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PHARMACEUTICALS IN WATER CYCLE: A REVIEW ON RISK ASSESSMENT AND WASTEWATER AND SLUDGE TREATMENT

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Abstract

Pharmaceuticals in the environment are considered as emerging contaminants which are particularly persistent and which could represent a threat both for animals and humans following long-term exposure. Pharmaceuticals include, among others, antibiotics, anti-inflammatory drugs, steroid hormones, antidepressants, β-blockers and lipid regulators. Excretion from humans is considered the main source of release of such compounds in the environment. The excreted compounds reach wastewater treatment plants (WWTPs), which demonstrated to be generally ineffective in removing emerging contaminants in the absence of advanced treatments. Due to the importance of the topic, which still represents an issue of great concern, this review analyses the scientific literature with the aim of investigating the role of different sources of release, the fate of pharmaceuticals in WWTPs, their typical levels in the aquatic environment, the estimated risk levels for the aquatic fauna and the potential effects on humans. In the last part of this study, different options to effectively reduce the concentrations of pharmaceuticals in effluents from WWTPs are reviewed and discussed, in order to provide environmental agencies and local administrators with an overview of the advanced treatments that are currently available to mitigate the impact of pharmaceuticals in downstream water bodies.

Keywords: emerging contaminants, risk assessment, sewage sludge, treatment options, wastewater

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1. Introduction

The so-called "emerging contaminants" (ECs) are new chemicals for which a regulatory status does not exist (or has been established only recently) and for which there is great uncertainty on their effects on the environment and human health (Deblonde et al., 2011). Among ECs, pharmaceuticals constitute a larger part of the main pollutants which have been an issue of great concern within the international scientific debate in the last decades. On average, an individual annually consumes about 15 g of pharmaceuticals and developed countries play a major role (Pal et al., 2010) and recent studies show that their use and consumption per capita, in the European Union, have doubled or nearly tripled since 2000 up to 2014 (Kalyva, 2017). In Europe, it is estimated that about 3000 pharmaceuticals are currently used, the main categories being anti-inflammatories, antibiotics, antidepressants, β-blockers, lipid regulators and steroid hormones (Al Aukidy et al., 2012).

The consciousness of the presence of pharmaceuticals in the environment dates back to 1976, when a metabolite of serum triglyceride-lowering drug (clofibric acid) was found in groundwater (Garrison et al., 1976).

Wastewater treatment plants (WWTPs) are originally designed to remove sulphur and organic nutrients, such as organic carbonaceous, nitrogenous, and phosphorus substances from wastewater (Barnabé et al., 2009; Tran et al., 2018), but not to solve the problem of the presence of pharmaceuticals in municipal effluents and sludge (Luo et al., 2014;

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Roberts et al., 2016). Rather, WWTPs are estimated to represent the main source of pharmaceuticals to the environment and, in particular, in the urbanized water cycle (Giebułtowicz and Nałęcz-Jawecki, 2016; Stamatelatou et al., 2011; Yang et al., 2017). PPCPs (Pharmaceuticals and Personal Care Products) are thus frequently detected in reclaimed surface water at concentrations ranging from ng/L to μg/L (Ebele et al., 2017) and many studies have shown an increase of pharmaceuticals concentrations up to 10-fold downstream from the discharge points of WWTPs (Aubertheau et al., 2016). This aspect has obvious repercussions on aquatic organisms and on human health (Barceló, 2012; Kalyva, 2017; Oldenkamp et al., 2013). Indeed, contamination of water may entail toxic effects for aquatic organisms, with consequences on the food chain, and into direct effects on humans through consumption of contaminated groundwater (Maamari et al., 2015).

In addition, food-chain contamination may be the result of the reuse of contaminated sewage sludge in agriculture: the application of sewage sludge to agricultural soils is favoured at international level, since sludge contributes to nutrients recycling and to improve soil fertility (Clarke and Smith, 2011) and, furthermore, it represents the reuse of a valuable resource, thus contributing to the attainment of EU objectives of a "circular economy" (Kacprzak et al., 2017). However, since conventional WWTPs are not able to completely remove unwanted substances, sludge may contain contaminants, such as metals, pathogens and organic pollutants (Rodríguez-Rodríguez et al., 2012, Torretta, 2012; Torretta and Katsoyiannis, 2013). The European Commission Directive 86/278/EEC, on "Sewage Sludge", established limit values for heavy metals and stated that only treated sludge, after a proper stabilization process, could be directly applied to land (EC Directive, 1986). This norm did not take into consideration any ECs, although their ubiquitous presence has been reported (Bondarczuk et al., 2016). Only recently, environmental quality standards for some micropollutants have been established in European countries (EC Directive, 2008).

The international scientific community and the European Commission look at this topic as a new sanitary emergency. In fact, after the introduction of the European Directive 98/8/EC (EC Directive, 1998), then revoked by the European Regulation 528/2012 (EU Regulation, 2012), and of the European Regulation 1907/2006 (EU Regulation, 2006), intended to banish environmentally toxic molecules, the same political address is foreseen for pharmaceuticals (Deblonde and Hartemann, 2013), being, some of them (e.g. estrogens), not only endocrine disruptors, but also group 1 carcinogens according to the World Health Organization classification (Chen et al., 2018). Indeed, till now, the potential risk for human beings, related to the environmental presence of pharmaceuticals, has not been widely investigated, due to the difficulties to determine their real toxicity. Among others, their presence at very low concentrations, even below the therapeutic doses, and, usually, in complex mixtures able to produce additive and/or synergic effects (Cooper et al., 2008; Ebele et al., 2017; Pal et al., 2010). If, for some micropollutants, the main solution may consist in the replacement with less harmful products, this possibility is much more limited in the case of pharmaceutical products, being conditioned by their needed therapeutic use. Nevertheless, in some countries, e.g. Sweden, there is an attempt to increase the awareness of general practitioners and healthcare workers of the consequences of the disposal of pharmaceutical residues into the environment. The European Union proposed environmental quality standards with respect to 33 priority pollutants in the Water Frame Directive (EC Directive, 2000), which will force European countries to develop monitoring and control of ECs (Belgiorno et al., 2007).

After analysing the main sources of pharmaceuticals in the environment and studying their fate in WWTPs, this review aims at providing the reader with the expected concentrations of pharmaceuticals in water and sludge and with the consequent risk levels expected for aquatic organisms. In addition, solutions to improve wastewater treatments will be presented and discussed, in order to provide environmental agencies and local administrators with alternatives on the management of pharmaceutical residues in wastewater and in the environment.

2. Sources of release

The presence of pharmaceuticals in the environment is due to many sources of release, among which the excretion through human body after their consumption. Persistence is one of the characteristics of pharmaceuticals, since reaching the target organs without being altered is their main requirement. For this reason, the excretion in sewage networks from domestic effluents represents one of the main causes of the environmental presence of pharmaceuticals (Nikolaou et al., 2007; Santos et al., 2013). Pharmaceuticals, as other emerging contaminants, follow the main paths of pollution in anthropized water cycle and they influence diffusion in human life and to the environmental compartments. Fig. 1 shows the main path of pollution diffusion in anthropized water cycle. The environmental presence of pharmaceuticals may be also due to their improper disposal: partially or wholly unused compounds and already expired medicines, instead of being brought back by dwellers to chemist's shops, are wrongly disposed of through sinks or household drains (Crouse et al., 2012; Kalyva, 2017; Pal et al., 2010). This pathway is particularly important for those pharmaceuticals (such as antibiotics) that would be metabolized by the body. Additional contributions are ascribed to rain, which is able to collect pollutants from air and surfaces through run-off from agricultural lands and intensive farming (Barnabé et al., 2009; Luo et al., 2014; Ortiz de García et al., 2013).

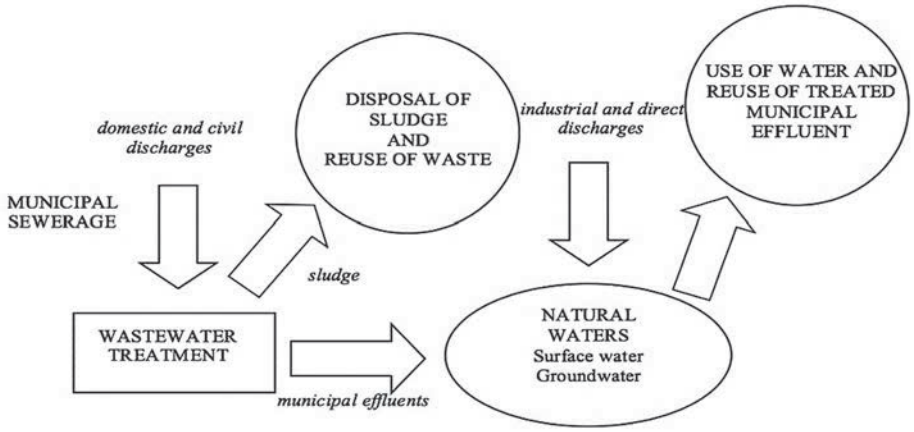

Fig. 1. Main path of pollution diffusion in anthropized water cycle

In addition, small communities may contribute to the release of ECs with the direct discharge of domestic wastewater into the environment (Li et al., 2014) or after limited treatments. Moreover, the pharmaceutical compounds can enter the environment not only through the discharge of treated effluents into surface water or through storm water overflow (Moldovan et al., 2009), but also through the direct contact with groundwater, which can happen in different ways: leakage from sewers, leakage from uncontrolled landfills, usage of treated wastewater for irrigation and spreading of sewage sludge (enriched by easily adsorbed pharmaceuticals) over agricultural soil as a fertilizer (Ebele et al., 2017; Kalyva, 2017; Ternes et al., 2007).

Human pharmaceuticals can enter the water cycle via different pathways: they can be improperly disposed of through household drains when unused or expired (Kümmerer, 2009) or can be excreted through human and animal urine and faeces as parent compounds or as metabolites (Boxall, 2004; Gros et al., 2010; Zhang et al., 2008): this is especially the case of antibiotics, most of which are metabolized in the range of 30% up to 90% (Bilal et al., 2019; Puckowski et al., 2016). In both cases, however, the main release vehicle is represented by sewers, through which pharmaceuticals enter WWTPs (Fent et al., 2006; Morosini et al., 2017; Stamatelatou et al., 2011) for being later discarged into the environment with a concentration of ng/L to μg/L. This is especially true for developed countries (such as USA, Finland, Japan, Spain and UK), where the majority of wastewater is collected by sewage systems and transferred to WWTPs (Bilal et al., 2019; Li et al., 2014; Moldovan et al., 2009). However, in developing countries, in many cases pharmaceutical manufacturers ignore the local environmental regulations and often release industrial wastewater directly into the domestic sewage networks or even into rivers and streams (Saif Ur Rehman et al., 2015). A recent study highlighted that, in India and Pakistan, only 24% and 2% of wastewater, respectively, are subject to treatments (Qadir et al., 2010), while in Kenya only 17% of urban areas is served by a sewage network (K'oreje et al., 2016). Another possible source for environmental contamination caused by pharmaceutical compounds is represented by the effluents from pharmaceutical manufactories and hospitals. Although the chemical and biotechnological sectors were found to constitute a minor concern in Europe (Straub, 2016), recent studies pointed out that pharmaceutical industries should not be neglected as a potential source of contamination of ECs in developing countries (Larsson et al., 2007; Larsson, 2008). In Europe, the contribution due to hospital discharges was found to be, at most, the 15-20% of the total amount of pharmaceuticals released each year into the environment, mainly limited to X-rays diagnostic media, cytostatic agents, antiseptics and disinfectants (Deblonde and Hartemann, 2013). However, even if hospital effluents are generally considered to pose the same hazard for the receiving environment as urban wastewaters, and are therefore co-treated at the same WWTP, a study by Verlicchi et al. (2012a) reveals that pharmaceutical compounds are found in consistently higher concentrations in hospital than in urban wastewaters, particularly commonly used drugs such as analgesics and antibiotics, thus requiring more specific management and treatment.

The concentrations of these active ingredients in hospital effluents are higher than in municipal wastewater. However, the total amount is generally much lower due to the little share of hospitals effluent in the municipal one in developed countries (Kalyva, 2017). Finally, pharmaceuticals used for prophylactic purposes in veterinary medicine (in particular, antibiotics belonging to tetracyclines, sulphonamides and macrolides) must also be considered. Such pharmaceuticals are introduced into the environment mainly through husbandry effluents (Pal et al., 2010), by means of direct run-off of on-ground faeces from pets and livestock (Cooper et al., 2008; Fent, 2008), or through the application of manure from medicated, in-house reared animals and from animals raised on pastures to the agricultural soil (Nikolaou et al., 2007). Manure, by leaching through soil, can reach groundwater or can be washed out, during storm run-off, coming to pollute surface water bodies (Ebele et

al., 2017). In some cases, animals are let free to have access to surface water reserves, where they may defecate, causing in this way a direct environmental contamination. The application of veterinary medicines in reared livestock represents the main entry route to the terrestrial environment (Patel et al., 2019). At last, also pharmaceuticals used in aquaculture (fish farming) can pollute the environment (Fent, 2008), through the direct discharge of effluents into surface water with no purification treatments before. Through the discharge of purified effluents into rivers and streams, pollutants can come indirectly in contact with groundwater and potentially to water used for drinking use. Following the partial biodegradation in wastewater and the immobilization of non-polar compounds in sewage sludge, untreated water-phase contaminants reach rivers and streams, while contaminants in sewage sludge may be spread in agriculture if sludge is used as a fertilizer. Contamination may reach fishes, agriculture and livestock and, as a consequence of food consumption, humans. The application of pharmaceuticals in aquaculture causes direct entry into aquatic environment (Patel et al., 2019).

Specific metabolites were found in natural water and wastewater (Petrie et al., 2015) such as: Clofibric acid, Salicylic acid, Norfluoxetine, Nortramadol, Norcodeine, Normorphine, Norbuprenorphine, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), 2-ethyl-5- methyl-3,3-diphenylpyrroline (EMDP), Norfentanyl, Norpropoxyphene, Nordiazepam, 7-Aminonitrazepam, Norketamine.

Presence of pharmaceuticals in water is probably influenced also by their period of use: some compounds, such as atenolol, furosemide, hydrochlorothiazide and ranitidine, the use of which is rather constant over the year, showed comparable input loads both in winter and in summer, while others, such as ibuprofen, ciprofloxacin, ofloxacin and sulphamethoxazole, characterized by a seasonal use, showed lower input loads in summer (Morosini et al., 2017). The sources of release and the environmental occurrence of pharmaceuticals can significantly differ from a region to another. According to a study by Aus der Beek et al. (2016), the most frequently detected pharmaceutical worldwide is diclofenac, followed by carbamazepine, sulfamethoxazole, ibuprofen, naproxen, estrone, ethinylestradiol and the metabolite of the lipid-lowering drug clofibric acid. The Western Europe and Others Group (WEOG) is characterized by the global average and maximum concentrations. Out of the 16 globally found pharmaceuticals, the maximum values can be detected in WEOG, followed by Asia and Latin American and Caribbean States Group (GRULAC). As regards Asia, antibiotics (such as norfloxacin, ofloxacin and ciprofloxacin) in surface waters, near production facilities, are the most found pharmaceuticals and at the highest concentrations. Diclofenac, naproxen, estradiol, clofibric acid and estriol are detected, in all the United Nations regional group, in comparable concentrations. Africa is the leader for carbamazepine, sulfamethoxazole, ibuprofen, trimethoprim and paracetamol environmental detection. The hormones estrone, estradiol and ethinylestradiol are found, at the highest concentrations, in South American surface waters.

Table 1 reports main pharmaceuticals, and their metabolites, detected in different environmental matrices and, for the most important of them, sources of release and amounts released are shown. As regards the aquatic environment (surface waters, groundwater and tap/drinking water), more than 100 different pharmaceuticals have been detected in several European countries and the Unites States. As regards, in particular, the detections in tap/drinking water, most of them come from WEOG, such as Spain and Germany, followed by Canada, China, France, Sweden and the United States. As regards the pharmaceuticals measured in manure and soil, the majority of detections derives from Europe, North America and China, followed by Brazil, Australia, Turkey, South Korea and Malaysia (Aus der Beek et al., 2016). In the same study, the authors highlight that the main emission pathway is urban wastewater, followed by hospitals and commercial animal husbandry. Sometimes, a regional pattern can be observed, e.g. in Asia, a lot of data on pharmaceutical concentrations comes from aquaculture and agriculture, while information about hospital sewage effluent is mainly available for WEOG countries.

3. Effects of pharmaceuticals in end receivers in the environment

A potential eco-toxicological risk must be considered connected to the WWTPs discharges; bioaccumulation in animal tissues and contamination of water entail a risk for humans. There is therefore a growing awareness about the possible sub-lethal changes to animal physiology and behaviours caused by PhACs - Pharmaceutical Active Compounds (McCallum et al., 2017). he available literature indicates that pharmaceuticals disposed of into the environment, in general, do not exhibit high acute ecotoxicity (Cunningham et al., 2006), since their concentrations are generally below the ones known to cause acute toxicity to aquatic organisms (Cooper et al., 2008). With regards to chronic effects, the current knowledge is still scarce, due to the complexity of biodiversity, the different methods of investigation and the unknown modes of action on lower organisms, which make toxicity prediction difficult (Cooper et al., 2008). A large number of effects was observed in fishes exposed to contaminated wastewater, such as intersex changes, stimulation of vitellogenesis in males and inhibition of the reproductive potential (De Mes et al., 2005; Jobling et al., 2006; Wennmalm, 2011). Some groups of pharmaceuticals are known for their toxic potential: immunosuppressive drugs (e.g., cyclosporine and mycophenolic acid) revealed to be toxic to planktons and algae and to cause defects to embryos of fishes (Giebułtowicz and Nałęcz-Jawecki, 2016).

Table 1. Main pharmaceuticals, and their metabolites, detected in different environmental matrices

Therapeutic category	***Substance***	***Known metabolites***	***Main sources of release***	***Amounts released (referred to the parent compound)***
Anesthetics	Ketamine	norketamine	If used for veterinary purposes, they can be released into the environment via animal treatment, inappropriate disposal of unused or expired medicines or livestock feed.[f]	0.0537 (Surface Water - River/Stream); [d] 0.0457 (Suspended particulate matter - Sewage).[d]
Analgesics	Tramadol	desmethyltramadol	WWTPs.[e]	0.004 (Surface Water - Lake);[d] 7.731 (Surface Water - River/Stream);[d] 1800 (Surface Water - unspecific);[d] 0.8144 (Suspended particulate matter - Sewage).[d]
	Oxycocodone	noroxycocodone, oxymorphone,		-
	Oxymorphone	noroxycodone, noroxymorphone		0.0035 (Surface Water - River/Stream);[d]
	Morphine	morphine-3-glucuronide, morphine-6-glucuronide, normorphine		0.0358 (Surface Water - River/Stream);[d] 21.7 (Surface Water - unspecific);[d] 0.1564 (Suspended particulate matter - Sewage).[d]
	Dihydrocodeine	dihydromorphine		0.0971 (Surface Water - River/Stream);[d] 0.079 (Surface Water - unspecific);[d] 0.1269 (Suspended particulate matter - Sewage).[d]
	Methadone	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), 2-ethyl-5- methyl-3,3-diphenylpyrroline (EMDP)		0.0244 (Surface Water - River/Stream);[d] 0.0691 (Suspended particulate matter - Sewage).[d]
	Fentanyl	norfentanyl, despropionylfentanyl		0.004 (Surface Water - unspecific).[d]
	Propoxyphene	norproxyphene		-

Antibiotics/Antibacterials	Amoxicillin	amoxicilloic acid	Main environmental source: agriculture (feed additives; growth promoters; usage of manure as fertilizer; surface runoff). Flushing of old prescriptions. Hospital waste and WWTPs. Direct excretion by pasture-reared animals; aquaculture.[a] WWTPs.[e] If used for veterinary purposes, they can be released into the environment via animal treatment, inappropriate disposal of unused or expired medicines or livestock feed.[f]	0.1 (Groundwater);[d] 0.004 (Surface Water - Lake);[d] 1.654 (Surface Water - River/Stream);[d] 0.245 (Surface Water - unspecific).[d]
	Erythromycin	erythromycin-H2Of		0.155 (Drinking water);[d] 2.38 (Groundwater);[d] 0.08 (Manure - Dung);[d] 0.16 (Manure - Liquid);[d] 3.04 (Sediment - Lake);[d] 1.85 (Sediment - River/Stream);[d] 0.21 (Soil);[d] 0.038 (Soil Water);[d] 0.0639 (Surface Water - Aquaculture);[d] 0.005 (Surface Water - Estuary);[d] 0.233 (Surface Water - Lake);[d] 4.2 (Surface Water - River/Stream);[d] 0.486 (Surface Water – Sea or Ocean);[d] 1.7 (Surface Water - unspecific);[d] 0.0026 (Tap Water);[d] 0.04 (Well Water – untreated).[d]
	Metronidazole	1-(β-hydroxymethyl-5-nitroimidazole 2-methyl-5-nitroimidazole-1yl-acetic acid		0.0193 (Drinking water);[d] 0.002 (Manure - Liquid);[d] 0.00126 (Sediment - River/Stream);[d] 0.054 (Sediment - unspecific);[d] 0.051 (Surface Water - Lake);[d] 7 (Surface Water - River/Stream);[d] 0.044 (Surface Water - unspecific).[d]

	Ofloxacin	desmethyl, N-oxide metabolites		0.022 (Drinking water);[d] 0.048 (Groundwater);[d] 0.3606 (Manure - Dung);[d] 0.024 (Manure - Liquid);[d] 0.02063 (Sediment - Aquaculture);[d] 362 (Sediment - Lake);[d] 113.27 (Sediment - River/Stream);[d] 0.39 (Sediment - unspecific);[d] 0.0033 (Soil);[d] 17.67 (Surface Water - Aquaculture);[d] 0.036 (Surface Water - Estuary);[d] 11 (Surface Water - Lake);[d] 10 (Surface Water - River/Stream);[d] 0.389 (Surface Water - Sea or Ocean);[d] 0.306 (Surface Water - unspecific);[d] 0.0792 (Suspended particulate matter - River/Stream);[d] 0.0792 (Suspended particulate matter - unspecific);[d] 0.48 (Well Water - untreated).[d]
	Chloramphenicol	glucuronide conjugates		9.07 (Dust);[d] 0.037 (Sediment - Aquaculture);[d] 4.19 (Sediment - River/Stream);[d] 260 (Surface Water - River/Stream);[d] 0.123 (Surface Water – Sea or Ocean);[d] 1.3 (Surface Water - unspecific).[d]
	Sulfamethoxazole	N4-acetylated metabolite		0.08 (Drinking water);[d] 1.99 (Groundwater);[d] 3.76 (Manure – Dung);[d] 6.8 (Manure – Liquid);[d] 0.082 (Riverbank Filtration);[d] 0.01885 (Sediment – Aquaculture);[d] 7.00E-04 (Sediment – Estuary);[d] 7.86 (Sediment – Lake);[d] 484.7 (Sediment - River/Stream);[d] 0.0011 (Sediment - unspecific);[d] 0.239 (Soil);[d] 0.7 (Soil Water);[d] 14.31 (Surface Water – Aquaculture);[d] 0.765 (Surface Water – Estuary);[d] 0.94 (Surface Water - Lake);[d] 29 (Surface Water - River/Stream);[d] 0.21215 (Surface Water – Sea or Ocean);[d] 11.5 (Surface Water - unspecific);[d] 0.02 (Tap Water);[d] 3.4 (Well Water – untreated).[d]

	Sulfapyridine	hydroxyl, acetyl metabolites		0.104 (Groundwater);[d] 0.097 (Manure – Liquid);[d] 1.4 (Sediment – Lake);[d] 0.00057 (Soil);[d] 0.085 (Surface Water - Lake);[d] 12 (Surface Water - River/Stream);[d] 0.121 (Surface Water - unspecific).[d]
	Trimethoprim	1,3-oxides, 3′ 4-hydroxy derivatives		0.015 (Drinking water);[d] 0.16 (Groundwater);[d] 17 (Manure – Dung);[d] 17 (Manure – Liquid);[d] 0.0182 (Sediment – Estuary);[d] 2.6 (Sediment - River/Stream);[d] 0.0016 (Sediment - unspecific);[d] 0.1 (Soil);[d] 1.372 (Soil Water);[d] 0.085 (Surface Water – Aquaculture);[d] 0.569 (Surface Water – Estuary);[d] 0.174 (Surface Water - Lake);[d] 13.6 (Surface Water - River/Stream);[d] 0.33 (Surface Water – Sea or Ocean);[d] 10 (Surface Water - unspecific);[d] 0.0013 (Tap Water);[d] 0.055 (Well Water – untreated).[d]
	Oxytetracycline	N-desmethyloxytetracycline		1.1 (Dust);[d] 0.19 (Groundwater);[d] 225 (Manure – Dung);[d] 36.1 (Manure – Liquid);[d] 0.27 (Sediment – Aquaculture);[d] 0.109 (Sediment – Lake);[d] 0.057 (Sediment - River/Stream);[d] 6.3 (Sediment – Sea or Ocean);[d] 4.9 (Sediment - unspecific);[d] 5.172 (Soil);[d] 71.7 (Soil Water);[d] 10.69 (Surface Water – Aquaculture);[d] 6.87 (Surface Water - Lake);[d] 56.1 (Surface Water - River/Stream);[d] 0.55 (Surface Water – Sea or Ocean);[d] 1.34 (Surface Water - unspecific);[d] 0.0314 (Suspended particulate matter – River/Stream);[d] 0.0314 (Suspended particulate matter – unspecific).[d]

Anti-cancers	Tamoxifen	hydroxytamoxifen	-	0.431 (Sediment – Estuary);[d] 0.224 (Surface Water - Estuary);[d] 0.0268 (Surface Water - River/Stream);[d] 0.212 (Surface Water - unspecific);[d] 0.289 (Suspended particulate matter – River/Stream).[d]
Antidepressants	Fluoxetine	norfluoxetine	-	0.00274 (Drinking water);[d] 0.018 (Groundwater);[d] 0.318 (Manure – Liquid);[d] 0.0088 (Soil);[d] 0.007 (Surface Water – Estuary);[d] 43 (Surface Water - River/Stream);[d] 0.034 (Surface Water - unspecific);[d] 0.0811 (Suspended particulate matter – River/Stream);[d] 0.0721 (Suspended particulate matter – Sewage);[d] 0.00082 (Tap Water);[d] 0.005 (Well Water – untreated).[d]
	Venlafaxine	desmethylvenlafaxine	-	-
	Dosulepin	desmethyldosulepin	-	-
	Amitriptyline	nortriptyline, 10-hydroxyamitriptyline 10-hydroxynortriptyline	-	-
	Nortriptyline	hydroxynortriptyline	-	-
Antiepileptics	Carbamazepine	hydroxylated (10,11-epoxide) conjugated metabolites	-	60 ng/L – 6.3 µg/L (in wastewater and surface water).[a] 0.601 (Drinking water);[d] 3.67 (Groundwater);[d] 0.015 (Manure – Dung);[d] 2.682 (Manure – Liquid);[d] 1 (Riverbank Filtration);[d] 0.00292 (Sediment - River/Stream);[d] 0.015 (Sediment - unspecific);[d] 0.0257 (Soil);[d] 0.7 (Soil Water);[d] 0.997 (Surface Water – Estuary);[d] 8.053 (Surface Water - Lake);[d] 11.56123 (Surface Water - River/Stream);[d] 0.119 (Surface Water – Sea or Ocean);[d] 6.1 (Surface Water - unspecific);[d] 0.0191 (Suspended particulate matter – River/Stream);[d] 0.258 (Tap Water);[d] 0.75 (Well Water – untreated).[d]
	Gabapentin	–	-	-

Beta blockers	Propranolol	4-hydroxypropranolol glucuronide conjugates	WWTPs.[e]	0.002 (Drinking water);[d] 0.096 (Groundwater);[d] 0.043 (Sediment – Lake);[d] 0.00042 (Sediment - River/Stream);[d] 0.0021 (Sediment - unspecific);[d] 4.00E-04 (Soil);[d] 0.224 (Surface Water – Estuary);[d] 0.129 (Surface Water – Lake);[d] 0.561 (Surface Water - River/Stream);[d] 0.024 (Surface Water - Sea or Ocean);[d] 0.59 (Surface Water - unspecific).[d]
	Metoprolol	no active metabolites		-
	Sulbutamol	sulfate conjugate		0.029 (Groundwater);[d] 8.00E-05 (Sediment - River/Stream);[d] 0.001 (Surface Water – Estuary);[d] 0.48 (Surface Water - River/Stream);[d] 0.001 (Surface Water - Sea or Ocean);[d] 0.471 (Surface Water - unspecific).[d]
	Atenolol	hydroxylated metabolite		0.034 (Drinking water);[d] 0.106 (Groundwater);[d] 0.166 (Manure – Liquid);[d] 0.28354 (Sediment - River/Stream);[d] 0.1 (Soil Water);[d] 0.293 (Surface Water – Estuary);[d] 0.28 (Surface Water - Lake);[d] 11.02 (Surface Water - River/Stream);[d] 0.088 (Surface Water – Sea or Ocean);[d] 0.58 (Surface Water - unspecific);[d] 0.018 (Tap Water);[d] 0.036 (Well Water – untreated).[d]
Bronchodilators	Theophylline	caffeine, 3-methylxanthine	-	-
Calcium-channel blockers	Diltiazem	desacetyldiltiazem N-monodemethyldiltiazem	-	0.0079 (Drinking water);[d] 0.015 (Groundwater);[d] 0.00389 (Soil);[d] 0.013 (Surface Water – Estuary);[d] 0.21 (Surface Water - River/Stream);[d] 0.004 (Surface Water – Sea or Ocean);[d] 0.13 (Surface Water - unspecific).[d]
Chronic bowel disorders	Sulfasalazine	5-Aminosalicylic acid3 sulfapyridine	-	-

Diuretics	Furosemide	*mainly* glucuronides	-	0.138 (Groundwater);[d] 0.0984 (Sediment – River/Stream);[d] 0.118 (Surface Water – Estuary);[d] 0.94 (Surface Water - River/Stream);[d] 0.255 (Surface Water - unspecific).[d]
Erectile dysfunctions	Sildenafil	N-desmethyl sildenafil	-	-
H2 receptor agonists	Ranitidine	N-oxide, S-oxide desmethyl ranitidine	-	6.00E-04 (Drinking water);[d] 0.01 (Groundwater);[d] 0.00041 (Sediment – River/Stream);[d] 0.57 (Surface Water - River/Stream);[d] 8.00E-04 (Surface Water – Sea or Ocean);[d] 0.11 (Surface Water - unspecific).[d]
	Cimetidine	cimetidine N-glucuronide, cimetidine suphoxide, hydroxymethylcimetidine	-	-
Antihypertensives	Valsartan	Valeryl 4-hydroxy valsartan	-	0.013 (Drinking water);[d] 0.0921 (Surface Water - Estuary);[d] 0.734 (Surface Water - River/Stream);[d] 0.029 (Surface Water – Sea or Ocean);[d] 6.26 (Surface Water - unspecific).[d]
Hypnotics	Temazepam	oxazepam	If used for veterinary purposes, sedatives can be released into the environment via animal treatment, inappropriate disposal of unused or expired medicines or livestock feed.[f]	-
	Diazepam	nordiazepam, temazepam, oxazepam		0.0235 (Drinking water);[d] 0.05 (Groundwater);[d] 0.00077 (Sediment – River/Stream);[d] 0.0012 (Sediment – unspecific);[d] 3.00E-04 (Soil);[d] 0.004 (Surface Water - Estuary);[d] 0.14 (Surface Water - River/Stream);[d] 0.003 (Surface Water – Sea or Ocean);[d] 0.12 (Surface Water - unspecific);[d] 0.00033 (Tap Water);[d] 0.001 (Well Water – untreated).[d]
	Oxazepam	glucuronide metabolite		-

Lipid regulators	Bezafibrate	glucuronides	WWTPs.[e]	0.027 (Drinking water);[d] 1.2 (Groundwater);[d] 8.00E-04 (Rain);[d] 0.11 (Riverbank Filtration);[d] 0.00013 (Sediment – River/Stream);[d] 0.00067 (Soil);[d] 0.02 (Soil Water);[d] 0.026 (Surface Water - Estuary);[d] 0.847 (Surface Water - Lake);[d] 15.06 (Surface Water - River/Stream);[d] 0.018 (Surface Water – Sea or Ocean);[d] 3.1 (Surface Water - unspecific);[d] 0.0019 (Tap Water);[d] 0.015 (Well Water – untreated).[d]
	Simvastatin	β-Hydroxyacid metabolite		-
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Acetaminophen	sulfate conjugate, paracetamol cysteinate, mercapturate	If used for veterinary purposes, they can be released into the environment via animal treatment, inappropriate disposal of unused or expired medicines or livestock feed.[f]	-
	Diclofenac	glucuronide, sulfate conjugates		≤ 1.59 µg/L[a] (in sewage); 0.01 - 0.5 µg/L[a] (in river waters); 1 - 6 ng/L[a] (in drinking waters). 12 - 560 ng/L[a] (in sewage waters in Greece). 0.14 (Drinking water);[d] 3.4 (Groundwater);[d] 0.004 (Manure - Liquid);[d] 0.43 (Riverbank Filtration);[d] 0.014 (Sediment - River/Stream);[d] 0.01 (Sediment - unspecific);[d] 4.00E-04 (Soil);[d] 0.1 (Soil Water);[d] 0.004 (Surface Water - Aquaculture);[d] 1.52 (Surface Water - Estuary);[d] 0.83 (Surface Water - Lake);[d] 18.74 (Surface Water - River/Stream);[d] 1.5 (Surface Water - Sea or Ocean);[d] 12.014 (Surface Water - unspecific);[d] 0.0025 (Tap Water);[d] 0.93 (Well Water - untreated).[d]

	Ibuprofen	2-4′-(2-Hydroxy-2-methylpropyl)-phenylpropionic acid 2-40-(2-carboxypropyl)-phenylpropionic acid, conjugated ibuprofen		≤ 3.35 µg/L[a] (in sewage); 0.01 – 0.5 µg/L[a] (in river waters); 1 – 6 ng/L[a] (in drinking waters). 1.35 (Drinking water);[d] 12.2 (Groundwater);[d] 5.863 (Manure - Liquid);[d] 0.2 (Riverbank Filtration);[d] 0.03 (Sediment – Lake);[d] 4.00E-04 (Sediment - River/Stream);[d] 0.1 (Sediment - unspecific);[d] 0.3185 (Soil);[d] 48.72 (Soil Water);[d] 0.05 (Surface Water - Aquaculture);[d] 0.928 (Surface Water - Estuary);[d] 4.706 (Surface Water - Lake);[d] 303 (Surface Water - River/Stream);[d] 1.5 (Surface Water – Sea or Ocean);[d] 200 (Surface Water - unspecific);[d] 0.152 (Suspended particulate matter - River/Stream);[d] 0.032 (Tap Water);[d] 9.595 (Well Water – untreated).[d]
	Naproxen	6-o-desmethyl naproxen conjugates		0.055 (Drinking water);[d] 5.58 (Groundwater);[d] 1.835 (Manure - Liquid);[d] 10 (Sediment – Lake);[d] 0.06 (Sediment – River/Stream);[d] 0.0158 (Sediment – unspecific);[d] 0.00286 (Soil);[d] 0.58 (Soil Water);[d] 0.214 (Surface Water - Estuary);[d] 0.85 (Surface Water - Lake);[d] 12.3 (Surface Water - River/Stream);[d] 2.05 (Surface Water – Sea or Ocean);[d] 32 (Surface Water - unspecific);[d] 0.0492 (Suspended particulate matter – River/Stream);[d] 0.008 (Tap Water);[d] 0.155 (Well Water – untreated).[d]

	Ketoprofen	2-(3-benzoylphenyl)-propanoic acid, glucuronides		0.051 (Drinking water);[d] 0.314 (Groundwater);[d] 0.014 (Manure - Dung);[d] 0.164 (Manure - Liquid);[d] 0.05 (Sediment – Lake);[d] 0.32 (Sediment – River/Stream);[d] 0.00046 (Soil);[d] 0.23 (Soil Water);[d] 0.0297 (Surface Water - Estuary);[d] 0.329 (Surface Water - Lake);[d] 9.808 (Surface Water - River/Stream);[d] 6.05 (Surface Water – Sea or Ocean);[d] 1 (Surface Water - unspecific);[d] 0.209 (Suspended particulate matter – River/Stream);[d] 0.003 (Tap Water);[d] 0.014 (Well Water – untreated).[d]
Steroid Estrogens	Estrone (E1)	sulfate and glucuronide conjugates	Main sources: WWTPs; application of manure directly into soil.[a] If used for veterinary purposes, hormones can be released into the environment via animal treatment, inappropriate disposal of unused or expired medicines or livestock feed.[f]	7.4 – 1267 ng/L[a] (river water impacted by livestock feedlot).
	17β-estradiol (E2)	sulfate and glucuronide conjugates		ND[b] - 313.6 ng/L[a] (river water impacted by livestock feedlot). 0.002 - 0.006 µg/L[c] (in freshwaters in Italy).
Synthetic Estrogens	17α-ethinylestradiol (EE2)	sulfate and glucuronide conjugates		Up to 48.14 ng/g dry weight[a] (coastal sediments).
Various	Codeine	codeine-6-glucuronide (*main*), free/conjugated morphine, norcodeine	-	0.24 (Groundwater);[d] 0.105 (Surface Water - Estuary);[d] 0.0044 (Surface Water - Lake);[d] 0.815 (Surface Water - River/Stream);[d] 340 (Surface Water - unspecific);[d] 0.9499 (Suspended particulate matter - Sewage);[d] 0.03 (Tap Water);[d] 0.01 (Well Water - untreated).[d]
	Buprenorphine	norbuprenorphine and glucuronides	-	-
	Ephedrine Pseudoephedrine	cathine	-	-
	Norephedrine	–	-	-

[a]Puckowski et al. (2016), data from literature: concentration of estrogens in drinking water up to 28 ng/L; [b]ND: not detected; [c]Zenker et al. (2014), data from literature; [d]Aus der Beek et al. (2016), data from literature: maximum concentration (µg/L or µg/kg, depending on environmental matrices of detection); [e]Corcoran et al. (2010), data from literature; [f]Patel et al. (2019), data from literature.

Estrogens in the aquatic environment demonstrated to induce reproductive adverse effects to the aquatic fauna (Chen et al., 2018; Malmborg and Magnér, 2015; Osachoff et al., 2014).

Antibiotics, especially sulfamethoxazole and ciprofloxacin, demonstrated to reduce photosynthesis and the assimilation of carbon by algae (Johansson et al., 2014); furthermore, the efficacy of antibiotics may be threatened by the continuous supply of antimicrobial resistance genes to the aquatic environment (Straub, 2016). Great uncertainty affects the role of the so-called "enantiomers", i.e. mirror images of their respective parent compounds. The effects of one enantiomer can be considerably higher than the other one of the same compound (Kasprzyk-Hordern, 2010).

During the last twenty years, several studies reported increased evidence of the linkage between long-term exposure to steroid hormones and adverse effects like infertility, cancer and birth defects (Nikolaou et al., 2007). Breast cancer in females and testicular and prostate cancer in males were found as possible adverse effects caused by long-term exposure to endocrine disruptor compounds (Fernandez et al., 1998). Among steroid hormones, the 17α-Ethinylestradiol (EE2) and the 17β-estradiol (E2) seem to be the most hazardous to humans and fishes, with EE2 being more recalcitrant to biodegradation than E2 (Manickum and John, 2014).

In the effluents of three WWTPs in Switzerland, mefenamic acid was ascribed as the pharmaceutical entailing the higher risk (Tauxe-Wuersch et al., 2005). As a result of a study carried out on the effluents of five WWTPs in China (Liu et al., 2015), erythromycin stood out as the pharmaceutical inducing the higher risk to the aquatic environment, especially to algae, confirming the generally higher threat posed by antibiotics (Verlicchi and Zambello, 2014).

As already mentioned, the presence of ECs in wastewater may also pose a risk to groundwater and, in some cases, to drinking water. As an example, studies on the urban area of Berlin (Germany) revealed the presence of clofibric acid and N-(phenylsulfonyl)-sarcosine up to concentrations of 170 and 105 ng/L level in tap water, respectively (Heberer and Stan, 1997). Phenazone, propiphenazone and clofibric acid were found in samples of potable water in Germany and residues of three phenazone-type pharmaceuticals have been identified in routine analysis of groundwater samples in the north-western districts of Berlin (Nikolaou et al., 2007).

According to the OECD (Organisation for Economic Co-operation and Development), in order to predict the bioaccumulation potential of a chemical compound, a comparison to its lipophilicity (i.e. the octanol-water partition coefficient, log K_{ow}) must be made. In particular, a log K_{ow} value higher than or equal to 3 reveals a tendency of the compound to partition into the lipid portion of an organism, thus showing a tendency to bioaccumulate (OECD, 2008). Since such a behaviour can be observed for some pharmaceuticals, it is important to define their Bioaccumulation Factor (BAF: the ratio of the compound in an organism, absorbed through dietary and ambient environment sources, to its concentration in the environment at a steady state, usually expressed as l/kg) to understand the risk they may pose to terrestrial and aquatic ecosystems. In general, the hydrophobic compounds, which show a low metabolization degree and a high log K_{ow} value, are more likely to exhibit bioaccumulation hazards to aquatic organisms (Ruhí et al., 2016). Nevertheless, recent studies have highlighted how some compounds with a log K_{ow} value lower than 2 (as also observed for pharmaceuticals in freshwater fish) can show high bioaccumulation, since this process is affected by other factors in addition to lipophilicity, among which the physicochemical properties of both the environment and the compound, some biological processes and the exposure route (Moreno-González et al., 2016). Another important index is the Bioconcentration Factor (BCF, usually expressed as l/kg), i.e. the distribution of the compound between aquatic organism and water at a steady state, with no dietary intake of the chemical (Arnot and Gobas, 2006; Puckowski et al., 2016; Zenker et al., 2014).

Bioaccumulation of some lipophilic compounds, among which antibiotics (roxithromycin, erythromycin and ketoconazole), anti-inflammatories (ibuprofen and diclofenac), β-blockers (propranolol), antiepileptics (carbamazepine) and steroid hormones (17α-ethinylestradiol), was observed to be higher in the liver of wild fish, followed by brain, gill and muscles. Furthermore, the bioaccumulation in fishes causes the transfer of contaminants through the food chain.

Following long-term exposure, even to low levels of contamination, concentrations of antibiotics and anti-inflammatory drugs 1000-times higher than those measured in water are likely to be found in the bile of wild fish (Liu et al., 2015). In Table 2, some indexes of bioaccumulation in different organisms are reported, based on the available literature on the topic.

Table 2. Indexes of bioaccumulation in different organisms found in literature

Therapeutic category	*Compound*	*Organism*	*BAF (l/kg)*	*BCF (l/kg)*	*Reference*
Antibiotics	Sulfadiazine	Willow plant	-	33.3	Puckowski et al. (2016)[a]
		Maize plant	-	2.6	
	Oxolinic acid	Bryophyte	450	-	
	Flumequine		140	-	
	Oxytetracycline		200	-	

Therapeutic category	*Compound*	*Organism*	*BAF (l/kg)*	*BCF (l/kg)*	*Reference*
	Ciprofloxacin	Aquatic plants	66300 (mean)	-	
	Norfloxacin		2120 (mean)	-	
	Enrofloxacin		1720 (mean)	-	
	Ofloxacin	Several samples of fish (liver and muscle) and prawns	> 5000	-	
	Roxithromycin	Fish inhabiting downstream rivers of WWTPs	7091	-	
	Erythromycin		7900	-	
	Enrofloxacin	Water, sediment and biota samples (crab and fish)	45407	-	
	Roxithromycin		5290	-	
	Oxytetracycline	Watermeal plant	-	1280	
	Roxithromycin	Wild fish (*Hemiculter leucisculus*)	Liver: 7091 (S1)[h]; 729 (S4)[h] Brain: 2091 (S1); 497 (S4) Muscle: 1273 (S1); 21 (S4) Gill: 1636 (S1); 41 (S4)	-	Liu et al. (2015)[h]
	Roxithromycin	Wild fish (*Carassius auratus*)	Liver: 920 (S2)[h]; 725 (S3)[h] Brain: 566 (S2); 630 (S3) Muscle: 142 (S2); 282 (S3) Gill: 540 (S2); 225 (S3)	-	
	Erythromycin	Wild fish (*Hemiculter leucisculus*)	Liver: 7900 (S1)[h]; 7559 (S4)[h] Brain: 2900 (S1); 1088 (S4) Muscle: 700 (S1); 971 (S4) Gill: 1200 (S1); 1412 (S4)	-	
	Erythromycin	Wild fish (*Carassius auratus*)	Liver: 31 (S2)[h]; 120 (S3)[h] Brain: 226 (S2); 160 (S3) Muscle: 528 (S2); 760 (S3) Gill: 1616 (S2); 1480 (S3)	-	
Steroid hormones	EE2	*D. magna*	-	228	Puckowski et al. (2016)[a]
		Oligochaete *L. variegatus*	-	190	
		Goldfish *Carassius auratus*	-	337	
		Invertebrates *Chironomus tentans* and *H. Azteca*	-	31 and 142, respectively	
		Fathead minnow *P. promelas*	-	610-660	
	EE2	Wild fish (*Hemiculter leucisculus*)	Liver: - (S1)[h]; 20,392 (S4)[h] Brain: - (S1); 8357 (S4) Muscle: - (S1); 857 (S4) Gill: - (S1); 4071 (S4)	-	Liu et al. (2015)[h]
	EE2	Wild fish (*Carassius auratus*)	Liver: 16,642 (S2)[h]; - (S3)[h] Brain: 7214 (S2); - (S3) Muscle: - (S2); - (S3) Gill: 5714 (S2); - (S3)	-	
Antihypertensive drugs	Propranolol	Algae *Scenedesmus obliquus* (first trophic level)	-	40.9-103.4	Puckowski et al. (2016)[a]
	Propranolol (Laboratory study)	Fish	0.03-0.16 (in the liver) 0.003-0.02 (in the muscle) 0.003-0.04 (in the gill) 0.003-0.03 (in the bile)	-	

Therapeutic category	***Compound***	***Organism***	***BAF (l/kg)***	***BCF (l/kg)***	***Reference***
	Propranolol (Laboratory study)	Blue mussels (*Mytilus edulis trossulus*)	36-160	-	
	Propranolol (Field study)	Crucian carp	2782 and 4000 (in the liver)	-	
	Propranolol (Field study)	-	51-491	-	
	Propranolol	Wild fish (*Hemiculter leucisculus*)	Liver: 4000 (S1)[h]; 1000 (S4)[h] Brain: 1000 (S1); 500 (S4) Muscle: - (S1); - (S4) Gill: - (S1); 500 (S4)	-	Liu et al. (2015)[h]
	Propranolol	Wild fish (*Carassius auratus*)	Liver: - (S2)[h]; - (S3)[h] Brain: 200 (S2); - (S3) Muscle: - (S2); - (S3) Gill: 133 (S2); - (S3)	-	
	Propranolol	Freshwater snail (*Planorbid* sp.)	1000	-	Puckowski et al. (2016)[a]
	Diltiazem	Freshwater snail (*Planorbid* sp.)	48	-	
	Carvedilol	Freshwater snail (*Planobarius corneus*)	-	57.3	
	Amiodarone	-	-	4090 (at pH 6) 1000000 (at pH 9)	
	Nicardipine	-	-	229 (at pH 6) 4590 (at pH 9)	
	Atenolol	Fish *Gambusia affinis*	0.13 and 0.08 (at 100 and 1000 µg/L, respectively)	-	
	Verapamil	*Hydropsyche* sp. (benthic organism)	390-670 (experimentally determined) vs 40 (calculated)	-	
	Valsartan	*Erpodella octoculata* (benthic organism)	6.2-12	-	
	Diltiazem	-	24	-	Zenker et al. (2014)[g]
Diuretic drugs	Hydrochlorothiazide	Noble pen shell (*Pinna nobilis*)	109.7-656.8	-	Moreno-González et al. (2016)[i]
	Hydrochlorothiazide	Cockle (*Cerastodema glaucum*)	321.1-590.3	-	
	Hydrochlorothiazide	Golden grey mullet (*Liza aurata*)	182.5	-	
Neuroactive drugs	Fluoxetine	Fish (*Japanese medaka*)	-	8.8-260 (in the body, depending on pH) 330-3100 (in the liver, depending on pH)	Puckowski et al. (2016)[a]; Zenker et al. (2014)[g]
	Norfluoxetine (Fluoxetine metabolite)	Fish (*Japanese medaka*)	-	80-650 (in the body)	
	∑Fluoxetine (Fluoxetine + Norfluoxetine)	Goldfish Wild Carp	386 (average value for caged goldfish) 906 (average value for wild goldfish) 231 (average value for wild carp)	-	Muir et al. (2017)[l]
	Fluoxetine	Marine mussel (*Mytilus galloprovincialis*)	-	200-800	Puckowski et al. (2016)[a]
	Carbamazepine	*Planorbid* sp.	-	3.2	
	Fluoxetine			3000	
	Sertraline			990	
	Norfluoxetine			510	
	Desmethylsertraline			16000	

Therapeutic category	*Compound*	*Organism*	*BAF (l/kg)*	*BCF (l/kg)*	*Reference*
	Mixture of 6 antidepressants	Brook trout	-	17-2426 (in the brain) 39-12250 (in the liver) 109-500 (in the muscles)	
	Carbamazepine	*Pseudokirchneriella subcapitata* and *Thamnocephalus platyurus*	2.2 and 12.6	-	
	Carbamazepine	Snails	241	-	
		Fish	3.4-265		
		Mussels	290-764		
	Carbamazepine and its metabolites	*Jenynsia multidentata*[e]	5-9	-	Chen et al. (2017)
	Carbamazepine	-	2.5-3.8	-	Zenker et al. (2014)[g]
	Carbamazepine	Wild fish (*Hemiculter leucisculus*)	Liver: 2750 (S1)[h]; 615 (S4)[h] Brain: 1000 (S1); 385 (S4) Muscle: 250 (S1); 77 (S4) Gill: 500 (S1); 269 (S4)	-	Liu et al. (2015)[h]
	Carbamazepine	Wild fish (*Carassius auratus*)	Liver: 1200 (S2)[h]; 235 (S3)[h] Brain: 400 (S2); 29 (S3) Muscle: 200 (S2); 8.8 (S3) Gill: 200 (S2); - (S3)	-	
	Carbamazepine	*Typha angustifolia*	-	904.47-1898.50[m]	Wang et al. (2019)
	∑Diazepam (Diazepam + Oxazepam)	Goldfish Wild carp	82 (average value for wild goldfish) 73.7 (average value for caged goldfish) 927 (average value for wild carp)	-	Muir et al. (2017)[l]
	Fluoxetine	Adult Zebrafish (*Danio rerio*)[f]	-	20.4±1.24[b] (L)[c] 20.0±1.91[b] (H)[c]	Chen et al. (2017)
	Sertraline			50.9±5.15[b] (L)[c] 69.4±17.26[b] (H)[c]	
	Carbamazepine			1.68±5.14[b] (L)[c] 1.41±7.13[b] (H)[c]	
	Sertraline	Brown trout	880-2400[n] (liver) 2800-4400[n] (kidney) 680-1500[n] (brain)	-	Grabicova et al. (2017)
	Fluoxetine	Mussel *Elliptio complanate* (in a stream near a WWTP effluent discharge)	125-1347	-	Du et al. (2014)[d]
	Fluoxetine	Unionid mussel (laboratory studies)	229-1221	-	
	Fluoxetine	*Typha angustifolia*	-	114.82-1477.39[m]	Wang et al. (2019)
Analgesic and anti-inflammatory drugs	Diclofenac, Naproxen and Ibuprofen	Rainbow trout (blood plasma)	-	0.02-4.9	Puckowski et al. (2016)[a]; Zenker et al. (2014)[g]
	Diclofenac	Rainbow trout	-	12-2732 (liver) 5-971 (kidney) 3-763 (gills) 0.3-69 (muscle)	Puckowski et al. (2016)[a]; Zenker et al. (2014)[g]
	Naproxen and its metabolites	Rainbow trout (bile)	-	320 to 950, to 2300 (depending on the individuals)	Puckowski et al. (2016)[a]
	Diclofenac	Bird and fish tissue	-	4.2	
	Ibuprofen			19	
	Indomethacin			19	
	Mefenamic acid			120	

Therapeutic category	Compound	Organism	BAF (l/kg)	BCF (l/kg)	Reference
	Ibuprofen	Fathead minnow and channel catfish[e]	-	0.08-1.4	Chen et al. (2017); Zenker et al. (2014)[g]
	Naproxen	Adult Zebrafish (*Danio rerio*)[f]	-	0.80±4.11[b] (L)[c] 1.41±8.11[b] (H)[c]	Chen et al. (2017)
	Ibuprofen			0.88±9.11[b] (L)[c] 1.11±4.17[b] (H)[c]	
	Diclofenac			0.18±7.46[b] (L)[c] 0.16±2.23[b] (H)[c]	
	Diclofenac	Wild fish (*Hemiculter leucisculus*)	Liver: 956 (S1)[h]; 34 (S4)[h] Brain: 608 (S1); 14 (S4) Muscle: 174 (S1); 5 (S4) Gill: 565 (S1); 6 (S4)	-	Liu et al. (2015)[h]
	Diclofenac	Wild fish (*Carassius auratus*)	Liver: 836 (S2)[h]; 121 (S3)[h] Brain: 291 (S2); 64 (S3) Muscle: 36 (S2); 6 (S3) Gill: 18 (S2); 44 (S3)	-	
	Diclofenac	-	2.5-29	-	Zenker et al. (2014)[g]
	Ibuprofen	-	58	-	
	Ibuprofen	*Typha angustifolia*	-	103.35-210.33[m]	Wang et al. (2019)

[a]Review of different literature studies; [b]Observed steady-state BCF (± standard deviation) in Zebrafish ∑tissues (i.e. based on the observed concentrations in plasma and analyzed tissues: liver, muscle, ovary); [c]L: low exposure group; H: high exposure group; [d]Data from literature; [e]Data from literature; [f]Laboratory investigation; [g]Review of different literature studies; [h]Different sampling sites (S1, S2, S3, S4) in the downstream rivers of WWTPs in Nanjing, China; [i]Field-derived BAFs calculated for compounds found in both biota tissue and seawater at the same sampling point; [l]Observed bioaccumulation factors using concentrations in surface waters (at different sampling points) and fish blood plasma; [m]Range of BCFs observed in the roots of the plant in three different reedbeds; [n]Calculated BAFs, after different periods of exposure, at locality 0.1-3 km downstream a WWTP effluent.

In addition, as previously mentioned, antibiotic resistance is increasing. In a study carried out in 2000, all samples collected from the Ohio River contained *Escherichia coli* characterized by some resistance to penicillin, tetracycline and vancomycin (Heberer, 2002). Samples containing the highest levels of antibiotics also contained bacteria with the greatest resistance. Furthermore, Ma et al. (2014) presented a study in which six samples were collected from different environments, including aquaculture farm sediments, activated sludge, biofilm, anaerobic digestion sludge and river water: a total of 181 subtypes of Antibiotic Resistance Genes (ARGs) were detected in the samples. In Table 3, some examples of ARGs are reported. Sewers receiving effluent from a hospital showed an increase in bacteria resistant to oxytetracycline, while those receiving effluent from a pharmaceutical plant showed an increase in bacteria resistant to multiple antibiotics (Cooper et al., 2008). The exposure of virulent bacteria present in sewage to antibiotic residues may induce resistance, which could represent a threat to human health (Ebele et al., 2017; Tong et al., 2018). The occurrence of pharmaceuticals in groundwater could enhance the dissemination of antibiotic resistance genes, potentially impacting the human health (Sharma et al., 2018). Antibiotic residues in the environment can also pose a risk to microbial organisms responsible for beneficial processes, while antibiotics in wastewater can cause adverse effects on bacteria associated with activated sludge treatment processes (Cooper et al., 2008).

4. Risk assessment

Since the long-term exposure of different organisms to emerging contaminants can derive in chronic toxicity, the evaluation of the possible ecotoxicological effects of such compounds (i.e., the so called "risk assessment") must be taken into account. The environmental risk assessment aims at evaluating the potential impact of individual substances on the environment by examining both exposures and effects on the ecosystem (EC, 2003). As regards pharmaceutical products, the real risk is evaluated on the combined effects of the exposure scenario and the relative hazard (Roos et al., 2012) and, since exposures depend mainly on the excretion in wastewaters, only the effects on aquatic ecosystem are taken into account (Tauxe-Wuersch et al., 2005).

The control of pharmaceuticals should be based on the effective removal capacity of WWTPs (which could be improved by changing some operating conditions or by implementing advanced technologies for removal of micropollutants) and by taking into account the hydraulic characteristics of the receiving water bodies in order to mitigate the potential ecotoxicological effects of pharmaceutical residues (Morosini et al., 2017).

Table 3. Examples of some ARGs found in literature

Antibiotics	***ARGs***	***References***
Aminoglycosides	*aac*C2	Szekeres et al. (2018)
	*aad*A1	Rizzo et al. (2013)
	*aad*A13	Rizzo et al. (2013)
	*aad*A2	Rizzo et al. (2013)
	*aad*B	Rizzo et al. (2013)
	*aad*D	Szekeres et al. (2018)
	*aph*A	Rizzo et al. (2013)
	*aph*A-3	Rizzo et al. (2013)
	*aph*A-6	Rizzo et al. (2013)
	*aph*2	Rizzo et al. (2013)
	*str*A	Rizzo et al. (2013)
	*str*B	Rizzo et al. (2013)
Bacitracin	*bcr*A	Tremblay et al. (2011)
	*bcr*B	Tremblay et al. (2011)
	*bcr*D	Tremblay et al. (2011)
	*bcr*R	Tremblay et al. (2011)
Beta-lactam antibacterials, penicillinis	*amp*C	Rizzo et al. (2013); Szekeres et al. (2018); Tong et al. (2016)
	*amp*G	Ju et al. (2019)
	bla_{CTX}	Felis et al. (2020)
	bla_{CTX-M}	Ju et al. (2019); Tong et al. (2016)
	bla_{IMP}	Szekeres et al. (2018)
	bla_{KPC}	Szekeres et al. (2018)
	bla_{NDM-1}	Szekeres et al. (2018)
	bla_{PER}	Szekeres et al. (2018)
	bla_{PSE}	Szekeres et al. (2018)
	bla_{OXA}	Felis et al. (2020); Ju et al. (2019)
	bla_{SHV}	Felis et al. (2020); Szekeres et al. (2018); Tong et al. (2016)
	bla_{TEM}	Felis et al. (2020); Ju et al. (2019)
	bla_{VIM}	Rizzo et al. (2013)[a]; Szekeres et al. (2018)
	*mec*A	Li and Webster (2018); Rizzo et al. (2013)[b]
Glycopeptides	*van*A	Hegstad et al. (2010)[c]; Rizzo et al. (2013)[c]; Szekeres et al. (2018)[c]; Tremblay et al. (2011)[c]
	*van*B	Hegstad et al. (2010)[d]; Ju et al. (2019); Szekeres et al. (2018)[d]; Tremblay et al. (2011)[d]
	*van*C	Hegstad et al. (2010)[e]
	*van*D	Hegstad et al. (2010)[e]
	*van*E	Hegstad et al. (2010)[e]
	*van*G	Hegstad et al. (2010)[e]
	*van*L	Hegstad et al. (2010)[e]
	*van*N	Hegstad et al. (2010)[e]
	*van*S	Ju et al. (2019)
	*van*W	Ju et al. (2019)
	*van*Z	Ju et al. (2019)[d]
Macrolides, lincosamides and streptogramins	*ere*A	Tong et al. (2018)
	*ere*A2	Rizzo et al. (2013)
	*erm*A	Ma et al. (2011)[e]; Szekeres et al. (2018)
	*erm*B	Felis et al. (2020); Ju et al. (2019); Ma et al. (2011)[e]; Mao et al. (2015); Rizzo et al. (2013); Szekeres et al. (2018); Tong et al. (2017); Tong et al. (2018); Tremblay et al. (2011)
	ermC	Felis et al. (2020); Mao et al. (2015); Szekeres et al. (2018)
	ermF	Felis et al. (2020); Ma et al. (2011)[e]; Rizzo et al. (2013); Tong et al. (2017); Tong et al. (2018)
	*erm*X	Tong et al. (2017); Tong et al. (2018)
	*lin*B	Tremblay et al. (2011)[f]
	*mac*A	Ju et al. (2019)
	*mac*B	Ju et al. (2019)
	*mef*A	Szekeres et al. (2018)
	*mef*A/E	Tong et al. (2017); Tong et al. (2018)
	mel	Ju et al. (2019)
	*mph*2	Ju et al. (2019)
	*mph*B	Tong et al. (2017); Tong et al. (2018)
	*msr*A	Szekeres et al. (2018)
	*msr*C	Tremblay et al. (2011)
	*vat*D	Tremblay et al. (2011)[g]
	*vat*E	Tremblay et al. (2011)[g]
Nitroimidazole	*nim*A	Ju et al. (2019)
Quinolone antibacterials	*aac(6')-Ib-cr*	Felis et al. (2020); Rizzo et al. (2013)
	*qep*A	Felis et al. (2020)
	*qnr*A3	Rizzo et al. (2013)

	*qnr*B	Mao et al. (2015)
	*qnr*B1	Rizzo et al. (2013)
	*qnr*B2	Rizzo et al. (2013)
	*qnr*B4	Rizzo et al. (2013)
	*qnr*B5	Rizzo et al. (2013)
	*qnr*S	Felis et al. (2020); Rizzo et al. (2013)
	*qnr*VC	Rizzo et al. (2013)
Sulfonamides	*sul*1	Felis et al. (2020); Huang et al. (2017); Ju et al. (2019); Ma et al. (2011); Mao et al. (2015); Miller et al. (2016); Rizzo et al. (2013); Szekeres et al. (2018)
	*sul*2	Felis et al. (2020); Huang et al. (2017); Ju et al. (2019); Ma et al. (2011); Mao et al. (2015); Rizzo et al. (2013); Szekeres et al. (2018)
	*sul*3	Ju et al. (2019); Rizzo et al. (2013); Szekeres et al. (2018)
Tetracyclines	*otr*A	Chee-Sanford et al. (2001)
	tet(A)	Felis et al. (2020); LaPara et al. (2011); Mao et al. (2015); Rizzo et al. (2013); Szekeres et al. (2018); Tong et al. (2016)
	tet(B)	Felis et al. (2020); Kümmerer (2008); Mao et al. (2015); Rizzo et al. (2013); Szekeres et al. (2018)
	tetB(P)	Chee-Sanford et al. (2001); Ma et al. (2011)
	tet(C)	Huang et al. (2016); Huang et al. (2017); Ma et al. (2011); Szekeres et al. (2018); Tong et al. (2016)
	tet(D)	Rizzo et al. (2013)
	tet(E)	Ma et al. (2011); Mao et al. (2015)
	tet(G)	Ma et al. (2011); Mao et al. (2015); Miller et al. (2016); Rizzo et al. (2013)
	tet(H)	Mao et al. (2015); Rizzo et al. (2013)
	tet(L)	Kümmerer (2008)
	tet(M)	Chee-Sanford et al. (2001); Felis et al. (2020); Kümmerer (2008); Schmitt and Römbke (2008); Rizzo et al. (2013); Tong et al. (2016); Tong et al. (2017); Tong et al. (2018); Tremblay et al. (2011)
	tet(O)	Chee-Sanford et al. (2001); Felis et al. (2020); Huang et al. (2016); Huang et al. (2017); Kümmerer (2008); Ma et al. (2011); Miller et al. (2016); Szekeres et al. (2018); Tong et al. (2016); Tong et al. (2017); Tong et al. (2018); Tremblay et al. (2011)
	tet(Q)	Chee-Sanford et al. (2001); Felis et al. (2020); Huang et al. (2016); Huang et al. (2017); Kümmerer (2008); Ma et al. (2011)
	tet(S)	Chee-Sanford et al. (2001); Mao et al. (2015); Rizzo et al. (2013); Tremblay et al. (2011)
	tet(T)	Chee-Sanford et al. (2001); Ma et al. (2011); Mao et al. (2015)
	tet(U)	Rizzo et al. (2013)
	tet(W)	Chee-Sanford et al. (2001); Felis et al. (2020); Kümmerer (2008); LaPara et al. (2011); Ma et al. (2011); Miller et al. (2016); Szekeres et al. (2018)
	tet(X)	Felis et al. (2020); Huang et al. (2016); Huang et al. (2017); LaPara et al. (2011); Ma et al. (2011); Mao et al. (2015); Tong et al. (2016)
Trimethoprim	*dfr*A1	Rizzo et al. (2013)
	*dfr*A12	Rizzo et al. (2013)
	*dfr*18	Rizzo et al. (2013)
	*dhfr*I	Rizzo et al. (2013)
	*dhfr*VIII	Rizzo et al. (2013)
	*dhfr*XV	Rizzo et al. (2013)

[a]Carbapenem; [b]Methilcillin; [c]Vancomycin; [d]Teicoplanin; [e]Erythromycin; [f]Lincomycin; [g]Quinupristin-Dalfopristin.

Moreover, there is a great need to develop detailed fate and transport models and databases allowing correlation between pharmaceuticals usage, effluent concentrations, environmental occurrence and effects (Grill et al., 2018). In order to determine a methodology useful to the risk assessment, several surveys and researches were carried out, together with prioritisation methodologies, which provide a useful tool for identifying which pharmaceuticals have the greatest potential to cause unintended effects in non-target organisms (Burns et al., 2017). However, the existing prioritization procedures are often difficult to compare to each other, since they highlight different compounds and they are applied to different scenarios, thus making very hard to understand, which are the substances posing a real hazard or to choose the most suitable scheme to be adopted in research and management (Letsinger and Kay, 2018). A study, carried out by Roos et al. (2012), proposed nine prioritization schemes, both risk and hazard-based, using a ranking of 582 active pharmaceutical substances. Seven key pharmaceuticals were selected and classified, according to their relative risk, on the basis of the following criteria:

- strong indicators of risk: evidence of adverse effects at concentrations regularly found in treated municipal effluents (e.g., ethinylestradiol and levonorgestrel);
- some indicators of risk: evidence of some environmental effects at concentrations approaching those found in municipal effluents (e.g., carbamazepine, diclofenac and fluoxetine);
- indicators of low environmental risk (e.g., atenolol and paracetamol).

In 2003, a classification system was proposed by the Stockholm County Council to evaluate the acute risk of widely used pharmaceuticals for the aquatic environment. This helped the general

practitioners to be more conscious in prescribing non-environmentally-hazardous drugs (Deblonde and Hartemann, 2013). This model is mainly based on eco-toxicological criteria and considers only the lethal effect of a pharmaceutical, while the assessment of pharmacological effects of metabolites and by-products and of the carcinogenic, mutagenic and reproductive effects is still lacking. Moreover, an environmental risk analysis should be extended to mixtures of compounds, since even more adverse effects are expected due to synergic actions. The classification of substances was made to assess the acute toxic risk and the environmental hazard posed by pharmaceuticals, by taking into account their persistence, bioaccumulation and toxicity. The risk of the specific substance is evaluated determining a parameter, the so-called "Risk Quotient", RQ, calculated as the ratio between the observed or "Predicted Environmental Concentration", PEC, and the corresponding "Predicted No-Effect Concentration", PNEC. The risk is evaluated as follows: RQ < 0.1, "negligible"; 0.1 < RQ < 1, "low"; 1 < RQ < 10, "moderate"; RQ > 10, "high".

Several studies applied the criteria of Swedish model to evaluate risk of pharmaceuticals. In order to simulate a "worst-case" scenario, some surveys applied this methodology to assess a potential acute risk of single compound by calculating the RQ as the ratio between the "maximum measured environmental concentration" and PNEC. Verlicchi et al. (2012b) determined the risk for life of aquatic organisms caused by several substances:

- compounds which showed a "high" risk: antibiotics (erythromycin, ofloxacin, sulphamethoxazole, clarithromycin, amoxicillin, tetracycline and azithromycin); psychiatric drugs (fluoxetine and diazepam); analgesics/anti-inflammatories (ibuprofen and mefenamic acid); lipid regulators (fenofibric acid, fenofibrate and gemfibrozil);
- compounds which showed a "moderate" risk: analgesics and anti-inflammatories (naproxen, phenazone, salicylic acid, codeine); antibiotics (penicillin G, trimethoprim and roxithromycin); β-blockers (propranolol and atenolol); lipid regulators (clofibrate and bezafibrate).

In a study carried out by Al Aukidy et al. (2012), an environmental risk analysis assessment was performed both for the treated effluents and for the receiving water bodies of two WWTPs in the Po Valley (Italy), with regards to 27 therapeutic pharmaceutical compounds: results showed that sulphamethoxazole, clarithromycin and azithromycin were the most harmful compounds. In a research concerning the municipal wastewater of Geneva (Switzerland), gabapentin, sulfamethoxazole, ciprofloxacin, piperacillin, ibuprofen, diclofenac and mefenamic acid were found to entail a "high" risk (RQ > 1) to the aquatic environment (Daouk et al., 2016). Ibuprofen and diclofenac, with the addition of gemfibrozil, were found to entail the highest risk also in the effluent from a Swedish WWTP (Brown et al., 2007). Algae, followed by Daphnis and fish, are the most sensitive organisms in the aquatic environment (Liu et al., 2015). Considerably higher RQ values can be determined in sludge, where pharmaceuticals and other ECs concentrate. In digested sludge, RQ values of E2, EE2 and gemfibrozil were estimated respectively 252, 12.1 and 4.63 (Martín et al., 2012).

5. Occurrence in water and wastewater

Pharmaceuticals can be found in water and wastewater as "parent" compounds, as hydrolyzed or as conjugated ones. Conventional WWTPs are currently unable to remove pharmaceutical compounds, so they can be found in effluents and surface water at level of ng/L or μg/L (Hernando et al., 2006). Most of the studies showing the ubiquitous occurrence of pharmaceuticals in the environment has been carried out in Western Europe and in North America: their concentrations may be very different from a country to another, as a consequence of different use patterns, water consumption and WWTPs operating conditions (Moldovan et al., 2009).

With regard to a study on influents of six WWTPs, Castiglioni et al. (2006) estimated that a median load of detected pollutants ranged from about 50 to 500 mg/day/1000 inhabitants. Many authors showed a collection of data on different PPCPs and their metabolites present in the raw influent and effluent of several WWTPs from various global locations (Table 4). In effluents of municipal WWTPs in Germany, 32 categories of therapeutic pharmaceuticals were detected (Nikolaou et al., 2007). Antibiotics, like sulfamethoxazole, were found in the effluent of a WWTP in Michigan (USA) at a concentration of 178 ng/L, while the average concentration of doxycycline and oxytetracycline resulted equal to 370 ng/L (Gao et al., 2012).

In a study carried out in France (Vulliet et al., 2011), 27 of a group of 51 target compounds were detected in surface water at least once: paracetamol, with the highest concentration of 71 ng/L, and salicylic acid and carbamazepine, which were quantified in more than 80% of samples.

Pharmaceuticals were detected in river (Zuccato et al., 2006): ofloxacin, atenolol, hydrochlorothiazide, ibuprofen and bezafibrate have been found in concentrations ranging from 100 to 1000 ng/L; carbamazepine and furosemide have been found in concentrations ranging from 10 to 100 ng/L; ciprofloxacin, sulphamethoxazole and ranitidine have been found in concentrations lower than 10 ng/L. The low polarity of several pharmaceuticals makes sorption to sediments an important route in WWTPs (Hernando et al., 2006; Kalyva, 2017). In addition, ECs can accumulate in sediments, which can act as a reservoir of hazardous pollutants (Petrie et al., 2015). Conjugated compounds, if subject to cleavage in the biodegradation process, can be transformed into their original parent compounds. Consequently, the concentration of some pharmaceuticals may even increase during wastewater treatment.

Table 4. Concentrations of different PPCPs and their metabolites in the raw influent and effluent of several WWTPs from various global locations

Therapeutic category	***Range of variability*** *(μg/L)*		***Reference***
	Raw influent	**Effluent**	
Analgesics/Anti-inflammatories	0.004–86.8	0.005–1.89	Balakrishna et al. (2017)
	0.060–89.134	1.040–1.076	Kosma et al. (2014)
	0.087–28.254	0.024–5.4015	Kot-Wasik et al. (2016)
	0.04–7.2	0.102–4.239	Yang et al. (2017)
	0.0016–373	0.001–57	Verlicchi et al. (2012b)
	0.005–8.984	0.001–1.713	Zhang et al. (2018)
Antibiotics/fungicides	0.0027–176.9	0.00014–11.67	Balakrishna et al. (2017)
	0.0044–0.188[a]	0.0005–0.052[a]	Ben et al. (2018)
	0.0013–2.766[b]	0.0004–0.831[b]	Ben et al. (2018)
	0.0011–1.687[c]	0.0001–0.795[c]	Ben et al. (2018)
	0.0007–0.627[d]	0.0004–0.0645[d]	Ben et al. (2018)
	0.032–2.626	0.012–0.533	Kosma et al. (2014)
	0.039–0.364[b]	0.0095–0.203[b]	Kot-Wasik et al. (2016)
	0.029–0.142[c]	0.012–0.098[c]	Kot-Wasik et al. (2016)
	0.001–32	0.001 and 6.7	Verlicchi et al. (2012b)
	0.011–1.02	0.0033–0.98	Yang et al. (2017)
	0.006–0.423	0.0007–0.428	Zhang et al. (2018)
	0.008–0.814[e]	0.0011–0.508[e]	Zhang et al. (2018)
	0.224–0.639[c]	0.0012–0.343[c]	Zhang et al. (2018)
	0.047–0.086[d]	0.0016–0.022[d]	Zhang et al. (2018)
	0.004–0.568	0.00055–0.296	Zhou et al. (2019)
	0.00018–4.971[b]	0.0001–1.333[b]	Zhou et al. (2019)
	0.00022–3.303[c]	0.00011–2.683[c]	Zhou et al. (2019)
	0.001–1.132[d]	0.0001–0.4[d]	Zhou et al. (2019)
Antidiabetics	3.819–16.791	0.0075–0.063	Kot-Wasik et al. (2016)
	0.12–16	not detected	Verlicchi et al. (2012b)
Antiepileptics	0.012–0.115	0.0002–0.055	Ben et al. (2018)
	0.017–0.355	0.028–0.417	Kosma et al. (2014)
	0.696–3.217	1.666–5.128	Kot-Wasik et al. (2016)
	15.78	0.097–7.57	Yang et al. (2017)
	0.063–2.499	0.043–0.673	Zhang et al. (2018)
	not detected–0.083	0.010–0.115	Zhou et al. (2019)
Antihistamines	0.0348–1.8	0.0015–0.108	Balakrishna et al. (2017)
	0.312–5.702	0.274–0.9825	Kot-Wasik et al. (2016)
Antihypercholesterolemics	0.38–0.41	0.28–0.34	Balakrishna et al. (2017)
	not detected–0.091	not detected	Kosma et al. (2014)
Antihypertensives	0.00061–41.4	0.00088–2.5	Balakrishna et al. (2017)
	0.044–1.709	0.029–0.265	Kot-Wasik et al. (2016)
	0.0025–10	0.0025 and 11	Verlicchi et al. (2012b)
	0.005–0.618	0.00015–0.047	Zhou et al. (2019)
Anti-ischemics	0.168–0.827	0.022–0.458	Kot-Wasik et al. (2016)
Antineoplastics	0.009–0.033	0.001–0.028	Kot-Wasik et al. (2016)
	0.019–0.36	0.002–2.9	Verlicchi et al. (2012b)
Antiplatelets	0.0048–0.658	0.0025–1.54	Balakrishna et al. (2017)
Artificial sweeteners	0.062–389	0.008–379	Balakrishna et al. (2017)
Bactericides/disinfectants	0.145–8.88	0.0224–5.86	Balakrishna et al. (2017)
	0.0001–3.931[f]	0.0001–0.466[f]	Ben et al. (2018)
	0.15–1.743	not detected–0.452	Kosma et al. (2014)
	0.009–0.038	0.003–0.016	Kot-Wasik et al. (2016)
	0.3–2.3	0.048–0.202	Yang et al. (2017)
	0.0007–0.982[f]	0.0005–0.366[f]	Zhang et al. (2018)
	0.007–2.379[f]	0.032–0.667[f]	Zhou et al. (2019)
Contrast agent iopromide	0.01–6.6	0.01–9.3	Verlicchi et al. (2012b)
Diuretics	0.485–5.072	0.207–4.314	Kot-Wasik et al. (2016)
	0.004–6	0.004–1.8	Verlicchi et al. (2012b)
Fragrances	0.55–4.52	not available	Yang et al. (2017)
Hormones	0.0009–0.3175	0.0001–0.015	Ben et al. (2018)
	0.235–4.183[g]	0.003–0.624[g]	Ben et al. (2018)
	not detected–0.421	not detected–0.611	Kosma et al. (2014)
	0.041–1.53	0.009–0.013	Kot-Wasik et al. (2016)
	0.007–0.041	<0.001–0.009	Yang et al. (2017)
	0.002–3	0.0002–0.11	Verlicchi et al. (2012b)
Illicit drugs	0.005–4.72	0.011–2.24	Balakrishna et al. (2017)
Insect repellents	0.066–1.2	0.04–0.624	Yang et al. (2017)
	0.048–1.359	0.023–0.469	Zhang et al. (2018)
Lipid regulators	0.0036–0.105	0.0004–0.087	Ben et al. (2018)

	0.033–0.946	0.027–0.356	Kosma et al. (2014)
	0.001–30	0.0015–80	Verlicchi et al. (2012b)
	---	420	Yang et al. (2017)
	0.005–0.284	0.0003–0.082	Zhang et al. (2018)
	0.0045–0.505	0.0017–0.136	Zhou et al. (2019)
Preservatives	0.015–10	0.00014–0.21	Yang et al. (2017)
Psychiatric drugs	0.0025–0.386[h]	0.0017–0.105[h]	Balakrishna et al. (2017)
	0.0009–0.071[i]	0.0004–0.071[i]	Balakrishna et al. (2017)
	0.0025–25	0.001–20	Verlicchi et al. (2012b)
	0.084–0.697	0.011–0.546	Zhang et al. (2018)
Receptor antagonists	0.014–11	0.006–7.8	Verlicchi et al. (2012b)
Sedatives/hypnotics/ anxiolytics	0.003–8.2	0.0025–0.9	Balakrishna et al. (2017)
Stimulants	0.016–102.84	0.019–51.7	Balakrishna et al. (2017)
	0.046–24.108	0.0005–0.3765	Ben et al. (2018)
	0.213–96.648	0.054–1.181	Kosma et al. (2014)
	2.8205–22.194	0.047–0.442	Kot-Wasik et al. (2016)
	3.794–39.666	0.016–1.791	Zhang et al. (2018)
UV-filters	0.005–3.96	0.0011–1.5	Balakrishna et al. (2017)
	0.008–0.601	0–0.347	Yang et al. (2017)
Vasodilators	0.0235–0.028	0.012–0.014	Kot-Wasik et al. (2016)
β-blockers	0.0008–3.665	0.0003–0.516	Ben et al. (2018)
	0.108–0.503	0.052–0.169	Kot-Wasik et al. (2016)
	0.006–25	0.01–0.17	Verlicchi et al. (2012b)
	0.06–0.638	0.093–0.388	Yang et al. (2017)
	0.003–1.175	0.0019–1.373	Zhang et al. (2018)
	0.0049–0.601	0.041–0.347	Zhou et al. (2019)
β-agonists	0.05–0.15	0.005–73	Verlicchi et al. (2012b)

[a]Dihydrofolate reductase inhibitor (Trimethoprim); [b]Fluoroquinolones; [c]Macrolides; [d]Tetracyclines; [e]Lincosamide; [f]Sulfonamides; [g]Phenolic estrogenic compounds; [h]Antidepressants; [i]Antischizophrenics.

In addition to biodegradation and sorption, photolysis and biotic hydrolysis represent other minor routes of pharmaceutical removal (Nikolaou et al., 2007). The metabolism and the excretion rates of pharmaceuticals strongly depend on the single substance. A work by Johnson and Williams (2004) focused on a model developed to predict the fate of EE2, which revealed that about 30% of EE2 is excreted by the body as unmodified, while 27% is excreted as conjugated compounds. Part of the free form of EE2 (about 60%) is estimated to be subject to biodegradation and transformation on the way to WWTPs, while the remaining 40% is capable to enter the first wastewater treatment stages (Johnson and Williams, 2004). If compared to volatile organic compounds, volatilization is considered a minor removal route for hormones and pharmaceuticals in general, due to their low Henry's constant (De Mes et al., 2005; Estrada-Arriaga and Mijaylova, 2010; Peng et al., 2018).

The properties of both the pollutant and the sludge may predict the fate of these compounds in a WWTP (Barnabé et al., 2009): especially, the chemical structure of the molecule, its chemical properties (the octanol-water partition coefficient above all) and the physic-chemical properties of the sludge (e.g., the size of suspended solids, the cation exchange and the organic fraction) are the main parameters which determine to which phase (liquid or solid) each molecule will preferentially partition (Verlicchi and Zambello, 2015). In Table 5, the main physicochemical properties, the half-lives (HL_s) and the type of degradation process are reported for some compounds of interest.

Table 5. Main physicochemical properties, half-lives and type of degradation process for some compounds of interest

Compound	***Physicochemical properties***	***Reference***	***Half-Life (HL or $t_{1/2}$)***	***Type of degradation process; first order kinetic parameters; reaction rate constant k_{biol} (l/gSSday)***	***Degradation (%)***	***Reference***
Analgesic and anti-inflammatory drugs						
Ketoprofen	pK_a[e] = 4.45 log P[f] = 3.12	Puckowski et al. (2016)	0.54-2.4 min[a]	Photodegradation	-	Baena-Nogueras et al. (2017)
	pK_a = 4.45 log K_{ow} = 3.12/-0.44 P_v^n = 3.72E-7 log K_d = 1.2	Papageorgiou et al. (2016)[a]	0.02 h	Photodegradation[b] k = 30.48 h^{-1}	100	
	-	-	-	Biodegradation[c] -	0	
	-	-	-	Biodegradation[d] -	0	

Diclofenac	pK_a = 4.15 log P = 4.40	Puckowski et al. (2016)	39 min[a]	Photodegradation	-	
	pK_a = 4.18 log K_{ow} = 1.87	Chen et al. (2017)[l]	0.17 h	Photodegradation[b] k = 4.04 h^{-1}	99	
	pK_a = 4.2 log K_{ow} = 4.51/0.7 P_v^n = 6.14E-0.8 log K_d = 1.2	Papageorgiou et al. (2016)[a]	-	Biodegradation[c] -	0	
	-	-	193 h	Biodegradation[d] k = 0.0012 h^{-1}	58	
	-	-	-	k_{biol} < 0.04 – 1.2 k_{biol} ≤ 0.002 – < 0.1	-	Papageorgiou et al. (2016)[a]
	Water solubility: >9 mg·mL^{-1} in deionized water at 25°C pK_a = 4.2 K_{oc}^o = 833.0 log K_{ow} = 0.70-4.51 K_d = 0.72	Bottoni et al. (2010)[a]	5 days (in water)	-	-	Bottoni et al. (2010)[a]
Naproxen	pK_a = 4.15 log P = 3.18	Puckowski et al. (2016)	0.93 h	Photodegradation[b] k = 0.74 h^{-1}	99	Baena-Nogueras et al. (2017)
	pK_a = 4.84 log K_{ow} = 1.06	Chen et al. (2017)[l]	-	Biodegradation[c] -	0	
	pK_a = 4.2 log K_{ow} = 3.5 P_v^n = 1.89E-0.6 log K_d = 1.1	Papageorgiou et al. (2016)[a]	746 h	Biodegradation[d] k = 0.0012 h^{-1}	38	
	-	-	-	k_{biol} < 0.2 k_{biol} = 1 – 1.9 k_{biol} = 0.4 – 0.8 k_{biol} = 0.08 – 0.4	-	Papageorgiou et al. (2016)[a]
	Water solubility: insoluble pK_a = 4.15 K_{oc}^o = 349.0 log K_{ow} = 3.18; 3.24 K_d = 217	Bottoni et al. (2010)[a]	14 days (in water)	-	-	Bottoni et al. (2010)[a]
Ibuprofen	pK_a = 4.91 log P = 3.70	Puckowski et al. (2016)	23 h	Photodegradation[b] k = 0.03 h^{-1}	55	Baena-Nogueras et al. (2017)
	log K_{ow}^g = 3.97; 4 K_d^h = 10-60 pK_a = 4.5-5.2	Morosini et al. (2017)[a]	1386 h	Biodegradation[c] k = 0.0005 h^{-1}	10	
	pK_a = 4.4 log K_{ow} = 3.97	Wang et al. (2019)[i]	2310 h	Biodegradation[d] k = 0.0003 h^{-1}	28	
	pK_a = 4.41 log K_{ow} = 1.50	Chen et al. (2017)[l]	-	-	-	-
	Water solubility: 21 mg·L^{-1} at 25°C pK_a = 4.91 K_{oc}^o = 394.0 log K_{ow} = 3.97 (4.13-4.9) K_d = 454	Bottoni et al. (2010)[a]	20; 32 days (in water)	-	-	Bottoni et al. (2010)[a]
∑Ibuprofen (Ibuprofen + 2-hydroxy-ibuprofen)	log K_{ow} = 3.97	Muir et al. (2017)[m]	1.5 days	-	-	Muir et al. (2017)[m]
Antibacterials (Personal care products)						
Triclosan	pK_a = 7.8 log K_{ow} = 4.76	Wang et al. (2019)[i]	-	Photodegradation k = 0.17–0.23 $days^{-1}$[a]; Biodegradation up to 95% in 5 days[a]	-	Baena-Nogueras et al. (2017)
	pK_a = 7.80 log K_{ow} = 4.70	Chen et al. (2017)[l]	0.69 h	Photodegradation[b] k = 1.01 h^{-1}	100	
	pK_a = 4.5/8.1 log K_{ow} = 4.8/5.34 P_v^n = 5.20E-06 log K_d = 4.3	Papageorgiou et al. (2016)[a]	866.43 h	Biodegradation[c] k = 0.0008 h^{-1}	21	
	-	-	66 h	Biodegradation[d] k = 0.0396 h^{-1}	97	
Neuroactive drugs						
Fluoxetine	pK_a = 10.07 log P = 4.05	Puckowski et al. (2016)	< 12 days	Biodegradation in marine waters	-	Benotti and Brownawell (2009)
	pK_a = 10 log K_{ow} = 4.05	Wang et al. (2019)[i]	-	Photodegradation[b] -	0	

	pK_a = 10.1 log K_{ow} = 1.25	Chen et al. (2017)[l]	315.48 h	Biodegradation[c] k = 0.0047 h^{-1}	81	Baena-Nogueras et al. (2017)
	-	-	651 h	Biodegradation[d] k = 0.0022 h^{-1}	45	
∑Fluoxetine (Fluoxetine + Norfluoxetine)	log K_{ow} = 3.82	Muir et al. (2017)[m]	3.0 days	-	-	Muir et al. (2017)[m]
Carbamazepine	pK_a = 13.90 log P = 2.45	Puckowski et al. (2016)	> 100 days	Biodegradation in marine waters	-	Benotti and Brownawell (2009)
	log K_{ow} = 2.45 K_d = 11; 20-68 pK_a = 13.9	Morosini et al. (2017)[a]	-	Photodegradation[b] -	0	Baena-Nogueras et al. (2017)
	pK_a = 15.4 log K_{ow} = 2.45	Wang et al. (2019)[i]	-	Biodegradation[c] -	0	
	pK_a = 13.9 log K_{ow} = 2.45	Chen et al. (2017)[l]	-	Biodegradation[d] -	0	
	pK_a = 7/13.9 log K_{ow} = 2.47 P_v^n = 1.84E-07 log K_d = 1.82/0.1	Papageorgiou et al. (2016)[a]	-	$k_{biol} \leq 0.1$ k_{biol} < 0.03/< 0.6 k_{biol} < 0.005 - < 0.008	-	Papageorgiou et al. (2016)[a]
∑Diazepam (Diazepam + Oxazepam)	log K_{ow} = 2.24	Muir et al. (2017)[m]	0.6 days	-	-	Muir et al. (2017)[m]
Norfluoxetine	pK_a = 9.06 log P = 5.25	Puckowski et al. (2016)	-	-	-	-
	pK_a = 9.05 log K_{ow} = 2.16	Chen et al. (2017)[l]				
Sertraline	pK_a = 9.50 log P = 2.88	Puckowski et al. (2016)	-	-	-	-
	pK_a = 9.47 log K_{ow} = 2.91	Chen et al. (2017)[l]				
	log K_{ow} = 5.29	Muir et al. (2017)[m]	35 days	-	-	Muir et al. (2017)[m]
	pK_a = 9.47	Papageorgiou et al. (2016)[a]	-	-	-	-
Antibiotics						
Sulfamethoxazole (Sulphonamides - SAs)	SAs are fairly water soluble, polar compounds; resistant to biodegradation and hydrolysis; quite persistent. pK_a = 4.5 – 10.6 log P = -0.1 – 1.7	Puckowski et al. (2016)	> 100 days	Biodegradation in marine waters	-	Benotti and Brownawell (2009)
	pK_a = 5.7 log K_{ow} = 0.89 P_v^n = 6.93E-08 log K_d = 2.1-2.7 (2.3-2.6)	Papageorgiou et al. (2016)[a]	3.73 h	Photodegradation[b] k = 0.19 h^{-1}	100	Baena-Nogueras et al. (2017)
	-	-	-	Biodegradation[c] -	0	
	--		312 h	Biodegradation[d] k = 0.0048 h^{-1}	89	
	-	-	-	k_{biol} = 0.3	-	Papageorgiou et al. (2016)[a]
Trimethoprim	-	-	> 100 days	Biodegradation in marine waters	-	Benotti and Brownawell (2009)
		-	-	Photodegradation[b] -	0	Baena-Nogueras et al. (2017)
		-	-	Biodegradation[c] -	0	
		-	159 h	Biodegradation[d] k = 0.011 h^{-1}	100	
Norfloxacin (Fluoroquinolones - FQs)	FQs show negligible volatilization; high affinity for sludge, sediments and soils; moderately soluble in water; relatively stable and primarily degraded via photolysis. pK_a = 6.9 / 8.6 log P = -1.0 – 1.6	Puckowski et al. (2016)	0.03 h	Photodegradation[b] k = 20.32 h^{-1}	100	

	-	-	363 h	Biodegradation[c] $k = 0.0022\ h^{-1}$	88	
	-	-	192 h	Biodegradation[d] $k = 0.0072\ h^{-1}$	99	
Ciprofloxacin (Fluoroquinolones – FQs)	FQs show negligible volatilization; high affinity for sludge, sediments and soils; moderately soluble in water; relatively stable and primarily degraded via photolysis. $pK_a = 6.9 / 8.6$ log P = -1.0 – 1.6	Puckowski et al. (2016)	0.04 h	Photodegradation[b] $k = 19.43\ h^{-1}$	100	
	$pK_a = 6.38$ $\log K_{ow} = 0.4$ $\log K_d = 4.3$	Papageorgiou et al. (2016)[a]	378 h	Biodegradation[c] $k = 0.0021\ h^{-1}$	89	
	-	-	212 h	Biodegradation[d] $k = 0.006\ h^{-1}$	97	
Antihypertensive drugs						
Atenolol	$\log K_{ow} = 0.16$ $K_d = 15; 64$ $pK_a = 9.6$	Morosini et al. (2017)[a]	-	Photodegradation[b] -	0	Baena-Nogueras et al. (2017)
	-	-	-	Biodegradation[c] -	0	
	-	-	630 h	Biodegradation[d] $k = 0.0015\ h^{-1}$	39	
Propranolol	$pK_a = 9.53$ log P = 3.48	Puckowski et al. (2016)	-	Photodegradation[b] -	0	
	-	-	255 h	Biodegradation[c] $k = 0.003\ h^{-1}$	78	
	-	-	445 h	Biodegradation[d] $k = 0.0025\ h^{-1}$	74	
Other PhACs						
Hydrochlorothiazide	$\log K_{ow} = -0.07$ $K_d = 0.1; 20.2\text{-}25.8$ $pK_a = 7.0; 9.2; 7.9$	Morosini et al. (2017)[a]	0.43 h	Photodegradation[b] $k = 1.61\ h^{-1}$	98	Baena-Nogueras et al. (2017)
	-	-	630 h	Biodegradation[c] $k = 0.0011\ h^{-1}$	18	
	-	-	861 h	Biodegradation[d] $k = 0.001\ h^{-1}$	20	
EE2	$pK_a = 10.4$ log P = 3.67	Puckowski et al. (2016)	-	-	-	-

[a]Data from literature; [b]measured at pH 7 after 24 h of incubation; [c]measured (after a lag phase) in freshwater after 28 days of incubation; [d]measured (after a lag phase) in seawater after 28 days of incubation; [e]pK_a: acidic dissociation constant; [f]log P: log (partition coefficient); [g]log K_{ow}: log (octanol-water partition coefficient); [h]K_d: distribution coefficient (l/kg); [i]pK_a estimated from SPARC; log K_{ow} obtained from EPI suite; [l]pK_a: estimated values, obtained from SCIfinder; K_{ow} (l/kg): estimated values at pH = 7; [m]log K_{ow} from the US EPA Chemistry Dashboard; $t_{1/2}$: predicted biotransformation half-life; [n]P_v: vapour pressure (mm Hg); [o]K_{oc} (soil organic carbon/water partition coefficient).

Besides the sorption onto suspended solids, non-polar compounds can also bond to fats, lipids and oils present in the sludge (Barnabé et al., 2009). Therefore, non-polar compounds may be removed during the sedimentation processes occurring in WWTPs, leading to primary and secondary sludge (Birkett and Lester, 2003). The sorption of estrogenic compounds (estrone E1, E2, EE2 and estriol E3) onto sludge was studied by Andersen et al. (2005), Clara et al. (2004a) and Huang et al. (2019), who found out a linear adsorption relationship after the application of the Freundlich isotherms. Two processes contribute to sorption: adsorption and absorption. The first is caused by electrostatic interactions between the positive functional groups of the contaminants and the membranes of microorganisms (carrying a negative charge); the second is related to the interaction between hydrophobic contaminants and the lipophilic membranes of microorganisms (Suárez et al., 2008; Verlicchi and Zambello, 2015). Acidic pharmaceuticals, such as ibuprofen, diclofenac, clofibric acid and bezafibrate, are not readily adsorbed by sludge and remain in the aqueous phase; on the contrary, basic pharmaceuticals, like fluoroquinolone antibiotics and steroid hormones (and their conjugated compounds) can be found adsorbed onto the sludge to a larger extent (Hamid and Eskicioglu, 2012; Nikolaou et al., 2007).

In WWTPs, direct metabolism by heterotrophic microorganisms and co-metabolism by autotrophs operating ammonia oxidation are considered as the main biodegradation routes (Hamid and Eskicioglu, 2012). However, biodegradation of pharmaceuticals reveals difficult, since it is limited by the presence of specific groups, like chlorine atoms and aromatic rings (Silva et al., 2012; Verlicchi and Zambello, 2014). The high half-lives of several pharmaceuticals suggest that, in order to enhance their removal, a higher HRT (Hydraulic Retention Time) should be required. The quality of the influent is another crucial parameter to take into account when looking for pharmaceuticals in sewage.

This aspect is strictly bound to the origin of wastewater: for example, hospital wastewater can lead to an increase of concentration of some specific pharmaceuticals found in WWTPs influent, such as contrast media or disinfectants (Deblonde et al., 2011). The removal of pharmaceuticals is also influenced by seasonality (Morosini et al., 2017; Roberts et al., 2016; Vieno et al., 2005).

Indeed, both biodegradation and sorption depend on temperature: the first one occurs to a minor extent when temperature decreases, due to a decreased biological activity, while sorption generally increases; photodegradation is less effective during winter (Deblonde et al., 2011). A higher removal rate in summer than in winter was observed for some pharmaceutical compounds while others presented almost the same removal rate in both the seasons (Castiglioni et al., 2006). Table 6 reports pharmaceuticals seasonal removal in WWTPs, while an overview of some new technical solutions for enhancing the ECs removal is provided in the following paragraphs. In touristic areas, a strong seasonality can be observed concerning the load of pharmaceuticals entering WWTPs (Eggen and Vogelsang, 2015). Rainfall can also affect the removal performance of a WWTP, since the microbial activity is reduced and sorption and flocculation phenomena can be altered (Radjenović et al., 2007). The lowest removal rate is reported for the class of antiepileptics and the highest for antidepressants (Deblonde et al., 2011). As regards the removal rate of pharmaceuticals in WWTPs, Gros et al. (2010) observed, in a long term study, three different behaviours:

- an increase in concentration along the passage through the WWTPs;
- no significant to medium removal efficiency;
- high removal efficiency.

The first one was, for instance, the case of the antiepileptic carbamazepine, which generally presented poor or no elimination with higher concentrations in the effluents, in agreement with other studies (Clara et al., 2004b; Vieno et al., 2007). In some cases, this increase of concentration was demonstrated to occur by the conversion of carbamazepine glucuronides and other conjugated metabolites to the parent compound by enzymatic processes taking place in WWTPs (Subedi et al., 2015; Vieno et al., 2007).

Table 6. Seasonal removal of pharmaceuticals in WWTPs based on activated sludge process

Substance	***Removal rate*** *(%)*		***Reference***
	Summer	**Winter**	
Amoxycillin	100	75	Castiglioni et al. (2006)
Atenolol	55	10	Castiglioni et al. (2006)
	62-97	51-87	Mohapatra et al. (2016)
Atorvastatin	100	52-100	Mohapatra et al. (2016)
Bezafibrate	87	15	Castiglioni et al. (2006)
	71	59	Kosma et al. (2014)
Bisphenol-A	100	36-81	Mohapatra et al. (2016)
Caffeine	100	95-99	Mohapatra et al. (2016)
Cephalexin	46-100	42-100	Mohapatra et al. (2016)
Chloramphenicol	63-100	33-63	Prabhasankar et al. (2016)
Ciprofloxacin	63	60	Castiglioni et al. (2006)
	89-100	32-96	Mohapatra et al. (2016)
Clarithromycin	84-93	0-60	Mohapatra et al. (2016)
Cotinine	100	43-100	Mohapatra et al. (2016)
Diclofenac	75-98	0-68	Mohapatra et al. (2016)
Diethyltoluamide (DEET)	98-100	27-70	Mohapatra et al. (2016)
Dilantin	0-27	0	Mohapatra et al. (2016)
Enalapril	100	18	Castiglioni et al. (2006)
Erythromycin-H_2O	81-100	63-87	Mohapatra et al. (2016)
	31-100	65	Prabhasankar et al. (2016)
Furosemide	54	8	Castiglioni et al. (2006)
Gemfibrozil	100	0-97	Mohapatra et al. (2016)
Hydrochlorothiazide	44	24	Castiglioni et al. (2006)
Ibuprofen	93	38	Castiglioni et al. (2006)
	100	91-100	Mohapatra et al. (2016)
Levofloxacin	97-100	0-100	Mohapatra et al. (2016)
Naproxen	100	85-100	Mohapatra et al. (2016)
	100	22-76	Prabhasankar et al. (2016)
Nonylphenol	90-97	54-94	Mohapatra et al. (2016)
Ofloxacin	57	43	Castiglioni et al. (2006)
Paracetamol	98	85	Kosma et al. (2014)
Ranitidine	84	39	Castiglioni et al. (2006)
Sulphamethoxazole	71	17	Castiglioni et al. (2006)
	96-97	0-85	Mohapatra et al. (2016)
	100	60	Prabhasankar et al. (2016)
Triclosan	92-100	51-95	Mohapatra et al. (2016)
Trimethoprim	99	0-93	Mohapatra et al. (2016)
	100	78-94	Prabhasankar et al. (2016)

Antiepileptics, such as carbamazepine, are considered the most persistent pharmaceuticals, due to the poor removal efficiency that WWTPs demonstrated towards them (Clara et al., 2005; Hernando et al., 2006). This makes carbamazepine one of the most frequently detected pharmaceuticals in the effluents from WWTPs (Mohapatra et al., 2014). In the study carried out by Gao et al. (2012), the concentration of carbamazepine in the effluent (155 ng/L) was even higher than its concentration in the influent (110 ng/L). The second type of behaviour, i.e. no significant to medium removal efficiency, was observed, among others, for diclofenac, macrolide antibiotics, like azithromycin and clarithromycin, β-blockers, lipid regulators and cholesterol lowering statin drugs, which presented average removal efficiencies respectively in the range 35%-70% (Gracia-Lor et al., 2012; Gros et al., 2010; Jelic et al., 2012). High removal efficiencies have been reported for the antihypertensive enalapril, non-steroidal anti-inflammatory drugs (e.g., ibuprofen, salicylic acid, acetaminophen) and some antibiotics (e.g., tetracycline, sulfamerazine and chlortetracycline) (Gao et al., 2012; Gracia-Lor et al., 2012; Gros et al., 2010). Sorption onto primary sludge represents a minor route of removal for several pharmaceuticals, with the exception of diclofenac, nonylphenol, galaxolide and tonalide (Luo et al., 2014), for which it represents the major route. Camacho-Muñoz et al. (2012) found a positive correlation between the tendency of a compound to be sorbed and its potential elimination through activated sludge treatment.

In addition to the main parameters reported above, pH also influences the sorption of a compound to solids. For instance, charge repulsion occurs in hormones when the pH is higher than the dissociation constant, since, in such conditions, the charge of hormones becomes negative due to dissociation of the phenolic hydroxyl group (Schäfer et al., 2011). This mechanism can be explained with the release of carbamazepine by sludge occurring when its concentration in water decreases. The presence of steroid hormones was analyzed by Manickum and John (2014) in a WWTP located in South Africa. E1, E2 and testosterone were found as the most abundant hormones in the effluent, with concentrations of 23, 20 and 11 ng/L respectively (Manickum and John, 2014). In spite of their lower concentrations compared to other pharmaceuticals, steroid hormones may induce high estrogenic effects and, thus, their relatively low concentrations should not be neglected (Luo et al., 2014).

Higher levels of concentrations in the effluent of a WWTP are usually found in developing countries (Fang et al., 2012). In an industrial region in India, the maximal total concentration of pharmaceuticals reached the value of 2.5 mg/L (Fick et al., 2009); among them, ciprofloxacin, cetirizine, norfloxacin and terbinafine, while a maximal influent concentration of 31 mg/L was measured for ciprofloxacin in a previous study (Larsson et al., 2007).

Carbamazepine, atenolol, triclocarban and triclosan, trimethoprim and sulfamethoxazole, ibuprofen and acetaminophen and caffeine are the most commonly detected, at higher concentrations, in municipal wastewater from Indian WWTPs (Balakrishna et al., 2017).

The concentrations of pharmaceuticals in sewage sludge were determined in several recent studies and, therefore, very little information is available on partition behaviour between phases (Narumiya et al., 2013).

Concentrations may differ by orders of magnitude (from below the Method Quantification Limit - MQL to greater than 10 μg/g dw - dry weight, depending on the compound; Tran et al., 2018) from a WWTP to another, due to the different types of compartments used (e.g., aerobic, anoxic and anaerobic) and to the SRT (Sludge Retention Time) (Verlicchi and Zambello, 2015). However, some general trends can be observed. Concentrations of 34, 67 and 27 μg/kg on dw basis were measured by Gao et al. (2012) for sulfamethoxazole in primary, secondary and dewatered sludge, respectively. In the same three matrices, acetaminophen was detected at concentrations of 109, 111 and 113 μg/kg dw, respectively (Gao et al., 2012). The same authors found that the antibiotic tetracycline, which was absent in primary sludge, was present in secondary and dewatered sludge in concentrations of 750 and 566 μg/kg dw, respectively. Hydrolysis of conjugates and/or the higher content of organic matter may explain the generally higher concentrations observed in secondary sludge (Martín et al., 2012). Pharmaceuticals with a high affinity to the solid phase, such as serotonin reuptake inhibitors, some antibiotics, *β*-blockers, carbamazepine and ketoconazole, can be found at relatively high concentrations in sewage sludge. For instance, the antibiotics ciprofloxacin and norfloxacin were detected at the maximal concentrations of 3.73 mg/kg and 4.33 mg/kg on total solid basis, respectively (Malmborg and Magnér, 2015). Anti-inflammatory drugs, like ibuprofen and diclofenac, whose tendency to sorption is lower if compared with other pharmaceuticals, can be anyway present in sludge if the WWTP is subject to high mass load (Malmborg and Magnér, 2015; Martín et al., 2012).

6. Treatment options for ECs removal

6.1. Wastewater treatment unit

The removal efficiency of primary sedimentation, essentially achieved through adsorption (Manickum and John, 2014), is low (< 20%) for the majority of pharmaceuticals (83%). Only a few pharmaceuticals (17%) show satisfying removal efficiencies (> 80%) after a secondary treatment (Ortiz de García et al., 2013). In the case of steroid hormones, for instance, low removal efficiencies are explained with the oxidation of E2 to E1 by heterotroph

microorganisms in the biological compartment (which actually increases E1 concentration) and with the low biodegradability of EE2 (De Mes et al., 2005; Hamid and Eskicioglu, 2012; Ting and Praveena, 2017). The efficiency of secondary treatments increases if the nitrification and denitrification processes complement the carbonaceous process (Guerra et al., 2015; Raboni et al., 2013; Raboni et al., 2014; Raboni and Torretta, 2017). Nitrogen removal seems to promote removal of some pharmaceuticals, such as ibuprofen, naproxen, erythromycin, EE2, bisphenol A and nonylphenol (Fernandez-Fontaina et al., 2012; Suárez et al., 2010).

Naproxen, ibuprofen, diclofenac and salicylic acid showed enhanced removal under anaerobic conditions (Avila et al., 2010; Hijosa-Valsero et al., 2010; Li et al., 2014). As well known, a general correspondence between the increase of HRT and the increase of the removal efficiency is observed (Kalyva, 2017) and this is especially valid for hormones (Ejhed et al., 2017; Froehner et al., 2011) and anti-inflammatories such as ketoprofen, clofibric acid and acids (Zhang et al., 2012). In addition, higher SRT values allow the establishment of a more microbial biocenosis, which can play a key role in the degradation of some persistent pharmaceuticals (Stamatelatou et al., 2011). Diclofenac can be significantly biodegraded when the SRT is at least 8 days (Nikolaou et al., 2007). Other authors suggest that a minimum SRT of 10 days should be granted to obtain satisfying removal efficiencies (Clara et al., 2005; Koh et al., 2009). Compounds that are biodegradable and show low tendency to absorb in sewage sludge are more influenced by HRT (Gros et al., 2010), whereas compounds that have high tendency to absorb in sewage sludge and are less biodegradable are more influenced by SRT. Anyway, promoting biodegradation with increased HRT and SRT may not be useful for many pharmaceuticals (Straub, 2016). Alternative and tertiary treatments are then required to decrease the pollutant load of effluents. Table 7 briefly reports results of some studies carried out on tertiary treatment of water and wastewater contaminated by pharmaceuticals. Fig. 2 summarizes the removal efficiencies of four different treatment processes (among those reported in Table 7, i.e. applied to the water line of WWTPs) towards four selected pharmaceuticals (carbamazepine; EE2, clofibric acid and nonylphenol) belonging to different therapeutic categories and frequently detected in aquatic environments. The mean refers to the average removal efficiency showed by the treatment towards the mixture of the four compounds. Only slight improvements with respect to the conventional biological removal can be achieved with membrane bioreactors (Oulton et al., 2010).

Ozonation shows high removal performance on steroid hormones, antibiotics, carbamazepine and anti-inflammatories, but lower removal efficiencies are reported for the anti-inflammatory ibuprofen, the anxiolytic diazepam and the lipid-regulator bezafibrate, whose second-order rate constants are lower by several orders of magnitude (Huber et al., 2003; Luo et al., 2014).

Fenton reactions, which involve ferrous or ferric salts and the strong oxidizer hydrogen peroxide (H_2O_2) and ultraviolet (UV) radiation, can also generate hydroxyl radicals (OH·). However, Fenton reactions require an additional stage to remove the ions dissolved in the solution (Mohapatra et al., 2014). Fenton oxidation of bisphenol A was also studied by Torres et al. (2007): with a treatment of 40-90 min duration, with 15 mg/L of iron(II) sulphate and continuous addition of H_2O_2 at 4.5 mg/hour, at pH = 3-6.7, a removal efficiency higher than 90% was observed in deionized water; the contradictory aspect was that no removal was observed in natural water.

Furthermore, UV photo-oxidation showed to be generally ineffective if not coupled with other processes, like catalysis and Fenton oxidation (Luo et al., 2014).

Table 7. Tertiary treatments of water and wastewater contaminated by pharmaceuticals

Treatment process		***Substance***	***Removal efficiency (%)***	***Reference[a]***
Ozonation	semi-continuous reactor 2% O_3 36 l/hour flow 4 min duration pH 5.5 182.6 mg/L initial concentration	Amoxicillin	90	A
Ozonation	10 liter sample of municipal secondary effluent duration: 12 min 5 µg/L initial concentration 50 µg/L O_3	Carbamazepine	69.9	B
		EE2	67.5	
		Clofibric acid	68.4	
		Nonylphenol	78.1	
Ultrasonic ozonation	10 liter sample of municipal secondary effluent duration: 12 min 5 µg/L initial concentration 30 µg/L O_3 240 W ultrasonic power	Carbamazepine	84.1	B
		EE2	81.6	
		Clofibric acid	82.9	
		Nonylphenol	88.3	
Photocatalysis + ozonation	10 liter sample of municipal secondary effluent duration: 12 min 5 µg/L initial concentration 30 µg/L O_3 1 mW/cm^2 UV-light intensity TiO_2-based catalyst in concentration of 100 mg/L	Carbamazepine	85.9	B
		EE2	79.4	
		Clofibric acid	82.0	
		Nonylphenol	89.6	

Activated carbon adsorption	batch tests 50-ml sample 1.2 µg/L of carbamazepine 0.3 µg/L of sulfamethoxazole 20 mg/L powdered activated carbon 30 min contact time	Carbamazepine	94	C
		Sulfamethoxazole	< 31	
Photocatalysis	3.5 hours treatment 1 g/L TiO_2 85-ml volume initial concentration 0.82 mg/L thin films of TiO_2, Ag/TiO_2 and Pt/TiO_2 15-W UV lamp	E2	98	D
Ultrasonic cavitation	40 - 90 min in deionized water initial concentration 27 mg/L power of 80 W frequency of 300 kHz	Bisphenol A	90 - 100	E

[a]*Reference: (A) Andreozzi et al. (2005); (B) Zhou et al. (2015); (C) Ruhl et al. (2014); (D) Coleman et al. (2005).; (E) Torres et al. (2007).*

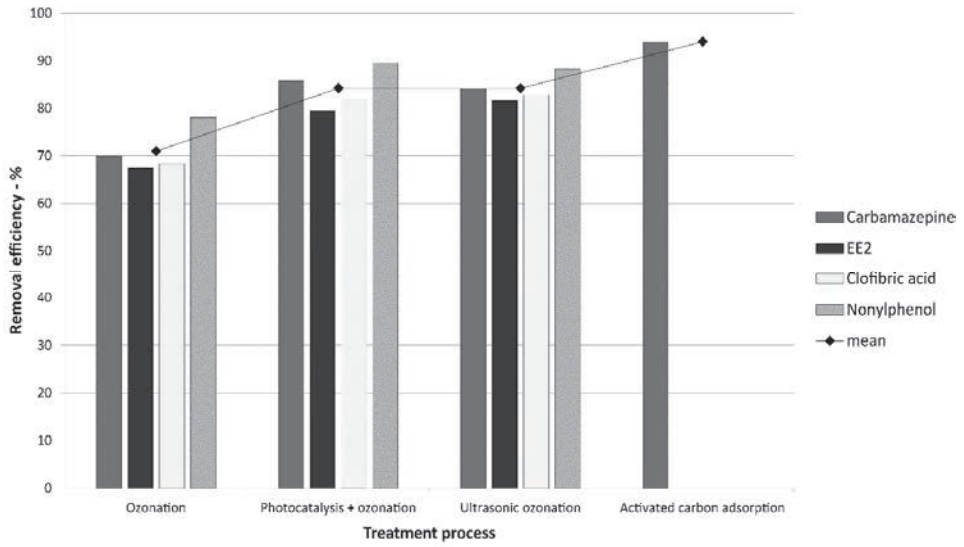

Fig. 2. Removal efficiencies of different treatment processes (water line of WWTPs) towards pharmaceuticals belonging to various therapeutic categories

Photocatalysis, for instance, generates OH· from UV irradiation of a metal oxide semiconductor, commonly anatase (TiO_2). Ultrasounds are also used to destroy the unwanted compounds by the high temperature and pressure that develop in the bubbles formed by acoustic cavitation (Papadaki et al., 2004). Slightly higher removal efficiencies were obtained with Ag/TiO_2 and Pt/TiO_2 (Zhou et al., 2015).

Activated carbon adsorption is also proposed as a viable solution to further remove compounds recalcitrant to biodegradation. Adsorption on activated carbon is greatly influenced by the molecular size of pharmaceuticals, by their hydrophobicity, etc. (Kaur et al., 2017). For this reason, as in the case of other tertiary treatment processes, not all contaminants are removed at the same extent (Straub, 2016; Torretta et al., 2013). A survey carried out on treatment of secondary effluent added with 66 ECs with an average concentration of 40-80 mg/L (Prieto-Rodríguez et al., 2013) obtained the following results:

- solar heterogeneous photocatalysis, carried out for 30 min with 20 mg/L of TiO_2 in a parabolic collector plant, showed a removal of 85% in a 35 l sample;
- solar photo-Fenton oxidation, carried out in a parabolic collector plant, for 3 min, with 5 mg/L of Fe^{2+} and 15 mg/L of H_2O_2, at pH of 2.8, obtained a removal of 84% in a 75 l sample;
- ozonation dosed with 0.69 g/h O_3 (ozone) for 20 min, with a power of 20 W, showed a removal of 90% in a 50L sample.

6.2. Sludge treatment unit

Primary and secondary treatments produce excess sludge with a potential high content of hydrophobic ECs and many of them were found in anaerobically digested sludge at concentrations ranging from g/kg dry to mg/kg dry (Narumiya et al., 2013). Therefore, sewage sludge must be regarded as a potential source of contamination, given its possible use in agriculture (Auirol et al., 2006; Marcoux et al., 2013; Narumiya et al., 2013).

A way to limit the load of contaminants in sewage sludge was proposed by Eriksson et al. (2008) and consists of reintroducing the biological stage after the application of tertiary treatments. More focused solutions concern the treatment of sewage sludge itself. Anaerobic digestion and aerobic processes (composting) demonstrated to be able to reduce ECs concentrations, due to biodegradation and loss of organic matter (Aemig et al., 2019; Martín et al.,

2012). However, the removal of some emerging contaminants in anaerobic digestion does not always coincide with that occurring in activated sludge process (Narumiya et al., 2013). Other processes of the sludge treatment line (e.g., conditioning and dewatering) show very limited effects on the concentration of pharmaceuticals (Jelic et al., 2012).

Pre-treatments with advanced oxidation processes are also studied for application to sewage sludge. Ozonation and Fenton processes, for instance, demonstrated to increase solubility, reduce viscosity and, overall, facilitate biodegradation (Verma et al., 2007). Table 8 briefly reports the results of some studies carried out on the treatment of sewage sludge containing pharmaceuticals.

Besides conventional treatments, like composting and anaerobic digestion, ozonation showed interesting results for persistent compounds like carbamazepine, although no significant effect is expected for hydrophobic contaminants, whose tendency to be sorbed onto sludge probably protects them from O_3 attack (Carballa et al., 2007a). Recent advanced oxidation processes make use of biological approaches based on white-rot fungi, which showed high removal efficiencies even for carbamazepine (Marco-Urrea et al., 2010; Mir-Tutusaus et al., 2018).

Fig. 3 summarizes the removal efficiencies of six different treatment processes (among those reported in Table 8, i.e. applied to the sewage sludge line of WWTPs) towards four selected pharmaceuticals (carbamazepine; EE2, ibuprofen and trimethoprim) belonging to different therapeutic categories and frequently detected in aquatic environments. The mean refers to the average removal efficiency showed by the treatment towards the mixture of the four compounds and the vertical bars represent the range of removal efficiencies showed by a treatment towards a specific compound under different operating conditions. When the value was negligible, it has been assumed equal to zero.

Table 8. Treatment of sewage sludge containing pharmaceuticals

Treatment process		***Substance***	***Removal efficiency (%)***	***Reference[a]***
Anaerobic digestion	mesophilic 37°C thermophilic 55°C SRT 10-30 days initial concentrations 4-400 µg/L	Naproxene Antibiotics Sulfamethoxazole Roxithromycin	< 80	A
		E1	60-95	
		EE2	40÷90	
		Ibuprofen	30-60	
		Iopromide Carbamazepine	< 40	
Anaerobic digestion Composting	-[b]	Naproxene	98	B
		Salicylic acid	94	
		Ibuprofen	85	
		E2	75	
		Carbamazepine	50	
		Caffeine	70	
Anaerobic digestion	thermophilic loading rate 2.4 kgVS/m^3 retention time 20 days	Oxazepam Trimethoprim	> 80	C
		Ibuprofen, E1, E2, EE2 Diclofenac Carbamazepine	< 30	
Pasteurization	30 min at 73-75°C	Oxazepam Trimethoprim	> 30	
		EE2	negligible	
Fenton	sulfuric acid and H_2O_2	Fluoxetine Metoprolol Trimethoprim	> 50	
		Diclofenac E2, EE2;	< 20	
		Oxazepam Ibuprofen	negligible	
Anaerobic digestion Ozonation	20 mg/L O_3 2 hours	Hormones and Sulfamethoxazole	80	D
		Carbamazepine	66	
		Diazepam	50	
		Ibuprofen	20-50	
		Iopromide	20	
Biological Fenton-like process	process mediated by fungus *Trametes versicolor* 6 hours incubation period initial concentration 10 mg/L	Carbamazepine Atenolol Clofibric acid	80	E

[a](A) Carballa et al. (2007b); (B) Martín et al. (2012); (C) Malmborg and Magnér (2015); (D) Carballa et al. (2007a); (E) Marco-Urrea et al. (2010); [b]Not reported.

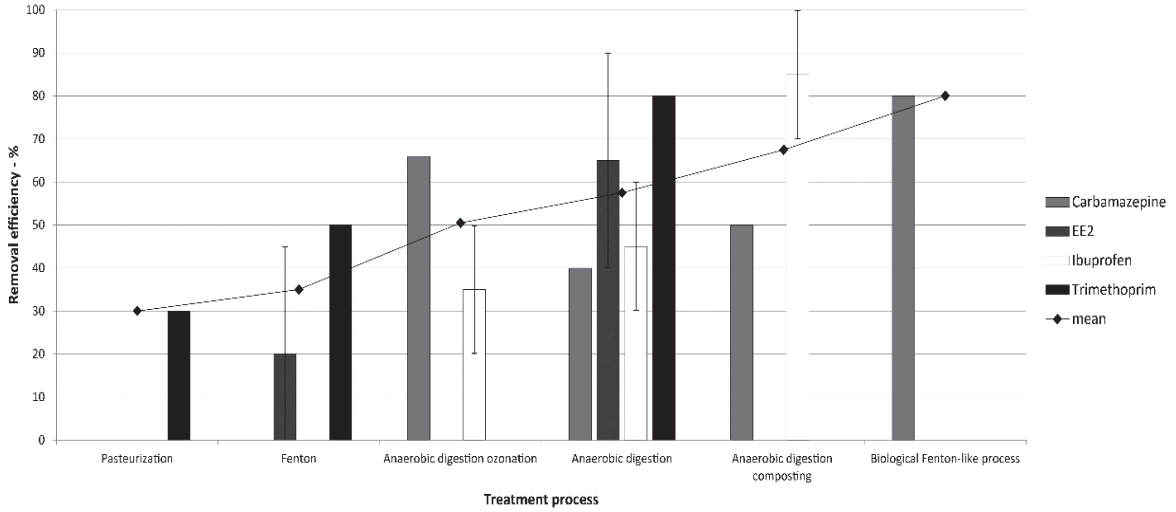

Fig. 3. Removal efficiencies of different treatment processes (sewage sludge line of WWTPs) towards pharmaceuticals belonging to various therapeutic categories

7. Conclusions

The environmental occurrence of pharmaceuticals and other ECs is an issue of great concern due to their potential to pose a risk to aquatic organisms and to human beings. On the basis of the available literature on this topic, a detailed framework was presented concerning the sources of pharmaceuticals in the environment, their fate and occurrence in WWTPs, their risk on aquatic organisms, the potential consequences for humans and the available options to reduce the release of pharmaceuticals from WWTPs.

In order to better understand their potential effects on aquatic organisms and on humans, toxicity data on a wider number of compounds (including metabolites and by-products) are needed, especially regarding long-term exposure, but, for some compounds not yet widely investigated, they are not available and, in most cases, they mainly refer to acute effects. Due to the bioactive properties of pharmaceuticals and their continuous release into the environment, in fact, risk assessments, based on chronic toxicity, persistence and bioaccumulation, seem to be more appropriate. Moreover, to perform a full risk assessment, exposure scenarios and exposure pathways must be considered, hence it is necessary to increase the knowledge on target aquatic species and dose-response relationships and to define PNECs for the large majority of pharmaceuticals currently on the market. Finally, there is a great need to develop detailed fate and transport models and databases allowing correlation between pharmaceuticals usage, effluent concentrations, environmental occurrence and effects.

Among other specific issues not covered yet, some crucial aspects emerge, such as the still scarce number of investigated pharmaceutical compounds in the influents and effluents of WWTPs, often limited to some countries, and the lack of information about the environmental impact of mixtures of pharmaceuticals and the hazard posed by metabolites and by-products.

Even if it is urgent to apply, right now, advanced technological solutions to upgrade the existing WWTPs and to take into account the hydraulic characteristics of the receiving water bodies, in order to mitigate the potential ecotoxicological effects of pharmaceutical residues, it is also important to adopt a suitable behaviour for reducing the discharge and the disposal of pharmaceuticals into the environment: the Swedish classification system, which aims at increasing the awareness of general practitioners and healthcare workers in prescribing non-environmentally-hazardous drugs, could be an example to follow.

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