residues/metabolites in WWTPs could be mineralization to carbon dioxide and water. In the case of lipophilic-type pharmaceutical compounds, the end fate is adsorption on suspended solids or release in the effluent as broken-down residues or as degraded products [60]. From WWTP effluent sources, the persistent pharmaceuticals can afterward be transported to groundwater and/or surface water matrices, whereas the pharmaceutical products used in the aquaculture are directly released into the surface water bodies [61–63].

6 Concluding Remarks and Outlook

In conclusion, based on the above-discussed literature with suitable examples, environmental contamination with a range of emerging anthropogenic pollutants has become a global problem. This chapter is of particular interest, which spotlights a diverse source of pharmaceuticals such as analgesics/anti-inflammatories (narcotic analgesics, nonnarcotic analgesics, and nonsteroidal anti-inflammatory drugs (NSAID)) and synthetic antibiotic (β-lactams, macrolides, fluoroquinolones, aminoglycosides, sulfonamide, and tetracycline). Some of them are β-lactams (amoxicillin and penicillin)), cardiovascular pharmaceuticals (β-blockers/diuretics), estrogens and hormonal compounds (estriol, estradiol, estrone, and 17-α-ethinylestradiol), and antiepileptic drugs (carbamazepine) in the water matrices. A brief transmission fate of pharmaceutical-related ECs and their metabolized compounds to soils, groundwater, and surface water bodies is also given from point-based source and nonpoint-based source pollution. The growing water contamination with a controlled or uncontrolled discharge of incompletely or inadequately treated industrial wastes and WWTP effluents harshly distressing the whole living ecosystem. Considering the above-discussed scenarios, there is a dire need to develop highly efficient bioremediation strategies that are clean, green, sustainable, and environmental-friendly and can replace the in-practice inefficient remediation approaches.

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Conflict of Interest Authors declare no conflict of interests in any capacity, including competing or financial.

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