Assessment of Pharmaceuticals in Water Systems: Sustainable Phytoremediation Strategies

11

Ana V. Dordio, A. J. Palace Carvalho, and A. P. Pinto

Abstract

The contamination of aquatic environments with pharmaceuticals has become over the latest years one of the top concerns in Environmental Science and in regard to Public Health and Safety policies. Although reported environmental concentrations of any single pharmaceutical compound are usually too low to induce acute ecotoxicological problems on its own, the prolonged exposure to these pseudo-persistent pollutants (which are originally designed to interfere with biochemical processes) is expected to potentially cause chronic effects in the long term. In addition, the wide variety of drugs already detected in the environment raises the possibility of cumulative effects of substances with similar modes of action or even of synergistic effects that may potentiate the harmful effects of some of the compounds. Therefore, the clarification of the current situation in terms of their removal from wastewaters under the currently used wastewater treatment processes, the impacts they may cause or are already causing in ecosystems and to human health, and the prospects for improvements of future

A. V. Dordio
Chemistry Department, School of Sciences and Technology, University of Évora, Évora, Portugal

MARE – Marine and Environmental Science Centre, University of Évora, Évora, Portugal

A. J. P. Carvalho
Chemistry Department, School of Sciences and Technology, University of Évora, Évora, Portugal

LAQV-REQUIMTE, University of Évora, Évora, Portugal

A. P. Pinto (✉)
Chemistry Department, School of Sciences and Technology, University of Évora, Évora, Portugal

Institute of Mediterranean Agricultural and Environmental Sciences (ICAAM), University of Évora, Évora, Portugal
e-mail: app@uevora.pt

R. Prasad (ed.), *Phytoremediation for Environmental Sustainability*,
https://doi.org/10.1007/978-981-16-5621-7_11

wastewater treatment plants design and operation are urgently needed. This chapter presents a review of the current knowledge on the sources, occurrence, and fate of a variety of classes of pharmaceuticals in the environment, WWTPs, sewage sludge and/or biosolids, and some crop plants and macrophytes. A summary of the most commonly detected pharmaceuticals and typical concentration levels at which they occur is presented, organized by therapeutical class. Wastewater treatment plants, which are the major source of pharmaceuticals in the aquatic environment, are analyzed in some detail, focusing on the efficiencies of pollutant removal that are typical of these conventional means. Ensuingly, alternative or complementary solutions provided by some advanced wastewater treatment technologies are briefly discussed. In this regard, a phytoremediation technology for wastewater treatment is gaining increasing acceptance and widespread use: the constructed wetlands systems, which are discussed in further detail in the final part of the text. The chapter concludes with an overall appreciation of this subject, pointing out some relevant topics that are still scarcely explored and, therefore, may lead to interesting new avenues of research in this field.

Keywords

Wastewater · Sewage sludge · Biosolids · Clean-up · Phytoremediation

11.1 Introduction

Pharmaceuticals are one of the cornerstones of the extraordinary improvements to human health care occurring over the last century. Accordingly, an enormous amount and variety of pharmaceuticals are released annually in the market and the trend is for a continuing growth in their consumption and of the release of new pharmaceutical substances (OECD 2018). However, notwithstanding the benefits they provide, the extensive use of pharmaceuticals also raises new problems, including environmental ones. In fact, in the last decades a broad diversity of pharmaceuticals started being detected in a variety of sample types, from treated wastewater, sludge, biosolids, manure, surface water, groundwater, plant and animal tissues to drinking water samples (Fent et al. 2006; Kummerer 2009; Fatta-Kassinos et al. 2011; Lapworth et al. 2012; Carvalho et al. 2014; Tasho and Cho 2016; Ebele et al. 2017; Al Farsi et al. 2017; Tran et al. 2018; Patel et al. 2019). Pharmaceutical's residues may already have been present as pollutants in aquatic environments for a longer period, but the problem has gone unnoticed until recently, due to the low concentrations at which they typically occur. It was only thanks to the improved ability of modern analytical chemistry to quantify pollutants down to trace levels (ng L^{-1} or μg L^{-1}), even in complex matrices such as environmental samples or wastewaters, which was made possible by the significant advances in new analytical methodologies and instrumentation over the last decades that awareness to this situation was raised.

Pharmaceuticals, as trace environmental pollutants, are relevant despite their usually low concentrations for several reasons (Fent et al. 2006; Petrovic and Barceló 2007; Enick and Moore 2007; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018; Patel et al. 2019):

- Pharmaceuticals are continuously introduced in the environment (for this reason they are referred to as "pseudo-persistent" pollutants), i.e. even if removal rates in wastewater treatment plants (WWTPs) are high (which is not usually the case) they are overcome by a continuous input due to their high consumption rates;
- Even if most pharmaceutical substances occur in the environment only at low concentrations, the huge variety of pharmaceutical substances currently in use potentially may produce large cumulative effects, or even worse, as several different substances may have similar modes of action or act on the same targets, they may present synergistic effects, thus intensifying their adverse action beyond what the low concentrations of any single substance would lead to predict;
- Pharmaceuticals are originally developed with the intention of performing a biological effect; their beneficial effects to treat diseases are, however, usually harmful to healthy individuals and, therefore, are potentially hazardous substances;
- Pharmaceuticals often have the same type of physicochemical behavior as other harmful xenobiotics (persistence in order to avoid the substance to be inactivated before having a curative effect, and lipophilicity in order to be able to traverse cell membranes); and.
- The low concentrations and high toxicity of pharmaceuticals make this type of pollutants, in general, very difficult to remove by conventional wastewater treatment processes.

Indeed, many of these compounds receive inefficient treatment in WWTPs because the latter were designed to deal with bulk pollutants and are not well suited to cope with the special characteristics of pharmaceuticals (as well as other micropollutants). Therefore, a substantial amount of pharmaceutical pollutants present in wastewater are eventually still present in the treated WWTP effluent and discharged with it in the receiving water bodies. This has been considered the main route for contamination of the aquatic environment by pharmaceuticals (Fent et al. 2006; Nikolaou et al. 2007; Aga 2008; Verlicchi et al. 2012b; Michael et al. 2013; Luo et al. 2014; Evgenidou et al. 2015; Petrie et al. 2015; Noguera-Oviedo and Aga 2016; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018). However, because pharmaceuticals are typically present in the environment at minute concentrations, their analysis and the monitoring of the environmental situation in that regard require sophisticated and laborious analytical tools for their separation and accurate quantification. Therefore, the presence of pharmaceuticals in the environment is emerging as a topic of major concern, but the full picture is still far from being clearly delineated. Nevertheless, as severe risks to the environment and human health resulting from an increased environmental exposure to pharmaceuticals are predictable (or even observed in some cases such as those of the antibiotics, whose presence

in the environment has been the cause of the development of antibiotic resistance bacteria, among other harmful effects) there is an urgent need of finding ways to retain and remove these pollutants before they reach the receiving water bodies.

In the present chapter, pharmaceuticals are briefly described in terms of their chemical characteristics and behavior as pollutants, an overview is presented of the several sources of environment contamination with pharmaceuticals, of their possible environmental fates and of their ecotoxic effects. A summary of the most commonly detected pharmaceuticals, grouped by therapeutical class, as well as typical concentration levels in which they occur is also presented based on the available data collected from the literature. The major source of pharmaceutical contamination, the effluent discharge by WWTPs, is analyzed in more detail, with an assessment of the available data on typical pharmaceutical loads at WWTPs' input and discharge streams as well as typical efficiencies of removal of these pollutants at these conventional wastewater treatment facilities. The majority of published studies focus on the aqueous phase and, therefore, almost all available data on the pharmaceuticals that exit the WWTPs refer to pharmaceutical concentrations in WWTP effluents, whereas very scarce information is reported in regard to pharmaceuticals present in particulate phases, i.e. sludges and biosolids. However, the few data available on solid phases are also discussed briefly in this chapter, as this is an important topic given the common practice of biosolids application in soils as fertilizer and the consequent risks of soil contamination with pharmaceuticals. Finally, some of the advanced wastewater treatment technologies that have been considered as alternative or complementary to conventional wastewater treatment processes in an attempt to improve the removal of pharmaceutical from wastewaters are briefly discussed, analyzing some of the reasons why these have not yet been widely adopted. However, a phytoremediation technology for wastewater treatment is gaining increasing popularity, the constructed wetlands systems (CWS) are discussed in some more detail. Phytotechnologies have gained a good reputation as generally interesting low-cost and low-maintenance wastewater treatment technologies for non-conventional pollutants such as heavy metals and organic xenobiotics. Nowadays, CWS are becoming an alternative to conventional wastewater treatment processes or are being integrated in WWTPs as a secondary or tertiary treatment stage and may potentially become a cost-effective solution for the mitigation of much of the pharmaceutical (Dordio et al. 2010; Hijosa-Valsero et al. 2010, 2011, 2016, 2017; Ávila et al. 2010, 2014; Dordio and Carvalho 2011, 2013, 2017; Reyes-Contreras et al. 2012; Verlicchi and Zambello 2014; Zhang et al. 2014, 2018b; Li et al. 2014; Ávila and García 2015; Vymazal et al. 2017; Matamoros et al. 2017; Vo et al. 2018; Liu et al. 2019). The chapter concludes with an overall appreciation of this subject, pointing out some relevant topics that are still scarcely explored and, therefore, may lead to interesting new avenues of research in this field.

11.2 Pharmaceuticals in the Environment: Characteristics, Sources, and Fate

Pharmaceuticals, whether for human or veterinary use, are xenobiotic compounds that are designed to produce a biological effect on some part of the body of the individuals that ingest them (or use them via external application). Although it may be regarded as a class of chemical substances, the term "pharmaceuticals" is actually a general denomination that refers to the purpose with which they are used (i.e. for the diagnosis, prophylaxis, or therapy of a disease) and does not, in fact, imply a resemblance between pharmaceutical compounds in terms of their physical and chemical characteristics. Pharmaceuticals indeed comprise a wide variety of organic substances with very diverse properties. A few of these are common among many pharmaceuticals because they usually must perform their function in a same common medium, the cell. Therefore, they usually must be at least moderately soluble in aqueous media but still be able to traverse a hydrophobic medium (the lipidic cell membrane). In most other respects, pharmaceuticals span a large variety of families of chemical compounds and therefore present a wide diversity in most other physical and chemical properties.

Pharmaceuticals molecules can be large and chemically complex, varying widely in molecular weight (ranging typically from 200 to 1000 Da), structure, functionality, and shape, due to the diversity of processes in which pharmaceuticals must intervene. In general pharmaceuticals are polar amphiprotic molecules, frequently possessing more than one ionizable group, thus leading to the speciation of the compounds. Therefore, the degree of ionization and, consequently, many of their properties are pH dependent. As they are usually polar, pharmaceuticals are characterized by at least some moderate hydrophilicity that favors their solubility in water, which is the medium where they commonly must take effect. However, some of them also present some lipophilicity. It is important to note that the classification of pharmaceuticals according to their active substances, within subgroups of pharmaceuticals, also does not imply that they follow a definite chemical behavior. In fact, small changes in chemical structure may have significant effects on solubility, polarity, and other properties. This in turn may lead to pharmaceuticals from the same class (or even similar active substances) undergoing through a divergent environmental fate (i.e. the way, as they reach the environment, they will ultimately distribute among the different environmental compartments and subsequently be transformed/degraded, bioaccumulated, or stabilized). Polarity, water solubility, hydrophobicity, and volatility are some of the most important properties of pharmaceuticals that can contribute to their fate in aquatic environments. In addition, some other pharmaceuticals properties such as octanol–water partition coefficients ($\log K_{ow}$), solid-water distribution coefficients ($\log K_d$), organic carbon based sorption coefficients ($\log K_{oc}$), and dissociation constants (pK_a) also have a shaping role in their environmental fate by influencing sorption, partitioning, hydrolysis, photodegradation, and biodegradation processes.

Only a fraction of the pharmaceuticals that are ingested by humans or animals are effectively absorbed by their bodies, being the remnant excreted via feces or urine or

washed out (in the case of external application). The percentage of ingested drug that is absorbed by the body, as well as the portion that is subsequently metabolized, differs among different compounds. Pharmaceuticals can be released without suffering any kind of modifications (i.e. as the parent compound) or be excreted in modified forms of the original pharmaceutical (i.e. the metabolites) following its metabolic transformation in the organism (non-biological, human or microbial).

These modified compounds may differ only slightly from the parent substance, or they may exhibit more severe transformations, structural and chemical, leading altogether to whole new chemical compounds. Additionally, some metabolites may be easily reverted to the original parents or be further transformed in non-metabolic reactions, whereas some metabolites are rather stable compounds that resist most further transformations.

The excreted pharmaceuticals and metabolites that are introduced in domestic and hospital wastewaters or result from veterinary use (livestock and aquacultures) are, however, only one among other sources of pharmaceutical pollution. Pharmaceuticals, their metabolites and other transformation/degradation products can enter in the environment through a large and sometimes unexpected variety of routes (Fig. 11.1).

Improper disposal of unused or expired drugs, which therefore may escape adequate waste treatment (in landfills), may be a source of contamination of soil and, through leaching, of water bodies. In addition, at the manufacturing stage, some significant pharmaceutical pollution may also be produced, despite all the measures taken by the industry to limit and/or to mitigate it. In regard to the domestic wastewaters that are treated in municipal wastewater treatment plants (WWTPs), they too are an important (and probably the main) route of entry for pharmaceuticals (and metabolites or transformation products) in the environment despite the treatment they receive at the WWTPs (Fent et al. 2006; Nikolaou et al. 2007; Aga 2008; Verlicchi et al. 2012b; Michael et al. 2013; Luo et al. 2014; Evgenidou et al. 2015; Petrie et al. 2015; Noguera-Oviedo and Aga 2016; Tran et al. 2018). In fact, except for the most biodegradable ones, many pharmaceuticals are poorly removed by the conventional wastewater treatment processes used in most WWTPs, because these have been designed to deal with bulk pollutants as awareness for the problem of pharmaceutical pollution is a relatively recent issue (Fatta-Kassinos et al. 2011; Verlicchi et al. 2012b; Luo et al. 2014; Evgenidou et al. 2015; Gavrilescu et al. 2015; Tran et al. 2018). Conventional wastewater treatment processes, which are typically either of physical (screening, sedimentation, etc.) or biological (activated sludge, lagoon, etc.) nature, do not present sufficiently high efficiencies in the removal of this type of organic micropollutants due to the wide variety of their characteristics, to the low concentrations at which they are present in wastewaters, and to their generally low biodegradability (due to the chemical complexity of these molecules). Therefore, most of these contaminants are usually still present in the treated effluents from WWTPs, which represent the most important source point for aquatic exposure to pharmaceuticals (Fatta-Kassinos et al. 2011; Luo et al. 2014; Evgenidou et al. 2015; Barra Caracciolo et al. 2015; Noguera-Oviedo and Aga 2016; Tran et al. 2018; Patel et al. 2019). However, in addition to this major contribution, wastewaters from

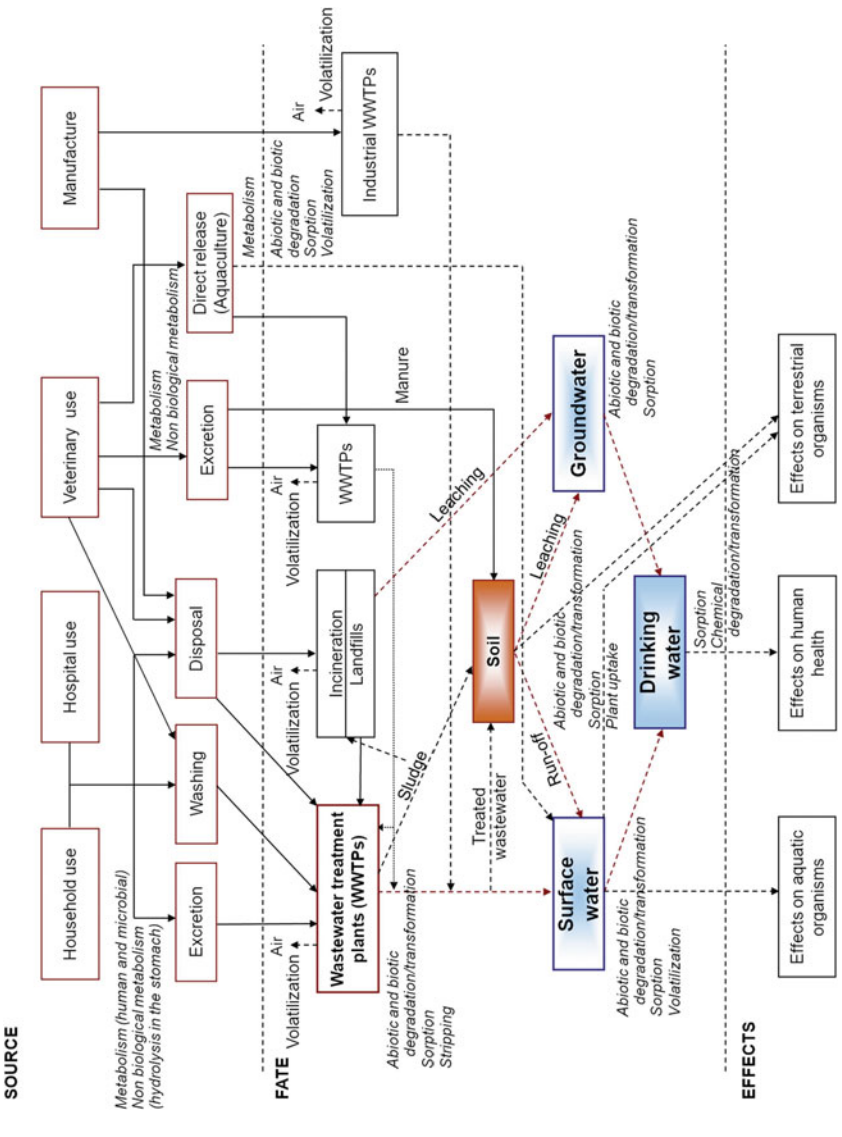

Fig. 11.1 Sources, pathways, and impacts of pharmaceuticals in the environment. (Sources: Halling-Sørensen et al. 1998; Heberer 2002; Farré et al. 2008; Lapworth et al. 2012)

hospitals (Sim et al. 2011; Lapworth et al. 2012; Verlicchi et al. 2012a; Frédéric and Yves 2014; Mendoza et al. 2015; Petrie et al. 2015), the pharmaceutical industry (Sim et al. 2011; Gadipelly et al. 2014; Tran et al. 2018), and landfill leachates (Eggen et al. 2010; Lapworth et al. 2012; Ramakrishnan et al. 2015; Masoner et al. 2016; Lu et al. 2016) are other minor (but significant) inputs of pharmaceutical contaminants to the water resources.

Veterinary use of pharmaceuticals is another significant, although sometimes overlooked, source of contamination of soil, groundwater as well as surface water (Kim et al. 2011; Sim et al. 2011; Du and Liu 2012; Mo et al. 2015; He et al. 2016; Tasho and Cho 2016). An important source of soil contamination is the practice of irrigating fields with reclaimed water if the wastewater treatment is inefficient for the removal of pharmaceuticals, as well as from the application of livestock manure, sewage sludge, and biosolids to soil as fertilizer or compost (Gottschall et al. 2012, 2013; García-Santiago et al. 2016; Tasho and Cho 2016; Topp et al. 2017; Tran et al. 2018). The presence of pharmaceuticals in the soil may then lead to the contamination of surface water by run-off or of groundwater by leaching (Nikolaou et al. 2007; Sabourin et al. 2009; Bottoni et al. 2010; Lapworth et al. 2012; Du and Liu 2012; Li 2014; Sui et al. 2015). Additionally, contamination originating from aquaculture (where mostly antibiotics are abundantly applied directly in the water) usually occurs via direct discharge in the environment (Tijani et al. 2013; Rico and Van den Brink 2014; Li 2014; He et al. 2016; Topp et al. 2017).

The occurrence of pharmaceuticals at trace levels (ngL^{-1}–μgL^{-1}) in different environmental compartments, in particular the aquatic media, has been already reviewed by several authors (Fent et al. 2006; Nikolaou et al. 2007; Petrovic and Barceló 2007; Kümmerer 2009b; Fatta-Kassinos et al. 2011; Silva et al. 2011; Tijani et al. 2013; Petrie et al. 2015; Wilkinson et al. 2017; Patel et al. 2019).

Many of the compounds that have become ubiquitous in surface waters, ground waters, soils, and river sediments and even inside plant and animal tissues are mostly from the classes of the anti-inflammatory drugs, antibiotics, blood lipid regulators, beta-blockers, and neuroactive drugs (Nikolaou et al. 2007; Miége et al. 2009; Lapworth et al. 2012; Carvalho et al. 2014; Sui et al. 2015; Tasho and Cho 2016; Wilkinson et al. 2017; Ebele et al. 2017; Riaz et al. 2018; Patel et al. 2019). However, environmental concentrations may vary spatially, temporally, and socio-economically, with variations depending upon usage patterns, locations (with heavy inputs from manufacturing facilities and hospitals), removal in wastewater treatment plants (WWTPs), dilution by rainfall, sampling uncertainties, and analysis techniques.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and diclofenac are widely consumed pharmaceuticals, a fact that is facilitated by these substances being over-the-counter drugs, and owing to their high consumption rates they are also very often detected in ground and surface waters (Fent et al. 2006; Petrovic and Barceló 2007; Sui et al. 2015; Wilkinson et al. 2017).

Among the blood lipid regulators, residues of fibrates (i.e. fibric acid derivatives such as clofibrate, bezafibrate, gemfibrozil, and fenofibrate; these have been highly prescribed drugs in the past but have now been largely substituted by other

substances in many countries) also continue to be frequently detected in natural water bodies, particularly in the form of their bioactive metabolite clofibric acid. In fact, clofibric acid is one of the earliest pharmaceutical residues to be detected in aquatic environments and a notoriously persistent water contaminant of pharmaceutical origin, with a persistence in the environment that is estimated in 21 years (Khetan and Collins 2007). Currently, other pharmaceuticals from the blood lipid regulators class also commonly present in water bodies are the statins (e.g. atorvastatin, simvastatin, and lovastatin) and niacin (or nicotinic acid) (Sui et al. 2015; Tran et al. 2018; Patel et al. 2019).

Several beta-blockers are also frequently detected in surface waters. In many studies, the presence of atenolol, metoprolol, propranolol, and sotalol in environmental samples is typically reported, but among these, atenolol seems to be the most frequently found worldwide waters (Fent et al. 2006; Verlicchi et al. 2012b; Luo et al. 2014; Sui et al. 2015; Ebele et al. 2017; Tran et al. 2018).

Within the neuroactive drugs class, carbamazepine, fluoxetine, and some benzodiazepines such as diazepam are the most studied and frequently detected substances (Luo et al. 2014; Li 2014; Cunha et al. 2017; Ebele et al. 2017). In particular, carbamazepine has an especially recurrent presence in the aquatic environment due to a long history of clinical usage and a very recalcitrant behavior of this drug (Fent et al. 2006; Verlicchi et al. 2012b; Luo et al. 2014; Sui et al. 2015; Tran et al. 2018). Water contamination with antibiotics presents special significance among the wide variety of pharmaceutical residues detected in the environment not only due to their extensive use and the high frequency of their detection in environmentally relevant concentration levels, but also for the serious risks posed to the aquatic environments and to human health. In fact, the wide ubiquity of several classes of antibiotics such as sulfonamides (e.g. sulfamethoxazole), macrolides (e.g. roxithromycin, ciprofloxacin), tetracyclines (e.g. oxytetracycline), and fluoroquinolones (e.g. ofloxacin, ciprofloxacin) in aquatic environments as well as in soils and sediments has been confirmed repeatedly by numerous studies (Kummerer 2009; Kim et al. 2011; Du and Liu 2012; Michael et al. 2013; Larsson 2014; Gothwal and Shashidhar 2015; Goel 2015; Tasho and Cho 2016; Ebele et al. 2017; Tran et al. 2018; Xie et al. 2018).

In all countries with developed medical care systems, other types of compounds, such as X-ray contrast media or antimicrobial agents (e.g. triclosan, triclocarban), can also be expected to be present at appreciable concentrations in waters (Heberer 2002; Yang et al. 2017; Tran et al. 2018; Patel et al. 2019).

Several studies have also shown that the use of reclamation water from WWTP effluents for irrigation of crops or the use of biosolids and manure as fertilizer or compost could result in pharmaceutical contamination of the soils (Christou et al. 2017). Moreover, as some of these pharmaceuticals have the potential to be taken up by plants, there is a risk that crops grown on contaminated soil can also become contaminated and, thereby, becoming a threat to public health (Picó and Andreu 2007; Wu et al. 2010, 2015; Carvalho et al. 2014; Tasho and Cho 2016; Al Farsi et al. 2017; Xie et al. 2018; Riaz et al. 2018). Conversely, the uptake of pharmaceuticals by plants can be explored as an advantageous feature because it

can be used to assist in the reduction of the pollutant load in contaminated water and soil in phytoremediation technologies (Dordio and Carvalho 2013; Zhang et al. 2014; Carvalho et al. 2014; Li et al. 2014; Dordio and Carvalho 2017). Table 11.1 presents some assessments of plant uptake of pharmaceuticals, grouped by therapeutical class, from soil and contaminated water, the latter usually obtained in hydroponic experiments.

As Table 11.1 illustrates, several plant species, both from crops and macrophyte species, have already being studied in an environment exposed to pharmaceuticals (either in soil or hydroponic conditions). Among crop plants, the most studied ones are carrots, while among macrophytes (the type of plants mostly used in phytoremediation) the most studied species include *Typha* and *Phragmites*. An important aspect that is assessed in some studies is the capability of the plants to uptake pharmaceuticals, because in regard to crop plants it may lead to the unwanted result of introducing pharmaceutical contaminants into the food chain whereas in regard to macrophytes it is a desirable property for the purpose of phytoremediation. Pharmaceuticals whose uptake by some plants has already been proven span most of the therapeutical classes, but the most frequently studied are the antibiotics (sulfonamides, tetracyclines, macrolides, and fluoroquinolones) (Carvalho et al. 2014; Azanu et al. 2016; Al Farsi et al. 2017; Madikizela et al. 2018).

Once reaching the environment, pharmaceuticals, their metabolites and transformation products may be submitted to a variety of biotic or abiotic processes that may responsible for their transport, transfer among the various environmental compartments, and transformation/degradation, ultimately determining their fate in the environment. These processes are potentially the same ones that also determine the environmental fate of other organic micropollutants, namely sorption, hydrolysis, biodegradation, redox reactions, photodegradation, volatilization, and precipitation/dissolution (Fig. 11.1) (Petrovic and Barceló 2007; Farré et al. 2008; Aga 2008; Caliman and Gavrilescu 2009; Kümmerer 2009b; Lapworth et al. 2012; Tijani et al. 2013; Li 2014; Wilkinson et al. 2017). Understanding pharmaceutical biodegradability, conjugation, and deconjugation, metabolic pathways, persistence, and sorption are essential to predict their environmental fate. Some of these pathways may contribute to reduce the concentration or availability (through their stabilization in inert forms) of some pharmaceuticals in the environment, or even to their full elimination, thereby lowering their potential to harm human health and aquatic life. However, some pharmaceutical metabolites or transformation products resulting from some of these processes may be more persistent and/or even more toxic than their parent compounds (Celiz et al. 2009; Fatta-Kassinos et al. 2011; Escher and Fenner 2011; Luo et al. 2014; Postigo and Richardson 2014; Barra Caracciolo et al. 2015; Bletsou et al. 2015; Noguera-Oviedo and Aga 2016; Yang et al. 2017; Patel et al. 2019).

Some of the major differences between pharmaceuticals and other common organic micropollutants (such as, for example, pesticides, PCBs, PAHs, or explosives) are that pharmaceutical molecules are in general designed to be sufficiently hydrophilic and water soluble (because they are usually supposed to function in that medium). This implies that aquatic environments are the most relevant ones in

Table 11.1 Removal and/or uptake of same pharmaceuticals by some crop plant and some macrophytes

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
Antibiotics	Amoxicillin			*Triticum aestivum* L. (wheat)	Franklin et al. (2016)		
				Daucus carota L. (carrot), *Lactuca sativa* L. (lettuce)	Azanu et al. (2016)		
	Azithromycin	*Lactuca sativa* (lettuce), *Spinacia oleracea* (spinach), *Daucus carota sativus* (carrots)	Jones-Lepp et al. (2010)				
	Chlortetracycline			*Oryza sativa* (rice), *Cichorium endivia* (sweet oat), *Cucumis sativus* (cucumber)	Liu et al. (2009)		
	Ciprofloxacin					*Juncus acutus* L. (spiny rush)	Christofilopoulos et al. (2016)
						Phragmites australis (common reed)	Liu et al. (2013)

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
	Clindamycin	*Lactuca sativa* (lettuce), *Spinacia oleracea* (spinach), *Daucus carota sativus* (carrots)	Jones-Lepp et al. (2010)				
	Enrofloxacin					*Phragmites australis* (common reed)	Carvalho et al. (2014)
	Ofloxacin			*Triticum aestivum* L. (wheat)	Franklin et al. (2016)		
						Cyperus alternifolius (umbrella papyrus)	Yan et al. (2016)
	Oxytetracycline					*Phragmites australis* (common reed)	Liu et al. (2013)
	Roxithromycin					*Cyperus alternlifolius* (umbrella papyrus)	Yan et al. (2016)
		Lactuca sativa (lettuce), *Spinacia oleracea* (spinach), *Daucus carota sativus* (carrots)	Jones-Lepp et al. (2010)				

	Sulfadiazine	*Pisum sativum* (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
						Eichhornia crassipes (water hyacinth)	Lin and Li (2016)
	Sulfadimethoxine	*Hordeum vulgare* L. (barley)	Ferro et al. (2010)				
	Sulfamethazine			*Oryza sativa* (rice), *Cichaorium endivia* (sweet oat), *Cucumis sativus* (cucumber)	Liu et al. (2009)		
						Phragmites australis (common reed)	Liu et al. (2013)
	Sulfamethoxazole			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
						Eichhornia crassipes (water hyacinth)	Lin and Li (2016)
						Cyperus alternlifolius (umbrella papyrus)	Yan et al. (2016)
						Juncus acutus L. (spiny rush)	Christofilopoulos et al. (2016)

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
		Pisum sativum (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
				Solanum lycopersicum (tomato)	Christou et al. (2017)		
				Oryza sativa (rice), *Cichaorium endivia* (sweet oat), *Cucumis sativus* (cucumber)	Liu et al. (2009)		
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		
	Sulfamonomethoxine	*Pisum sativum* (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
	Tetracycline					*Phragmites australis* (common reed)	Carvalho et al. (2014)
						Phragmites australis (common reed)	Arslan Topal (2015)
				Daucus carota L. (carrot), *Lactuca sativa* (lettuce)	Azanu et al. (2016)		

						Lemna gibba (gibbous duckweed)	Arslan Topal (2015)
						Chrysopogon zizanioides (vetiver grass)	Datta et al. (2013)
				Oryza sativa (rice), *Cichaorium endivia* (sweet oat), *Cucumis sativus* (cucumber)	Liu et al. (2009)		
	Trimethoprim			*Oryza sativa* (rice), *Cichaorium endivia* (sweet oat), *Cucumis sativus* (cucumber)	Liu et al. (2009)		
		Pisum sativum (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
				Solanum lycopersicum (tomato)	Christou et al. (2017)		

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
Antifungal/ antimicrobials	Triclocarban					*Typha* spp. (cattails)	Zarate et al. (2012)
		Cucumis sativus (Cucumber), *Solanum lycopersicum* (tomato), *Brassica oleracea* (cabbage), *Abelmoschus esculentus* (okra), *Capsicum annuum* (pepper), *Solanum tuberosum* (potato), *Beta vulgaris* (beet), *Allium cepa* (onion), *Brassica oleracea* (broccoli), *Apium graveolens* (celery), *Asparagus officinalis* (asparagus)	Mathews et al. (2014)				
				Glycine max (L.) Merr. (soybean)	Wu et al. (2010)		
	Triclosan			*Hordeum vulgare* (barley), *Festuca pratense* (meadow fescue), *Daucus carota* ssp. (carrot)	Macherius et al. (2012)		

						Lemna minor (common duckweed)	Matamoros et al. (2012)
				Glycine max (L.) Merr. (soybean)	Wu et al. (2010)		
		Cucumis sativus (Cucumber), *Solanum lycopersicum* (tomato), *Brassica oleracea* (cabbage), *Abelmoschus esculentus* (okra), *Capsicum annuum* (pepper), *Solanum tuberosum* (potato), *Beta vulgaris* (beet), *Allium cepa* (onion), *Brassica oleracea* (broccoli), *Apium graveolens* (celery), *Asparagus officinalis* (asparagus)	Mathews et al. (2014)				
		Daucus carota (carrot), *Raphanus sativus* (radish), *Lactuca sativa*	Prosser et al. (2014)				

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
		(lettuce), *Triticum aestivum* (spring wheat), *Glycine Max* (soybean)					
						Elodea canadensis (pondweed)	Matamoros et al. (2012)
Non-steroidal anti-inflammatory drugs (NSAIDs)	Acetaminophen	*Hordeum vulgare* L. (barley)	Ferro et al. (2010)				
						Lemna gibba (gibbous duckweed)	Allam et al. (2015)
						Phragmites australis (common reed)	Kotyza et al. (2010)
	Diclofenac			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
		Hordeum vulgare L. (barley)	Ferro et al. (2010)				
				Solanum lycopersicum (tomato)	Christou et al. (2017)		

						Cyperus alternlifolius (umbrella papyrus)	Zhai et al. (2016)
						Elodea canadensis (pondweed)	Matamoros et al. (2012)
						Lemna minor (common duckweed)	Matamoros et al. (2017)
						Phragmites australis (common reed)	Kotyza et al. (2010)
						Lemna gibba (Gibbous duckweed)	Allam et al. (2015)
						Typha spp. (cattails)	Bartha et al. (2014)
		Pisum sativum (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
				Daucus carota L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
						Eichhornia crassipes (water hyacinth)	Amos Sibeko et al. (2019)

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
	Ibuprofen			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
		Hordeum vulgare L. (barley)	Ferro et al. (2010)				
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		
						Elodea canadensis (pondweed), *Lemna minor* (common duckweed)	Matamoros et al. (2012)
						Eichhornia crassipes (water hyacinth)	Lin and Li (2016)
						Phragmites australis (common reed)	Kotyza et al. (2010)

						Typha spp. (cattails)	Dordio et al. (2010)
						Typha spp. (cattails)	Li et al. (2014)
						Eichhornia crassipes (water hyacinth)	Amos Sibeko et al. (2019)
	Indomethacin	*Pisum sativum* (pea), *Cucumis sativus* (cucumber	Tanoue et al. (2012)				
	Ketoprofen			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
		Pisum sativum (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		
	Naproxen			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
				Cucumis sativus (cucumbers),			

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
				Solanum lycopersicum (tomatoes)	Goldstein et al. (2014)		
						Elodea canadensis (pondweed), *Lemna minor* (common duckweed)	Matamoros et al. (2012)
						Scirpus validus (softstem bulrush)	Zhang et al. (2012)
						Eichhornia crassipes (water hyacinth)	Amos Sibeko et al. (2019)
β-Blockers	Atenolol					Typha spp. (cattails), *Phragmites australis* (common reed)	Dordio et al. (2009)
	Metoprolol			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
Hormones	Progesterone					*Lemna gibba* (gibbous duckweed)	Allam et al. (2015)

Lipid regulators	Atorvastatin			*Lactuca sativa* (lettuce), *Dacus carota* subsp. *sativa* (carrot), and *Lycopersicon esculentum* (tomato)	D'Abrosca et al. (2008)		
	Bezafibrate			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		
	Clofibric acid			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		
						Elodea canadensis (pondweed), *Lemna minor*	Matamoros et al. (2012)

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
						(common duckweed)	
						Scirpus validus (softstem bulrush)	Zhang et al. (2013a)
						Typha spp. (Cattails)	Dordio et al. (2009)
						Typha spp. (Cattails)	Dordio et al. (2010)
	Gemfibrozil			*Lactuca sativa* (lettuce), *Dacus carota* subsp. *sativa* (carrot), and *Lycopersicon esculentum* (tomato)	D'Abrosca et al. (2008)		
				Daucus carota L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		

Psycho/ neuroactive drugs	Carbamazepine			*Daucus carota* L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		
				Triticum aestivum L. (wheat)	Franklin et al. (2016)		
				Cucumis sativus (cucumbers), *Solanum lycopersicum* (tomatoes)	Goldstein et al. (2014)		
						Eichhornia crassipes (water hyacinth)	Lin and Li (2016)
						Cyperus alternlifolius (umbrella papyrus)	Yan et al. (2016)
						Typha spp. (cattails)	Dordio et al. (2010)
						Typha spp. (cattails)	Dordio and Carvalho (2011)
						Scirpus validus (softstem bulrush)	Zhang et al. (2013b)
				Glycine max (L.) Merr. (soybean)	Wu et al. (2010)		
		Pisum sativum (pea), *Cucumis sativus* (cucumber)	Tanoue et al. (2012)				
				Daucus carota L. (carrots), *Ipomoea batatas* (sweet potatoes)	Malchi et al. (2014)		

(continued)

Table 11.1 (continued)

Therapeutic class	Selected compounds	Crop plants—hydroponics		Crop plants—soil		Macrophytes—hydroponics or planted beds	
		Plants	References	Plants	References	Plants	References
	Chlordiazepoxide	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Clonazepam	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Diazepam	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Flurazepam	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Oxazepam	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Temazepam	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Triazolam	*Raphanus sativus* (radish), *Beta vulgaris* (silverbeet)	Carter et al. (2018)				
	Fluoxetine			*Glycine max* (L.) Merr. (soybean)	Wu et al. (2010)		

regard to the contamination with pharmaceuticals. Conversely, the spread of hydrophobic pharmaceuticals in aquatic environments is relatively limited and much slower. However, in that case they tend to accumulate in the fatty tissues of organisms (Ebele et al. 2017).

Pharmaceuticals are also designed to be chemically stable. In fact, some pharmaceuticals (e.g. clofibric acid, carbamazepine) can persist in the environment for many years and become biologically active through accumulation (Ebele et al. 2017).

The combination of high consumption and the properties of a significant water solubility and high resistance to degradation both by biotic and abiotic processes are the conditions that favor the introduction and persistence of pharmaceuticals in the aquatic environment. However, even when the susceptibility for (bio)degradation is moderate, some pharmaceuticals may reach steady-state levels in the environment (thus being known as pseudo-persistent pollutants) as result of their continuous introduction in sewage systems due to the continuingly high consumptions.

Before reaching the environment, pharmaceuticals have already passed through the digestive tracts of humans or animals and, in most cases, also through wastewater treatment processes. Two consequences of this pre-exposure to a special biotic environment and to biochemical metabolism can therefore be anticipated: (1) many pharmaceuticals will enter the aquatic environment in a modified form that is more stable in regard to biotic transformation or degradation and (2) those pharmaceuticals still remaining unaltered at the end of this path are probably highly resistant to biotic transformation or degradation. This understanding suggests certain inferences regarding the importance of abiotic processes for the fate of pharmaceutical compounds in the aquatic environment. Given the significant solubility in water of many pharmaceuticals, abiotic processes most likely to transform these water pollutants and more definitively remove them from the aquatic environment including hydrolysis and photodegradation. However, as most pharmaceuticals are, first of all, exposed to the digestive tract and, subsequently, remain for relatively long residence times in aqueous media within the WWTPs, hydrolysis reactions in such cases are less likely to play a relevant role in the fate of pharmaceuticals when they reach the aquatic environment. Conversely, direct photodegradation by sunlight may be an important elimination process for those pharmaceuticals that have significant absorbances in the spectrum region between 290 and 800 nm (Velagaleti 1997; Andreozzi et al. 2003; Boreen et al. 2003; Challis et al. 2014).

In addition to the physical and chemical properties of the pharmaceutical, environmental conditions (including temperature, sunlight, pH, content of organic matter in soils and sediments and redox conditions) can also influence the way abiotic and biotic processes affect its short-term behavior as well as its long-term environmental fate. Nevertheless, according to evidence accumulated over the years, many pharmaceuticals show, at least to some extent, a refractory behavior towards (bio)-degradation and transformation under ordinary conditions.

In summary, pharmaceuticals generally have the potential to reach and to persist in the aqueous environment for long periods. However, relatively little is known about the impending adverse effects to water organisms and to human health that can

arise from the cumulative exposure to an extensively varied blend of pharmaceuticals and their metabolites which are becoming progressively disseminated throughout several environmental compartments (notwithstanding the usually diminutive concentrations at which they occur). The design of pharmaceutical molecules is targeted for interacting with specific biochemical pathways. As a side-effect, when introduced in the environment, it is plausible that pharmaceuticals interfere with analogous pathways of other organisms which possess similar target organs, tissues, cells, or biomolecules. Even in such cases where organisms lack matching receptors for a particular pharmaceutical molecule, it may still induce a disruptive effect caused by an alternative mode of action. In fact, it should be pointed out that the specific modes of action of many pharmaceuticals are not well characterized and in many cases there may be not only one but several different modes of action occurring simultaneously. Therefore, the ecotoxicity of most pharmaceuticals, as well as their metabolites and transformation products, is hard to assess or predict (Fent et al. 2006; Celiz et al. 2009; Evgenidou et al. 2015; Yang et al. 2017). Furthermore, there is a risk that the environmental contamination with pharmaceuticals may propagate to crops, as some of these substances, possessing favorable chemical properties, have the potential to be taken up by plants. In general, there is an even broader risk that vegetation may uptake and accumulate pharmaceuticals, which will then take part of the diet of herbivores and, subsequently, be passed along the food chain (although, for the most part, possibly in a transformed form).

11.3 Assessment of Pharmaceuticals in Wastewater Treatment Plants

The evaluation of the presence of pharmaceuticals in wastewaters, as well as its removal efficiency by WWTPs, has been the focus of several recent reviews, which clearly shows the importance conceded to this subject in the present days (Fent et al. 2006; Nikolaou et al. 2007; Miége et al. 2009; Kümmerer 2009b; Verlicchi et al. 2012b; Michael et al. 2013; Tijani et al. 2013; Luo et al. 2014; Evgenidou et al. 2015; Petrie et al. 2015; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018; Patel et al. 2019). A survey of the data collected in reviews on the occurrence of the most relevant and commonly detected pharmaceuticals is presented in Table 11.2. The data describe the typical concentration ranges of each pharmaceutical that are quantified in WWTPs' influent and effluent streams as well as the assessed removal efficiencies in WWTPs of each pharmaceutical.

A brief inspection of Table 11.2 reveals that pharmaceuticals typically occur in WWTP influents or effluents at concentration levels in the range of the ng L^{-1} to μg L^{-1}. However, a feature that also stands out in these data is a quite significant variability of the concentration levels that are reported by different studies. This variability may result from a poorer accuracy of the chemical analyses due to the difficulties posed by such low concentration levels and the complex compositions of wastewater matrices. However, concentration levels of pharmaceuticals in

Table 11.2 WWTP influent and effluent concentrations and respective efficiencies of removal in conventional WWTPs, for selected pharmaceuticals, grouped by therapeutic class (sources: Luo et al. 2014; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018; Patel et al. 2019)

Therapeutic class	Selected compounds	Influent (μg L^{-1})	Effluent (μg L^{-1})	Removal (%)
Antibiotics	Amoxicillin	ND-6.52	ND-1.67	69.9–100
	Chloramphenicol	<MQL-2.43	ND-1.05	<0–99
	Clarithromycin	<MQL-8.0	0.005–7	<0–99
	Erythromycin	ND-10	ND-2.84	<0–82.5
	Norfloxacin	ND-0.68	0.0139–0.36	31–93
	Ofloxacin	ND-1.27	<MQL-8.6	<0–99
	Oxytetracycline	<MQL-47	<MQL-4.2	29–96
	Roxithromycin	ND-0.13	ND-0.14	<0
	Sulfamethoxazole	<MQL-11.6	<MQL-1.8	<0–99
	Tetracycline	0.029–1.300	0.016–0.85	12–100
	Trimethoprim	0.06–6.80	<0.01–3.05	0–81.6
Antifungal/antimicrobials	Miconazole	>MQL-0.6	<MQL-0.036	<0–99
	Thiabendazole	<MQL-0.22	<MQL-0.14	<0–88
	Triclocarban	0.097–8.89	ND-5.86	<0–99
	Triclosan	<MQL-6.82	<MQL-0.43	<0–100
Non-steroidal anti-inflammatory drugs (NSAIDs)	Acetaminophen/paracetamol	1.57–292	ND-0.03	98.7–100
	Codeine	<MQL-32.3	<MQL-15.59	<0–98
	Diclofenac	<0.001–94.2	< MQL-5.2	<0–98
	Ibuprofen	<0.0004–603	ND-69	72–100
	Fenoprofen	<MQL-2.26	<MQL-0.41	98.6–100
	Ketoprofen	<0.004–8.56	<0.003–3.92	10.8–100
	Mefenamic acid	<0.017–3.20	<0.005–2.40	0–70.2
	Naproxen	<0.002–611	<0.002–33.9	43.3–98.6
	Salicylic acid	0.58–63.7	ND-0.50	89.6–100
β-Blockers	Atenolol	0.1–33.1	0.13–7.60	0–85.1
	Metoprolol	0.002–1.52	0.003–0.25	3–56.4
	Propranolol	0.05–0.64	0.01–0.615	< 0–44
Hormones	Estrone (E1)	<MQL-0.67	<MQL-0.100	<0–100
	Estriol (E3)	<MQL-0.8	ND-0.28	18–100
	17α-ethinylestradiol (EE2)	<MQL-0.67	<MQL-0.11	33–100
Blood lipid regulators	Bezafibrate	0.05–7.6	0.02–4.30	9.10–70.5

(continued)

Table 11.2 (continued)

Therapeutic class	Selected compounds	Influent (μg L^{-1})	Effluent (μg L^{-1})	Removal (%)
	Clofibric acid	0–0.74	0.042–0.33	0–93.6
	Gemfibrozil	0.10–17.1	<0.025–5.24	0–92.3
	Pravastatin	0.023–0.33	<MQL-0.4	n.r.
Psycho/neuroactive drugs	Alprazolam	0.019–0.049	0.011–0.034	n.r.
	Carbamazepine	<0.04–3.78	<0.05–4.60	0–62.3
	Diazepam	<MQL-0.2	<MQL-0.24	n.r.
	Fluoxetine	<MQL-0.03	<MQL-0.001	n.r.

MQL method quantification limit, *ND* not detected, *n.r* not reported

wastewaters are also strongly affected by many factors, some of which may present a significant spatial and temporal variability. This includes variations, over time, and throughout locations in the world, of the production/sales/consumption levels of the pharmaceuticals (depending on rates of production, sales volume and market strategies, local prescription and usage practices, spatial and seasonal distributions of disease prevalence, etc.), thus affecting the inputs of WWTPs downstream. In addition, variability may also be associated with some aspects that relate with WWTP design, operation, and environmental conditions that affect the characteristics of the final WWTP effluents (water consumption per person and per day, WWTP size, plant configuration especially the type of bioreactor, hydraulic retention time, solids retention time, temperature, rainfall, sunlight) and water catchment characteristics (e.g. land use, population size, and population density).

The short sample of studies presented in Table 11.2 illustrates the therapeutical classes of pharmaceuticals whose occurrence typically predominate in wastewaters: those pharmaceuticals that are most commonly detected in WWTPs are mainly analgesics and anti-inflammatory drugs, antibiotics, blood lipid regulators, beta-blockers, or psycho/neuroactive drugs (Fent et al. 2006; Nikolaou et al. 2007; Miége et al. 2009; Kümmerer 2009b; Verlicchi et al. 2012b; Michael et al. 2013; Tijani et al. 2013; Luo et al. 2014; Evgenidou et al. 2015; Petrie et al. 2015; Yang et al. 2017; Tran et al. 2018). Non-steroidal anti-inflammatory drugs (NSAIDs) usually arise as those with higher loads in WWTP influents, which may be attributed to the fact that these are over-the-counter drugs and, thus, are highly consumed pharmaceuticals. Within this therapeutical class, the active substances ibuprofen, naproxen, diclofenac, and ketoprofen are usually referred as the most frequently detected and at the highest concentrations in WWTP influents. Meanwhile, in the effluents leaving the WWTPs, and even though the concentrations of these compounds are notably lowered (because they are reasonably biodegradable and, thus, typically well removed in WWTPs), NSAIDs are frequently still present at levels quite far from negligible. Indeed, because they enter the WWTP at such high loads, the remnant at the exit of the WWTP, even after large removals, still remains a significant amount (Aga 2008; Caliman and Gavrilescu 2009; Kümmerer 2009b; Li 2014; Tran et al. 2018). Hence, the concentrations of some NSAIDs in effluents of

WWTPs are frequently higher than their predicted no-effect concentrations (PNECs) for the aquatic ecosystems and consequently, the discharges of WWTP effluents into the receiving water bodies may pose potential long-term risks.

Numerous reports also evidence an ubiquitous occurrence of many antibiotics in effluents of WWTPs, thus reaffirming the concern relative to this class of pharmaceuticals, in particular the recurrent worries associated with the development of antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARGs) (Michael et al. 2013; Bouki et al. 2013; Mo et al. 2015; He et al. 2016; Singer et al. 2016; Topp et al. 2017; Xie et al. 2018; Shao et al. 2018; Barancheshme and Munir 2018; Abidelfatah et al. 2019; Koch et al. 2021). Apart from resistance selection, antibiotics in the influents of WWTPs can also directly influence the activities of microorganisms and, consequently, of wastewater treatment performance (Gonzalez-Martinez et al. 2014; Tran et al. 2018). Furthermore, if after an unsuccessful treatment they leave the WWTP in their original form or as some toxic metabolites, the discharge of antibiotic-containing effluents into the receiving water bodies can also harm the aquatic organisms and environment (Kümmerer 2009a; Kim et al. 2011; Du and Liu 2012; Verlicchi et al. 2012b; Larsson 2014; Gothwal and Shashidhar 2015; Goel 2015; Bengtsson-Palme and Larsson 2016; Shao et al. 2018). It was assessed in some studies that concentrations of many antibiotics in WWTP effluents were over their predicted-no-effect concentrations (PNECs) for ecological toxicity to aquatic organisms (Bengtsson-Palme and Larsson 2016; Tran et al. 2018). Among the classes of antibiotics investigated, sulfonamides (e.g. sulfamethoxazole), fluoroquinolones (e.g. ciprofloxacin, norfloxacin, ofloxacin), macrolides (e.g. clarithromycin, erythromycin, roxithromycin), and trimethoprim were frequently detected in both WWTP influent and effluent samples worldwide. In contrast, the occurrence of β-lactams (e.g. amoxicillin), tetracyclines (e.g. tetracycline and oxytetracycline), and chloramphenicol in WWTP influents and effluents is less reported for North American and European countries, while they are still present in WWTP influents and effluents from some Asian countries (Tran et al. 2018). Although β-lactams are among the most widely used prescribed antibiotics, their frequent absence from wastewaters may be attributed to a high susceptibility to chemical or enzymatic hydrolysis (Watkinson et al. 2007; Le Minh et al. 2010; Tran et al. 2018). Chemical hydrolysis and/or chemical transformations of β-lactams antibiotics can seemingly take place under acidic or alkaline conditions or by reactions with weak nucleophiles, e.g. water or metal ions (Le Minh et al. 2010). In addition, β-lactam antibiotics can be enzymatically hydrolyzed by β-lactamases.

Antifungal and antimicrobial agents are increasingly being recognized as another class of pollutants of concern for aquatic environments, similarly to the case of antibiotics, as they too have potential for inducing the development of ARGs and ARB and, generally, for causing adverse effects on aquatic organisms (Bouki et al. 2013; Singer et al. 2016; Tran et al. 2018; Barancheshme and Munir 2018). This type of substances (including miconazole, thiabendazole, triclocarban, and triclosan) is widely used in some household products such as hair shampoos, dermal creams, soaps, toothpastes, and shower gels. Miconazole and thiabendazole are also commonly used in therapeutic products for the treatment of fungal infections in humans.

In WWTP influents, concentration levels of antimicrobial agents (i.e. triclocarban and triclosan) seem to be usually higher than those of antifungal compounds (e.g. miconazole, thiabendazole) by at least one order of magnitude (Table 11.2). Conversely, the levels of most antifungal and antimicrobial agents in effluents exiting the WWTPs typically vary from below MQL to a few hundreds of ng L^{-1}, being usually much lower than those in the influent, implying some extent of removal of this kind of pharmaceutical pollutants in WWTPs. Generally, the concentrations of triclosan and triclocarban in WWTP effluents are often higher than their PNECs for aquatic organisms (Tran et al. 2018).

A number of beta-blockers are also detected in WWTP influents and effluents, namely atenolol, metoprolol, propranolol, and sotalol, among which atenolol is the most frequently found worldwide and in highest concentrations, followed by metoprolol and propranolol (Maurer et al. 2007; Luo et al. 2014; Evgenidou et al. 2015; Godoy et al. 2015; Tran et al. 2018). The high levels of atenolol in wastewaters may be attributed to its high consumption and high excretion rates as an unchanged drug (50%) in comparison with other beta-blockers (e.g. the excretion as unchanged drug of metoprolol and propranolol is approximately of 15% and 0.5%, respectively) (Evgenidou et al. 2015).

Carbamazepine, fluoxetine, and diazepam are among the neuroactive pharmaceuticals, those substances that are more commonly detected in wastewaters (Luo et al. 2014; Cunha et al. 2017; Tran et al. 2018). The anti-epileptic carbamazepine is in particular one of the prominent cases among pharmaceutical pollutants, with an especially frequent presence in the aquatic environment, a fact that is the result of a long history of clinical usage and of its notoriously recalcitrant behavior.

Estrogenic hormones form another class of water contaminants causing serious concern because of the high potential of these substances for causing endocrine disruption and other severe ecotoxic effects such as negatively affecting the sexual and reproductive systems in wildlife, fish, and humans (Gabet-Giraud et al. 2010; Chang et al. 2011; Hamid and Eskicioglu 2012; Liu et al. 2015; Tran et al. 2018). Detection of estrogens in wastewaters and sludge has been reported (Bolong et al. 2009; Radjenovic et al. 2009; Hamid and Eskicioglu 2012; Liu et al. 2015; Tran et al. 2018) for both natural (i.e. estrone and 17b-estradiol) and synthetic (17a-ethinylestradiol) hormones. The concentrations of these natural and synthetic estrogens that have been found in WWTP effluents sometimes exceed their PNECs for ecological toxicity to aquatic organisms, implying possible risks to aquatic ecosystems (Tran et al. 2018).

Among pharmaceuticals with high consumption rates, those that are more recalcitrant to biodegradation in general show a frequent occurrence in treated WWTP effluents. Notwithstanding, among those that are more amenable to be biodegraded in WWTPs and, therefore, attain high removals during the wastewater treatment, may still be also present at non-negligible levels in the treated effluents, due to the high influent loads in which they arrive at WWTPs. Consequently, they still may be introduced as pollutants into the receiving water bodies upon the discharge of the contaminated treated effluent, even though their removal efficiencies in WWTPs may be considered reasonably high.

11.3.1 Occurrence of Pharmaceuticals in Sewage Sludge and Biosolids

Sewage sludge is the solid or semi-solid residue originated in the primary (physical and/or chemical), secondary (biological), and tertiary (often nutrient removal) treatment stages. Sludge materials that receive additional treatment in order to adequate it for application to soil as fertilizer are designated as biosolids (i.e. treated sewage sludge). In fact, sludge is rich in nutrients such as nitrogen and phosphorous and contains valuable organic matter that is useful when soils are depleted or subjected to erosion. Agricultural application of sewage sludge and biosolids to soils is the most economical outlet for sludge (in comparison with incineration) and has become a widespread method for its disposal. This re-use of sludge is generally regarded as a beneficial practice that should be encouraged as it can provide a long-term solution as long as the re-used sludge quality complies with the requirements of public health safety and of environmental protection. As a matter of fact, sludge tends to concentrate heavy metals and poorly biodegradable trace organics that are insoluble or adsorbed to particulate matter, as well as potentially pathogenic organisms (viruses, bacteria, etc.). Therefore, the occurrence and abundance of these contaminants in sludges and biosolids, their fate as well as the potential risks they ultimately pose to public health and to the environment need to be assessed.

Considering the hydrophobic/lipophilic nature and interactions with sludge particles (e.g. cation bridging, hydrogen bonding), it is believed that pharmaceuticals can sorb onto sludge during primary and secondary sedimentation. Moreover, for some pharmaceuticals, such as antibiotic fluoroquinolones, sorption to sewage sludge represents the main removal route during wastewater treatment (Giger et al. 2003; Picó and Andreu 2007; Lillenberg et al. 2009; Michael et al. 2013; Zhou et al. 2013; Frade et al. 2014; Tran et al. 2018; Riaz et al. 2018).

However, most studies on pharmaceuticals' occurrence and fate in WWTPs focus only the aqueous phase and, therefore, data describing the presence and behavior of pharmaceuticals in the sludge and biosolids are scarce. This may be due to the considerable complexity of the sludge matrix and, as consequence, to the difficulties of performing chemical analyses on that medium. Notwithstanding, the characterization of pharmaceuticals in particulate phases is essential for assessing their fate in the environment, although very few studies have been conducted on this matter to date.

In the few studies available in the literature, which have been compiled in a review by Tran et al. (2018), pharmaceuticals levels in sludge and biosolids were found to span a wide range of concentrations (from below the MQL to greater than mg/g dw). This high variability may be attributed to the complex dependence on many factors, some of which also having a large variability of its own, such as pharmaceuticals usage patterns over time and throughout world locations, pharmaceuticals physical and chemical properties (e.g. water solubility, log K_{ow}, pK_a, etc.) and molecular features, influent wastewater and sludge characteristics (pH, organic matter, and cation concentration), wastewater and sludge treatments, the operational conditions, and environmental conditions (Tran et al. 2018). For

example, higher concentrations of several pharmaceuticals were observed in secondary sludge compared to those in primary sludge, which may be attributed to the occurrence of hydrolysis of pharmaceutical conjugates which regenerate their parent compounds or to a higher content of organic matter in secondary sludge (Urase and Kikuta 2005).

Among the pharmaceuticals assessed in sludges and/or biosolids in the few studies conducted so far, the most frequently targeted therapeutical groups are the antibiotics (often reported as typically the predominant class in sludges), in particular fluoroquinolones (e.g. ofloxacin), tetracyclines (e.g. oxytetracycline, minocycline, and tetracycline) and sulfonamides (e.g. sulfamethoxazole) (Picó and Andreu 2007; Lillenberg et al. 2009; Yang et al. 2012; Michael et al. 2013; Dorival-Garcia et al. 2013; Zhou et al. 2013; Frade et al. 2014; Tran et al. 2018; Riaz et al. 2018; Ezzariai et al. 2018), and the antimicrobial agents (e.g. triclocarban and triclosan) (Sabourin et al. 2009; Healy et al. 2017; Tran et al. 2018; Ezzariai et al. 2018). Reportedly, these pharmaceuticals can often be found in median concentrations in the upper 1000 ng/g dw (Tran et al. 2018), which is a cause of alert for the risk that it may provide selective pressure for the development of ARGs and ARB if those contaminated sludges and biosolids are used in agricultural activities and, thus, are a source of continuous exposure of the agricultural environment to these antibiotics and antimicrobial agents (Munir and Xagoraraki 2011; Topp et al. 2017; Xie et al. 2018; Shao et al. 2018; Abidelfatah et al. 2019; Pei et al. 2019). Conversely, β-lactams and chloramphenicol are usually rarely detected in sludges and/or biosolids, which may be due mainly to the fast degradation of these antibiotics during wastewater treatment as well as during the anaerobic digestion of the sludge.

Only few studies are available to date which report data on the occurrence of anti-inflammatories and even fewer reporting data on other therapeutic classes (namely neuroactive drugs, blood lipid regulators, hormones, β-blockers, etc.) (Maurer et al. 2007; Nieto et al. 2010; Jelic et al. 2011, 2012; Yu et al. 2011; Vieno and Sillanpää 2014; Tran et al. 2018).

Some less commonly prescribed pharmaceuticals are frequently detected in sludges and biosolids due to their recalcitrant behavior.

11.3.2 Why Are Pharmaceuticals Not Efficiently Removed in Conventional WWTPs?

As has been mentioned before, wastewater entering the municipal WWTPs typically contains a lot of different trace pollutant compounds (both of synthetic and natural origins). The degree to which such pollutants are removed after treatment in those WWTPs varies from near completion to almost none. Notwithstanding, most studies show that the removal of many pharmaceutical compounds in municipal WWTPs is clearly insufficient. Indeed, a significant fraction of the pharmaceuticals, their metabolites and transformation products entering the WWTPs are discharged with

the final effluent into the aquatic environment or are present in sludges and biosolids (see Sect. 11.3.1).

The treatment processes in municipal WWTPs are designed to remove bulk constituents of wastewater, such as suspended solids, biodegradable organic matter, pathogens, and nutrients, by physical, chemical, and biological processes available along three or four consecutive stages of a conventional treatment (Fig. 11.2).

Conversely, conventional WWTPs were not designed to deal with pharmaceuticals or trace organic pollutants in general. Typically, there is very little elimination of most organic micropollutants at the preliminary and primary treatments of wastewaters, and it is also unlikely that many pharmaceuticals will be removed during screening or primary sedimentation (Jelic et al. 2011; Hamid and Eskicioglu 2012; Verlicchi et al. 2012b; Luo et al. 2014; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018). In fact, in some cases there may even be an increase of the concentrations of some pharmaceuticals during these stages, caused by the simultaneous presence of conjugated derivatives (metabolites) of these compounds in the raw influent that are reverted back into the parent compound during wastewater treatment (Carballa et al. 2004; Tran et al. 2018). Secondly, pharmaceuticals excreted via urine and feces may be enclosed in fecal particles and be gradually released during wastewater treatment, thus also resulting in an apparent increase in concentration inside the WWTP (Gobel et al. 2007; Tran et al. 2018).

Given the low biological activity at these initial stages, any pollutant removal in this phase of treatment will depend on the tendency of each pharmaceutical to sorb to the solids of the primary sludge as well as on the extent of the suspended solids removal in the primary sedimentation tanks (Zhang et al. 2008; Monteiro and Boxall 2010; Hamid and Eskicioglu 2012; Luo et al. 2014; Tran et al. 2018). Usually, at this point, only the more hydrophobic compounds are expected to transfer to the solid phase and little to no loss of polar drugs is expected. In general, elimination of any compound by sorption to sludge is considered relevant only when the log K_d for that compound is higher than ~2.5–2.7 (i.e. corresponding to $K_d > 300–500$ L kg^{-1}) (Ternes et al. 2004; Joss et al. 2005; Tran et al. 2018). The removal of pharmaceuticals may also be affected by some other factors such as pH, retention time, temperature, and amount and type of solids present in the wastewater (Ternes et al. 2004; Joss et al. 2005; Carballa et al. 2008; Hamid and Eskicioglu 2012; Verlicchi et al. 2012b; Luo et al. 2014; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018).

At secondary (biological) treatment by activated sludge, removal of pharmaceuticals may occur by the same mechanisms as do other organic micropollutants, including sorption to secondary sludge, chemical degradation, or transformation (such as hydrolysis or photolysis) and biotransformation/biodegradation (aerobic, anoxic and anaerobic) (Monteiro and Boxall 2010; Hamid and Eskicioglu 2012; Verlicchi et al. 2012b; Luo et al. 2014; Wang and Wang 2016; Yang et al. 2017; Tran et al. 2018). Biodegradation of pharmaceuticals in this stage may occur to various extents, from complete mineralization (although that is rarely the case) to incomplete degradation (i.e. yielding still somewhat complex and

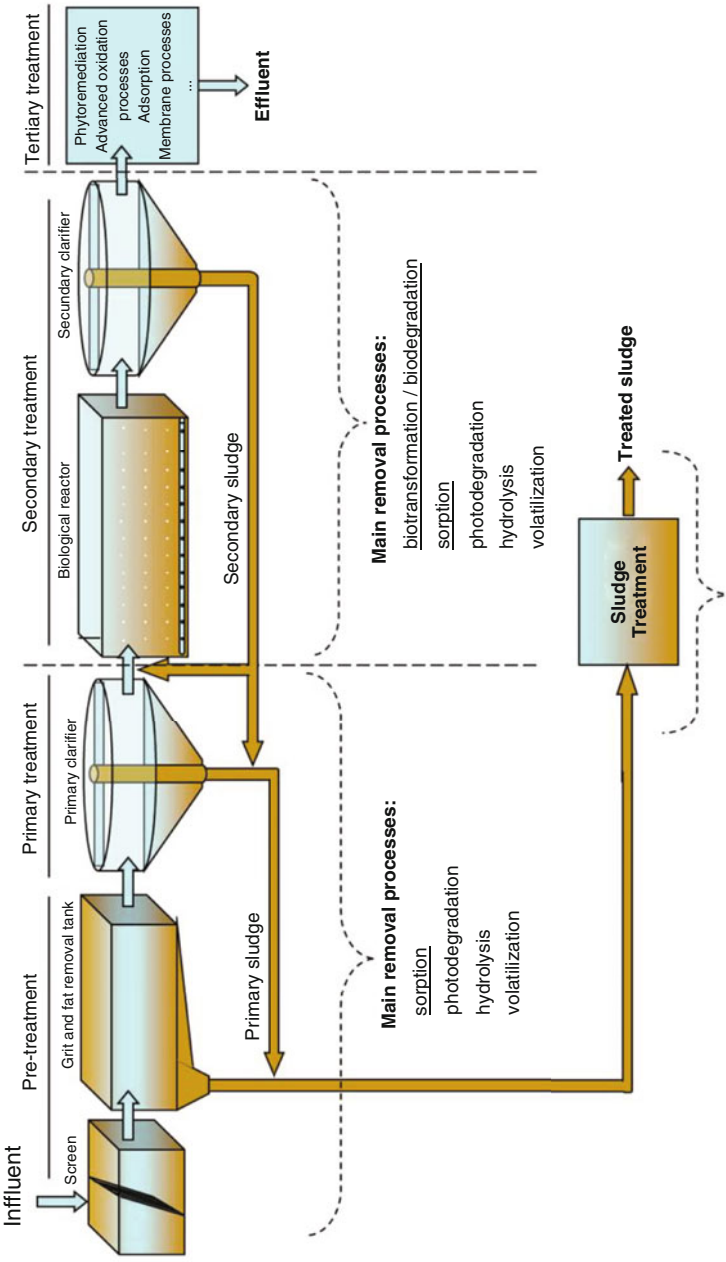

Fig. 11.2 Diagram of a conventional wastewater treatment plant and main removal processes of pharmaceuticals in each treatment stage

possibly still toxic transformation products instead of the simplest and mostly innocuous CO_2, etc.). In principle, two pathways for biodegradation may be possible, namely via metabolism or via co-metabolism. However, indications from numerous studies conducted so far suggest that biodegradation of pharmaceuticals in wastewater treatment processes takes place via co-metabolism rather than through metabolism. Indeed, the fact that many pharmaceuticals are toxic for microorganisms and are often present in wastewater at trace levels (ng/L – μg/L) makes them less suitable as an energy source and implies that most pharmaceuticals do not enter catabolic and anabolic pathways of microbial cells. In other words, the energy resulting from the biodegradation of pharmaceuticals is not sufficient to support microbial growth and induce the relevant enzymes/co-factors involved in the biodegradation. Therefore, the biodegradation of pharmaceuticals is highly dependent on the presence (and abundance) of primary substrates (e.g. ammonium, carbonate salts or organic carbon sources) as well as conditions for the development of microorganisms involved in co-metabolic biodegradation (Tran et al. 2018).

Additionally, considering the typically low volatility of most pharmaceuticals, compound loss through volatilization associated with the aeration (stripping) operation is expected to be negligible (Caliman and Gavrilescu 2009; Miége et al. 2009; Verlicchi et al. 2012b; Luo et al. 2014; Tran et al. 2018). In fact, Henry coefficients of at least $\sim 10^{-3}$ are generally regarded as the minimum requirement for significant stripping in a bioreactor with fine bubble aeration (Larsen et al. 2004). Pharmaceutical removals at this stage are also affected by environmental and operation conditions (Joss et al. 2005; Clara et al. 2005; Onesios et al. 2009; Verlicchi et al. 2012b; Luo et al. 2014; Tran et al. 2018).

Any pharmaceutical residues remaining in wastewaters after primary and secondary treatment may eventually be eliminated by tertiary or advanced treatments. However, in most countries only a reduced number of WWTPs include these stages of treatment. Advanced oxidation processes, membrane processes, and adsorption processes are some of the most common advanced treatment techniques that have been applied in wastewater treatment and demonstrated to be capable of removing pharmaceuticals to levels below detection limits (Fent et al. 2006; Snyder et al. 2007; Rosal et al. 2010; Dolar et al. 2012; Kit Chan et al. 2012; Feng et al. 2013; Ek et al. 2014; Rizzo et al. 2015; Rodriguez-Mozaz et al. 2015; Yang et al. 2017; Kanakaraju et al. 2018; de Andrade et al. 2018; Fonseca Couto et al. 2018; Pei et al. 2019). However, the effectiveness of some (or all) of these advanced techniques depends on the treatment conditions employed.

Notwithstanding, despite the sometimes high removal efficiencies that are attainable through these technologies, in most cases their implementation and operation are too expensive and complex for use on a large scale in wastewater treatment (Fent et al. 2006; Tahar et al. 2013). Moreover, the type of processes involved in some of these treatments may give origin to some transformation products that may in some cases be even more persistent or toxic than the parent compounds (Farré et al. 2008; Fatta-Kassinos et al. 2011; Postigo and Richardson 2014; Wang and Lin 2014; Evgenidou et al. 2015; Wang and Wang 2016; Yang et al. 2017).

Alternatively, the use of phytoremediation technologies such as constructed wetlands (CWs) for the removal of pharmaceuticals residues from wastewater is increasingly being seen as a more economic, while still very effective, option and has been increasingly studied and explored over the latest decades. In fact, these systems are becoming an option for secondary wastewater treatment systems or as treatment units for polishing secondary effluent from WWTPs. In addition to low cost, simple operation and maintenance (thereby not requiring highly skilled labor) and environmental friendliness are some of their most attractive characteristics.

11.4 Phytoremediation Strategies for Pharmaceuticals Clean-up: Constructed Wetlands

Constructed wetlands systems (CWS) are man-made structures that emulate natural wetlands for human use and benefits (Cooper et al. 1996; Vymazal et al. 1998; Kadlec and Wallace 2009; Dordio and Carvalho 2013). These systems consist of water saturated beds, containing (in addition to the water column) soil or other selected solid support matrix, emergent and/or submergent wetland vegetation, and microbial populations as the main components. For a long time, natural wetlands have been credited with the ability of depurating the water that inundated such areas. Based on this observation, the idea of constructing artificial wetlands was developed as an attempt to take advantage of many of the same processes that occur in natural wetlands, but within a more controlled environment, with systems designed for an enhanced water depurating action. In these engineered systems, it is sought to obtain an optimization of the operating conditions and selection of its components in order to achieve higher efficiencies, considering the roles played by each CWS component and drawing on some understanding of the mechanisms involved in the removal of pollutants in these systems. CWS optimization thus aims to potentiate the concerted action of all the components (support matrix, vegetation, and microbial population) through a variety of interdependent chemical, physical, and biological processes as illustrated in the scheme of Fig. 11.3.

In the past, CWS have been mainly used as wastewater treatment systems intended to serve as alternative or complementary systems to the conventional treatment for domestic wastewaters of small communities. Thus, initially CWS were mostly applied for the removal of bulk pollutants such as suspended solids, organic matter, excess of nutrients and pathogens. However, CWS are now also being used more often to provide a form of secondary or tertiary treatment for wastewaters. More recently, an increasing number of studies have been exploring the use of CWS to target more specific pollutants, especially those which are more recalcitrant to conventional wastewater treatment such as pharmaceuticals and other trace organic pollutants (Matamoros et al. 2008; Dordio et al. 2009, 2010; Hijosa-Valsero et al. 2010, 2016, 2017; Ávila et al. 2010, 2014; Reyes-Contreras et al. 2012; Dordio and Carvalho 2013; Verlicchi and Zambello 2014; Zhang et al. 2014, 2018b; Li et al. 2014; Ávila and García 2015; Vymazal et al. 2017; Matamoros et al. 2017; Liu et al. 2019). In fact, a wide variety of pharmaceuticals, spanning several different

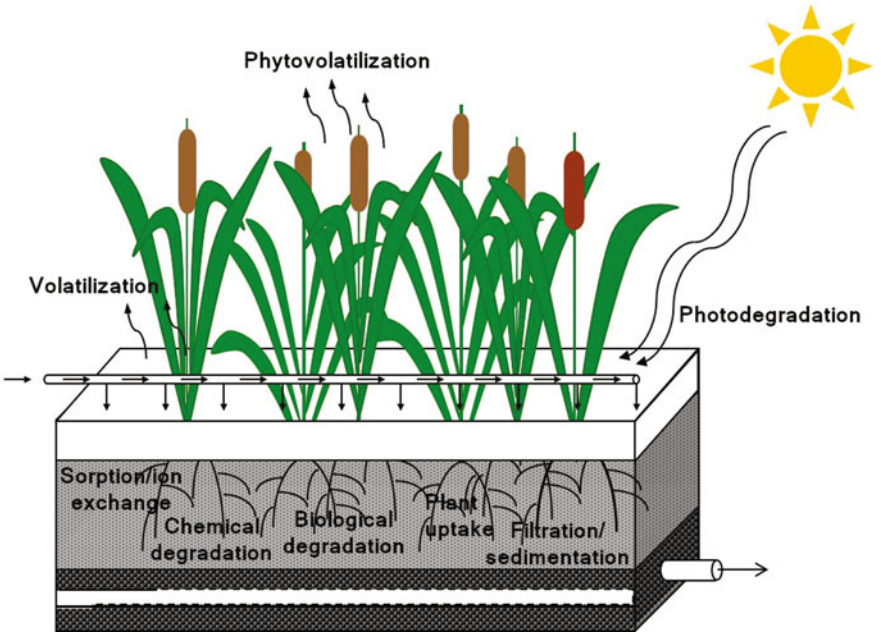

Fig. 11.3 Summary of the major physical, chemical, and biological processes controlling pollutant removal in a sub-surface flow CWS

therapeutic classes as well as various chemical structures and properties, have already been studied in respect to the capacities of CWS to remove them from water and wastewater (Matamoros et al. 2008, 2017; Dordio et al. 2009, 2010; Hijosa-Valsero et al. 2010, 2011, 2016, 2017; Ávila et al. 2010, 2014; Dordio and Carvalho 2011, 2013, 2017; Reyes-Contreras et al. 2012; Verlicchi and Zambello 2014; Zhang et al. 2014, 2018b; Li et al. 2014; Ávila and García 2015; Vymazal et al. 2017; Liu et al. 2019).

Studies have been performed on different types of CWS (namely Surface Flow Constructed Wetlands (SF), Horizontal Sub-surface Flow Constructed Wetlands (HSSF), Vertical Sub-surface Flow Constructed Wetlands (VSSF) and Hybrid Constructed Wetlands (hybrid CWS)), at different scales (microcosm scale, mesocosm (or pilot) scale, and full scale) as well as using different operating modes. The screening of different plant species and types of support matrix materials has also been a major study topic. So far, many of the studies conducted on this subject have demonstrated a noteworthy potential of CWS to remove a wide variety of pharmaceutical compounds and, thus, for providing an efficient and cost-effective solution for the decontamination of pharmaceutical-polluted wastewaters (Matamoros et al. 2008, 2017; Dordio et al. 2009, 2010; Hijosa-Valsero et al. 2010, 2011, 2016, 2017; Ávila et al. 2010, 2014; Dordio and Carvalho 2011, 2013, 2017; Reyes-Contreras et al. 2012; Verlicchi and Zambello 2014; Zhang

et al. 2014, 2018b; Li et al. 2014; Ávila and García 2015; Vymazal et al. 2017; Liu et al. 2019).

A comprehensive understanding of all the processes occurring in CWS that can contribute to the removal of organic xenobiotics such as pharmaceuticals from water still has not be achieved. Hence, these wastewater treatment systems have frequently been operated as "black boxes" and much of the design of CWS has been done in the past based on a heuristic approach, with little knowledge and consideration for the roles played by each component and how their effects could be enhanced and optimized. However, more recently, a greater interest has been emerging for studies on the mechanistic aspects of CWS functioning, focusing on the roles played by the CWS components and the processes in which they are involved. The knowledge accumulated through the years of study and use of CWS has increasingly been applied in the construction and operation of new systems. Accordingly, a greater variety of plant species, support matrix materials, and designs is being studied and introduced in newly constructed CWS (Brix 1997; Sundaravadivel and Vigneswaran 2001; Stottmeister et al. 2003; Calheiros et al. 2009; Truu et al. 2009; Zhang et al. 2010, 2014, 2018a, b; Hijosa-Valsero et al. 2011; Dordio and Carvalho 2013, 2017; Verlicchi and Zambello 2014; Carvalho et al. 2014; Li et al. 2014; Avila et al. 2014, 2017; Calheiros et al. 2017; Liu et al. 2019).

11.5 Conclusion and Final Remarks

This chapter provides an overview of available data on the sources, occurrence, and fate of a variety of classes of pharmaceuticals in environment, WWTPs, sewage sludge and/or biosolids, and some crop plants and macrophytes.

Pharmaceuticals that are typically detected in environmental samples, and reported in a large number of studies, are mainly from the therapeutical classes of analgesics and anti-inflammatory drugs, blood lipid regulators, beta-blockers, psycho/neuroactive drugs, and antibiotics. Antibiotics in particular are one of the most studied classes, probably because of its well-known adverse impacts on the environment and public health. However, other therapeutical classes probably also have very negative environmental effects (e.g. hormones and regulators of the endocrine system) and, thus, a more extensive study of pharmaceuticals' ecotoxicity needs to be pursued in the future.

Since the main sources of environmental contamination with pharmaceuticals are the effluents of WWTPs, pharmaceuticals removal in WWTPs were also summarized. However, most studies aimed at detecting and quantifying pharmaceuticals in WWTPs almost always focus exclusively on the aqueous phase and very few studies have addressed also the particulate phase. Therefore, scarce data is available on the occurrence and fate of pharmaceuticals in sewage sludge and biosolids and that is a gap which is direly needed to be filled in future studies, especially considering that biosolids are frequently used as soil fertilizer, with an obvious potential to contaminate crops.

From the comparison from pharmaceuticals concentration levels in WWTP influents and effluents it can be concluded that WWTPs are frequently the source of water contamination with pharmaceuticals mainly because they often do not achieve sufficiently high removal efficiencies for this type of pollutants (although in some cases the main reason is the very high loads in the WWTPs influents of some frequently prescribed pharmaceuticals).

Another feature that stands out from an overview of the available data on pharmaceuticals occurrence in different WWTPs is the large variability (of some orders of magnitude) in the measured concentrations that are reported, both for WWTPs' influents and effluents. This could be attributed to various factors such as differences in population size/demographic density and in pharmaceuticals usage patterns in separate regions and different periods of the year (e.g. some epidemic surges of some diseases have a seasonal periodicity), or to differences in climatic conditions, etc. However, other factors that may also affect the precision of pharmaceutical concentration data are related with the chemical analysis itself, such as the adequacy of the analytical methods and instrumentation used (i.e. to address the challenge of quantifying trace levels within very complex matrices) and, in particular, the sampling strategies. The use of less suitable sampling schemes may represent one of the major weaknesses of the reported data on the occurrence of pharmaceuticals (and other types of pollutants). As such, an effort to improve on the sampling methods (e.g. by using a composite sampling strategy instead of the common grab sampling strategy) or removal calculation approaches (e.g. time-shifted mass balancing or fractionated approaches) should be considered on the analytical side to enhance the convergence of concentration data and removal performance of WWTPs.

Notwithstanding, the variability of WWTP performance data cannot, of course, be attributed solely to chemical analysis limitations. Efficiencies of pharmaceuticals removal in WWTPs differ substantially for different compounds because their chemical nature and associated physicochemical properties vary widely among them. In addition, WWTP performance is very dependent on details of their design, operation, and environmental conditions. Optimization of wastewater treatment processes remains a task with top priority. One of the main aspects to be addressed in this regard is the enhancement of biological treatment efficiency, which is frequently low for many pharmaceuticals. Improvements have been attempted under more favorable conditions, e.g. increasing contact times (i.e. hydraulic and solid retention times), optimizing temperature and fine-tuning redox conditions. Certainly, more effective optimizations may be achieved if backed up by a comprehensive knowledge of the fate of pharmaceuticals in WWTPs. Thus, the pursuit of a more profound understanding of the factors that affect the environmental fate of organic micropollutants such as pharmaceuticals is an essential line of research for achieving a successful mitigation of this type of pollution.

Removal of the most recalcitrant pharmaceuticals can be significantly improved by applying advanced treatment processes downstream to the conventional biological treatment, prior to effluent discharge. Adsorption processes, advanced oxidation processes, and membrane processes are some of these promising advanced

technologies that have in many cases exhibited very high efficiencies in partially or fully (bio)degrading organic micropollutants (including pharmaceuticals) or removing them from the aqueous phase. However, two major issues preclude a full-scale application of some of these technologies: the relatively high costs generally involved in their implementation, operation and maintenance; and the fact that some of these processes yield final reaction products or lead to the formation of by-products whose ecotoxicity is not well known and are potentially hazardous. Indeed, the latter issue does not affect all advanced treatment processes, in particular it is not a problem that affects those processes that do not involve the occurrence of chemical reactions (e.g. adsorption processes). However, for those that do, the processes need to be studied in more detail in order to describe the optimal conditions that may favor mechanisms where the formation of such by-products is avoided or the conditions under which a complete decomposition may be achieved. In regard to economical considerations, attempts to lower the costs required to implement efficient wastewater treatment alternatives have been increasingly pursued by seeking and studying low cost reagents and materials (e.g. easily and widely available natural materials or agricultural wastes that may be used as efficient adsorbents) and by developing and/or optimizing cheaper technologies such as CWS.

In fact, CWS is becoming a relevant technology that is increasingly being introduced as an alternative (in the case of small communities) or complementary (as tertiary or polishing stages) treatment to the conventional wastewater processes. However, as living organisms (plants and microorganisms) are involved in the removal of pollutants in these systems, their responses to the various pollutants types and loads are more difficult to predict. Therefore, a prior study of the constructed wetlands' behavior with a given type of wastewater needs to be conducted (and possibly, a subsequent tweaking of its design—in terms of its plants and support matrix compositions—and/or operation) in order to assess its capacity to cope with the pollutants in question and, thus, assess its potential usefulness and reliability as a treatment option.

Some of the study topics with major relevance for enhancing the performance of constructed wetlands can be found by focusing on the roles played by each CW component and attempting to potentiate their action. For example, one can enunciate the following topics:

- the extent of pharmaceuticals uptake by plants and their subsequent metabolization within plant tissues, more data needs to be collected on this topic in order to better understand the role of plants in constructed wetlands, to characterize the fate of pharmaceuticals inside plants, and ultimately assess the risks posed by harvested and decaying plants and plant debris of constructed wetlands;
- the characterization of microorganism populations in constructed wetlands (including those endophytic to plants) as well as their processes of transformation of pharmaceuticals; the characteristics of these populations may eventually be modified and improved;

- finally, the evaluation of alternative (low cost) materials for the support matrix that may provide a fast-responding temporary retention of pharmaceuticals (by adsorption) while keeping them bioavailable for the slower biotic (i.e. provided by plants and microorganisms) removal processes that removed them more definitively; the role of this component may be useful to quickly respond to peak loads of pollutants, to moderate environmental conditions, and to mitigate the lower activities of the biotic components during the winter seasons (as the activity of adsorption processes is less sensitive to temperature variations).

References

Abidelfatah MN, Heitam F, Yeshayahu N (2019) The role of wastewater treatment plants in the environmental dissemination of antibiotic resistant bacteria (ARB) and resistance genes (ARG). J Water Resour Prot 11:14

Aga DS (2008) Fate of pharmaceuticals in the environment and in water treatment systems. CRC Press, Boca Raton

Al Farsi RS, Ahmed M, Al Busaidi A, Choudri BS (2017) Translocation of pharmaceuticals and personal care products (PPCPs) into plant tissues: a review. Emerg Contam 3:132–137

Allam A, Tawfik A, Negm A, Yoshimura C, Fleifle A (2015) Treatment of drainage water containing pharmaceuticals using duckweed (Lemna gibba). Energy Procedia 74:973–980

Amos Sibeko P, Naicker D, Mdluli PS, Madikizela LM (2019) Naproxen, ibuprofen, and diclofenac residues in river water, sediments and Eichhornia crassipes of Mbokodweni river in South Africa: an initial screening. Environ Forensic 20:129–138

Andreozzi R, Raffaele M, Nicklas P (2003) Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment. Chemosphere 50:1319–1330

Arslan Topal EI (2015) Uptake of tetracycline and metabolites in Phragmites australis exposed to treated poultry slaughterhouse wastewaters. Ecol Eng 83:233–238

Ávila C, García J (2015) Pharmaceuticals and personal care products (PPCPs) in the environment and their removal from wastewater through constructed wetlands. Compr Anal Chem 67:195–244

Ávila C, Pedescoll A, Matamoros V, Bayona JM, García J (2010) Capacity of a horizontal subsurface flow constructed wetland system for the removal of emerging pollutants: an injection experiment. Chemosphere 81:1137–1142

Avila C, Matamoros V, Reyes-Contreras C, Pina B, Casado M, Mita L, Rivetti C, Barata C, Garcia J, Bayona JM (2014) Attenuation of emerging organic contaminants in a hybrid constructed wetland system under different hydraulic loading rates and their associated toxicological effects in wastewater. Sci Total Environ 470:1272–1280

Ávila C, Pelissari C, Sezerino PH, Sgroi M, Roccaro P, García J (2017) Enhancement of total nitrogen removal through effluent recirculation and fate of PPCPs in a hybrid constructed wetland system treating urban wastewater. Sci Total Environ 584:414–425

Azanu D, Mortey C, Darko G, Weisser JJ, Styrishave B, Abaidoo RC (2016) Uptake of antibiotics from irrigation water by plants. Chemosphere 157:107–114

Barancheshme F, Munir M (2018) Strategies to combat antibiotic resistance in the wastewater treatment plants. Front Microbiol 8:2603

Barra Caracciolo A, Topp E, Grenni P (2015) Pharmaceuticals in the environment: Biodegradation and effects on natural microbial communities. A review. J Pharm Biomed Anal 106:25–36

Bartha B, Huber C, Schröder P (2014) Uptake and metabolism of diclofenac in Typha latifolia - how plants cope with human pharmaceutical pollution. Plant Sci 227:12–20

Bengtsson-Palme J, Larsson DGJ (2016) Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. Environ Int 86:140–149

Bletsou AA, Jeon J, Hollender J, Archontaki E, Thomaidis NS (2015) Targeted and non-targeted liquid chromatography-mass spectrometric workflows for identification of transformation products of emerging pollutants in the aquatic environment. TrAC Trends Anal Chem 66:32–44

Bolong N, Ismail AF, Salim MR, Matsuura T (2009) A review of the effects of emerging contaminants in wastewater and options for their removal. Desalination 239:229–246

Boreen AL, Arnold WA, McNeill K (2003) Photodegradation of pharmaceuticals in the aquatic environment: a review. Aquat Sci 65:320–341

Bottoni P, Caroli S, Caracciolo AB (2010) Pharmaceuticals as priority water contaminants. Toxicol Environ Chem 92:549–565

Bouki C, Venieri D, Diamadopoulos E (2013) Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review. Ecotoxicol Environ Saf 91:1–9

Brix H (1997) Do macrophytes play a role in constructed treatment wetlands? Water Sci Technol 35:11–17

Calheiros CSC, Duque AF, Moura A, Henriques IS, Correia A, Rangel AOSS, Castro PML (2009) Substrate effect on bacterial communities from constructed wetlands planted with *Typha latifolia* treating industrial wastewater. Ecol Eng 35:744–753

Calheiros CSC, Pereira SIA, Brix H, Rangel AOSS, Castro PML (2017) Assessment of culturable bacterial endophytic communities colonizing Canna flaccida inhabiting a wastewater treatment constructed wetland. Ecol Eng 98:418–426

Caliman FA, Gavrilescu M (2009) Pharmaceuticals, personal care products and endocrine disrupting agents in the environment—a review. Clean-Soil Air Water 37:277–303

Carballa M, Omil F, Lema JM, Llompart M, García-Jares C, Rodríguez I, Gómez M, Ternes T (2004) Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. Water Res 38:2918–2926

Carballa M, Fink G, Omil F, Lema JM, Ternes T (2008) Determination of the solid-water distribution coefficient (Kd) for pharmaceuticals, estrogens and musk fragrances in digested sludge. Water Res 42:287–295

Carter LJ, Williams M, Martin S, Kamaludeen SPB, Kookana RS (2018) Sorption, plant uptake and metabolism of benzodiazepines. Sci Total Environ 628-629:18–25

Carvalho PN, Basto MCP, Almeida CMR, Brix H (2014) A review of plant-pharmaceutical interactions: from uptake and effects in crop plants to phytoremediation in constructed wetlands. Environ Sci Pollut Res 21:11729–11763

Celiz MD, Tso J, Aga DS (2009) Pharmaceutical metabolites in the environment: analytical challenges and ecological risks. Environ Toxicol Chem 28:2473–2484

Challis JK, Hanson ML, Friesen KJ, Wong CS (2014) A critical assessment of the photodegradation of pharmaceuticals in aquatic environments: defining our current understanding and identifying knowledge gaps. Environ Sci Process Impacts 16:672–696

Chang H, Wan Y, Wu S, Fan Z, Hu J (2011) Occurrence of androgens and progestogens in wastewater treatment plants and receiving river waters: comparison to estrogens. Water Res 45:732–740

Christofilopoulos S, Syranidou E, Gkavrou G, Manousaki E, Kalogerakis N (2016) The role of halophyte Juncus acutus L. in the remediation of mixed contamination in a hydroponic greenhouse experiment. J Chem Technol Biotechnol 91:1665–1674

Christou A, Karaolia P, Hapeshi E, Michael C, Fatta-Kassinos D (2017) Long-term wastewater irrigation of vegetables in real agricultural systems: concentration of pharmaceuticals in soil, uptake and bioaccumulation in tomato fruits and human health risk assessment. Water Res 109: 24–34

Clara M, Kreuzinger N, Strenn B, Gans O, Kroiss H (2005) The solids retention time-suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants. Water Res 39:97–106

Cooper PF, Job GD, Green MB, Shutes RBE (1996) Reed beds and constructed wetlands for wastewater treatment. WRc Publications, Medmenham

Cunha DL, de Araujo FG, Marques M (2017) Psychoactive drugs: occurrence in aquatic environment, analytical methods, and ecotoxicity—review. Environ Sci Pollut Res 24:24076–24091

D'Abrosca B, Fiorentino A, Izzo A, Cefarelli G, Pascarella MT, Uzzo P, Monaco P (2008) Phytotoxicity evaluation of five pharmaceutical pollutants detected in surface water on germination and growth of cultivated and spontaneous plants. J Environ Sci Health Part A 43:285–294

Datta R, Das P, Smith S, Punamiya P, Ramanathan DM, Reddy R, Sarkar D (2013) Phytoremediation potential of vetiver grass [Chrysopogon Zizanioides (L.)] for tetracycline. Int J Phytoremediation 15:343–351

de Andrade JR, Oliveira MF, da Silva MGC, Vieira MGA (2018) Adsorption of pharmaceuticals from water and wastewater using nonconventional low-cost materials: a review. Ind Eng Chem Res 57:3103–3127

Dolar D, Gros M, Rodriguez-Mozaz S, Moreno J, Comas J, Rodriguez-Roda I, Barcelo D (2012) Removal of emerging contaminants from municipal wastewater with an integrated membrane system, MBR-RO. J Hazard Mater 239:64–69

Dordio A, Carvalho AJP (2011) Phytoremediation: an option for removal of organic xenobiotics from water. In: Golubev IA (ed) Handbook of phytoremediation. Nova Science Publishers, Hauppauge, pp 51–92

Dordio AV, Carvalho AJP (2013) Organic xenobiotics removal in constructed wetlands, with emphasis on the importance of the support matrix. J Hazard Mater 252–253:272–292

Dordio A, Carvalho AJP (2017) Removal processes of pharmaceuticals in constructed wetlands. In: Stefanakis A (ed) Constructed wetlands for industrial wastewater treatment. Wiley-Blackwell

Dordio A, Pinto J, Barrocas Dias C, Pinto AP, Palace Carvalho AJ, Teixeira DM (2009) Atenolol removal in microcosm constructed wetlands. Int J Environ Anal Chem 89:835–848

Dordio A, Carvalho AJP, Teixeira DM, Dias CB, Pinto AP (2010) Removal of pharmaceuticals in microcosm constructed wetlands using *Typha* spp. and LECA. Bioresour Technol 101:886–892

Dorival-Garcia N, Zafra-Gomez A, Camino-Sanchez FJ, Navalon A, Vilchez JL (2013) Analysis of quinolone antibiotic derivatives in sewage sludge samples by liquid chromatography-tandem mass spectrometry: comparison of the efficiency of three extraction techniques. Talanta 106: 104–118

Du LF, Liu WK (2012) Occurrence, fate, and ecotoxicity of antibiotics in agro-ecosystems. A review. Agron Sustain Dev 32:309–327

Ebele AJ, Abou-Elwafa Abdallah M, Harrad S (2017) Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. Emerg Contam 3:1–16

Eggen T, Moeder M, Arukwe A (2010) Municipal landfill leachates: a significant source for new and emerging pollutants. Sci Total Environ 408:5147–5157

Ek M, Baresel C, Magner J, Bergstrom R, Harding M (2014) Activated carbon for the removal of pharmaceutical residues from treated wastewater. Water Sci Technol 69:2372–2380

Enick OV, Moore MM (2007) Assessing the assessments: pharmaceuticals in the environment. Environ Impact Assess Rev 27:707–729

Escher BI, Fenner K (2011) Recent advances in environmental risk assessment of transformation products. Environ Sci Technol 45:3835–3847

Evgenidou EN, Konstantinou IK, Lambropoulou DA (2015) Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: a review. Sci Total Environ 505: 905–926

Ezzariai A, Hafidi M, Khadra A, Aemig Q, El Fels L, Barret M, Merlina G, Patureau D, Pinelli E (2018) Human and veterinary antibiotics during composting of sludge or manure: global perspectives on persistence, degradation, and resistance genes. J Hazard Mater 359:465–481

Farré ML, Pérez S, Kantiani L, Barceló D (2008) Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment. TrAC Trends Anal Chem 27:991–1007

Fatta-Kassinos D, Meric S, Nikolaou A (2011) Pharmaceutical residues in environmental waters and wastewater: current state of knowledge and future research. Anal Bioanal Chem 399:251–275

Feng L, van Hullebusch ED, Rodrigo MA, Esposito G, Oturan MA (2013) Removal of residual anti-inflammatory and analgesic pharmaceuticals from aqueous systems by electrochemical advanced oxidation processes. A review. Chem Eng J 228:944–964

Fent K, Weston AA, Caminada D (2006) Ecotoxicology of human pharmaceuticals. Aquat Toxicol 76:122–159

Ferro S, Trentin AR, Caffieri S, Ghisi R (2010) Antibacterial Sulfonamides: accumulation and effects in barley plants. Fresenius Environ Bull 19:2094–2099

Fonseca Couto C, Lange LC, Santos Amaral MC (2018) A critical review on membrane separation processes applied to remove pharmaceutically active compounds from water and wastewater. J Water Process Eng 26:156–175

Frade VMF, Dias M, Teixeira ACSC, Palma MSA (2014) Environmental contamination by fluoroquinolones. Braz J Pharm Sci 50:41–54

Franklin AM, Williams CF, Andrews DM, Woodward EE, Watson JE (2016) Uptake of three antibiotics and an antiepileptic drug by wheat crops spray irrigated with wastewater treatment plant effluent. J Environ Qual 45:546–554

Frédéric O, Yves P (2014) Pharmaceuticals in hospital wastewater: their ecotoxicity and contribution to the environmental hazard of the effluent. Chemosphere 115:31–39

Gabet-Giraud V, Miège C, Choubert JM, Ruel SM, Coquery M (2010) Occurrence and removal of estrogens and beta blockers by various processes in wastewater treatment plants. Sci Total Environ 408:4257–4269

Gadipelly C, Pérez-González A, Yadav GD, Ortiz I, Ibáñez R, Rathod VK, Marathe KV (2014) Pharmaceutical industry wastewater: review of the technologies for water treatment and reuse. Ind Eng Chem Res 53:11571–11592

García-Santiago X, Franco-Uría A, Omil F, Lema JM (2016) Risk assessment of persistent pharmaceuticals in biosolids: dealing with uncertainty. J Hazard Mater 302:72–81

Gavrilescu M, Demnerová K, Aamand J, Agathos S, Fava F (2015) Emerging pollutants in the environment: present and future challenges in biomonitoring, ecological risks and bioremediation. New Biotech 32:147–156

Giger W, Alder AC, Golet EM, Kohler HPE, McArdell CS, Molnar E, Siegrist H, Suter MJF (2003) Occurrence and fate of antibiotics as trace contaminants in wastewaters, sewage sludges, and surface waters. Chimia 57:485–491

Gobel A, McArdell CS, Joss A, Siegrist H, Giger W (2007) Fate of sulfonamides, macrolides, and trimethoprim in different wastewater treatment technologies. Sci Total Environ 372:361–371

Godoy AA, Kummrow F, Pamplin PA (2015) Occurrence, ecotoxicological effects and risk assessment of antihypertensive pharmaceutical residues in the aquatic environment—a review. Chemosphere 138:281–291

Goel S (2015) Antibiotics in the environment: a review. Emerging micro-pollutants in the environment: occurrence, fate, and distribution. American Chemical Society, pp 19–42

Goldstein M, Shenker M, Chefetz B (2014) Insights into the uptake processes of wastewater-borne pharmaceuticals by vegetables. Environ Sci Technol 48:5593–5600

Gonzalez-Martinez A, Rodriguez-Sanchez A, Martinez-Toledo MV, Garcia-Ruiz MJ, Hontoria E, Osorio-Robles F, GonzalezGÇôLopez J (2014) Effect of ciprofloxacin antibiotic on the partial-nitritation process and bacterial community structure of a submerged biofilter. Sci Total Environ 476–477:276–287

Gothwal R, Shashidhar T (2015) Antibiotic pollution in the environment: a review. Clean-Soil Air Water 43:479–489

Gottschall N, Topp E, Metcalfe C, Edwards M, Payne M, Kleywegt S, Russell P, Lapen DR (2012) Pharmaceutical and personal care products in groundwater, subsurface drainage, soil, and wheat grain, following a high single application of municipal biosolids to a field. Chemosphere 87: 194–203

Gottschall N, Topp E, Edwards M, Payne M, Kleywegt S, Russell P, Lapen DR (2013) Hormones, sterols, and fecal indicator bacteria in groundwater, soil, and subsurface drainage following a high single application of municipal biosolids to a field. Chemosphere 91:275–286

Halling-Sørensen B, Nors Nielsen S, Lanzky PF, Ingerslev F, Holten Lützhøft HC, Jørgensen SE (1998) Occurrence, fate and effects of pharmaceutical substances in the environment—a review. Chemosphere 36:357–393

Hamid H, Eskicioglu C (2012) Fate of estrogenic hormones in wastewater and sludge treatment: a review of properties and analytical detection techniques in sludge matrix. Water Res 46:5813–5833

He Z, Cheng X, Kyzas GZ, Fu J (2016) Pharmaceuticals pollution of aquaculture and its management in China. JMol Liq 223:781–789

Healy MG, Fenton O, Cormican M, Peyton DP, Ordsmith N, Kimber K, Morrison L (2017) Antimicrobial compounds (triclosan and triclocarban) in sewage sludges, and their presence in runoff following land application. Ecotoxicol Environ Saf 142:448–453

Heberer T (2002) Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol Lett 131:5–17

Hijosa-Valsero M, Matamoros V, Sidrach-Cardona R, Martín-Villacorta J, Bécares E, Bayona JM (2010) Comprehensive assessment of the design configuration of constructed wetlands for the removal of pharmaceuticals and personal care products from urban wastewaters. Water Res 44: 3669–3678

Hijosa-Valsero M, Matamoros V, Sidrach-Cardona R, Pedescoll A, Martín-Villacorta J, García J, Bayona JM, Bécares E (2011) Influence of design, physico-chemical and environmental parameters on pharmaceuticals and fragrances removal by constructed wetlands. Water Sci Technol 63:2527

Hijosa-Valsero M, Reyes-Contreras C, Domínguez C, Bécares E, Bayona JM (2016) Behaviour of pharmaceuticals and personal care products in constructed wetland compartments: influent, effluent, pore water, substrate and plant roots. Chemosphere 145:508–517

Hijosa-Valsero M, Sidrach-Cardona R, Pedescoll A, Sanchez O, Becares E (2017) Role of bacterial diversity on PPCPs removal in constructed wetlands. In: Stefanakis A (ed) Constructed wetlands for industrial wastewater treatment. Wiley-Blackwell, Hoboken

Jelic A, Gros M, Ginebreda A, Cespedes-Sínchez R, Ventura F, Petrovic M, Barcelo D (2011) Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. Water Res 45:1165–1176

Jelic A, Fatone F, Di Fabio S, Petrovic M, Cecchi F, Barcelo D (2012) Tracing pharmaceuticals in a municipal plant for integrated wastewater and organic solid waste treatment. Sci Total Environ 433:352–361

Jones-Lepp TL, Sanchez CA, Moy T, Kazemi R (2010) Method development and application to determine potential plant uptake of antibiotics and other drugs in irrigated crop production systems. J Agric Food Chem 58:11568–11573

Joss A, Keller E, Alder AC, Gobel A, McArdell CS, Ternes T, Siegrist H (2005) Removal of pharmaceuticals and fragrances in biological wastewater treatment. Water Res 39:3139–3152

Kadlec RH, Wallace SD (2009) Treatment wetlands. CRC Press, Boca Raton

Kanakaraju D, Glass BD, Oelgemöller M (2018) Advanced oxidation process-mediated removal of pharmaceuticals from water: a review. J Environ Manage 219:189–207

Khetan SK, Collins TJ (2007) Human pharmaceuticals in the aquatic environment: a challenge to green chemistry. Chem Rev 107:2319–2364

Kim KR, Owens G, Kwon SI, So KH, Lee DB, Ok YS (2011) Occurrence and environmental fate of veterinary antibiotics in the terrestrial environment. Water Air Soil Pollut 214:163–174

Kit Chan W, Jouët J, Heng S, Lun Yeung K, Schrotter JC (2012) Membrane contactor/separator for an advanced ozone membrane reactor for treatment of recalcitrant organic pollutants in water. J Solid State Chem 189:96–100

Koch N, Islam NF, Sonowal S, Prasad R, Sarma H (2021) Environmental antibiotics and resistance genes as emerging contaminants: methods of detection and bioremediation. Cur Res Microbial Sci. https://doi.org/10.1016/j.crmicr.2021.100027

Kotyza J, Soudek P, Kafka Z, Vanek T (2010) Phytoremediation of pharmaceuticals-preliminary study. Int J Phytoremediation 12:306–316

Kummerer K (2009) Antibiotics in the aquatic environment—a review—part I. Chemosphere 75: 417–434

Kümmerer K (2009a) Antibiotics in the aquatic environment—A review—Part II. Chemosphere 75: 435–441

Kümmerer K (2009b) The presence of pharmaceuticals in the environment due to human use—present knowledge and future challenges. J Environ Manage 90:2354–2366

Lapworth DJ, Baran N, Stuart ME, Ward RS (2012) Emerging organic contaminants in groundwater: a review of sources, fate and occurrence. Environ Pollut 163:287–303

Larsen TA, Lienert J, Joss A, Siegrist H (2004) How to avoid pharmaceuticals in the aquatic environment. J Biotechnol 113:295–304

Larsson DGJ (2014) Antibiotics in the environment. Upsala J Med Sci 119:108–112

Le Minh N, Khan SJ, Drewes JE, Stuetz RM (2010) Fate of antibiotics during municipal water recycling treatment processes. Water Res 44:4295–4323

Li WC (2014) Occurrence, sources, and fate of pharmaceuticals in aquatic environment and soil. Environ Pollut 187:193–201

Li YF, Zhu GB, Ng WJ, Tan SK (2014) A review on removing pharmaceutical contaminants from wastewater by constructed wetlands: design, performance and mechanism. Sci Total Environ 468:908–932

Lillenberg M, Yurchenko S, Kipper K, Herodes K, Pihl V, Sepp K, Lohmus R, Nei L (2009) Simultaneous determination of fluoroquinolones, sulfonamides and tetracyclines in sewage sludge by pressurized liquid extraction and liquid chromatography electrospray ionization-mass spectrometry. J Chromatogr A 1216:5949–5954

Lin YL, Li BK (2016) Removal of pharmaceuticals and personal care products by Eichhornia crassipe and Pistia stratiotes. J Taiwan Inst Chem Eng 58:318–323

Liu F, Ying GG, Tao R, Zhao JL, Yang JF, Zhao LF (2009) Effects of six selected antibiotics on plant growth and soil microbial and enzymatic activities. Environ Pollut 157:1636–1642

Liu L, Liu Yh, Liu Cx, Wang Z, Dong J, Zhu Gf, Huang X (2013) Potential effect and accumulation of veterinary antibiotics in Phragmites australis under hydroponic conditions. Ecol Eng 53:138–143

Liu Z, Lu G, Yin H, Dang Z, Rittmann B (2015) Removal of natural estrogens and their conjugates in municipal wastewater treatment plants: a critical review. Environ Sci Technol 49:5288–5300

Liu X, Guo X, Liu Y, Lu S, Xi B, Zhang J, Wang Z, Bi B (2019) A review on removing antibiotics and antibiotic resistance genes from wastewater by constructed wetlands: performance and microbial response. Environ Pollut 254(112):996

Lu MC, Chen YY, Chiou MR, Chen MY, Fan HJ (2016) Occurrence and treatment efficiency of pharmaceuticals in landfill leachates. Waste Manage

Luo Y, Guo W, Ngo HH, Nghiem LD, Hai FI, Zhang J, Liang S, Wang XC (2014) A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. Sci Total Environ 473–474:619–641

Macherius A, Eggen T, Lorenz WG, Reemtsma T, Winkler U, Moeder M 2012 Uptake of Galaxolide, Tonalide, and Triclosan by Carrot, Barley, and Meadow Fescue

Madikizela LM, Ncube S, Chimuka L (2018) Uptake of pharmaceuticals by plants grown under hydroponic conditions and natural occurring plant species: a review. Sci Total Environ 636: 477–486

Malchi T, Maor Y, Tadmor G, Shenker M, Chefetz B (2014) Irrigation of root vegetables with treated wastewater: evaluating uptake of pharmaceuticals and the associated human health risks. Environ Sci Technol 48:9325–9333

Masoner JR, Kolpin DW, Furlong ET, Cozzarelli IM, Gray JL (2016) Landfill leachate as a mirror of today's disposable society: pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States. Environ Toxicol Chem 35:1–13
Matamoros V, Garcia J, Bayona JM (2008) Organic micropollutant removal in a full-scale surface flow constructed wetland fed with secondary effluent. Water Res 42:653–660
Matamoros V, Nguyen LX, Arias CA, Salvadó V, Brix H (2012) Evaluation of aquatic plants for removing polar microcontaminants: a microcosm experiment. Chemosphere 88:1257–1264
Matamoros V, Rodríguez Y, Bayona JM (2017) Mitigation of emerging contaminants by full-scale horizontal flow constructed wetlands fed with secondary treated wastewater. Ecol Eng 99:222–227
Mathews S, Henderson S, Reinhold D (2014) Uptake and accumulation of antimicrobials, triclocarban and triclosan, by food crops in a hydroponic system. Environ Sci Pollut Res 21:6025–6033
Maurer M, Escher BI, Richle P, Schaffner C, Alder AC (2007) Elimination of b-blockers in sewage treatment plants. Water Res 41:1614–1622
Mendoza A, Aceña J, Pérez S, López de Alda M, Barceló D, Gil A, Valcárcel Y (2015) Pharmaceuticals and iodinated contrast media in a hospital wastewater: a case study to analyse their presence and characterise their environmental risk and hazard. Environ Res 140:225–241
Michael I, Rizzo L, McArdell CS, Manaia CM, Merlin C, Schwartz T, Dagot C, Fatta-Kassinos D (2013) Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: a review. Water Res 47:957–995
Miége C, Choubert JM, Ribeiro L, Eusèbe M, Coquery M (2009) Fate of pharmaceuticals and personal care products in wastewater treatment plants—conception of a database and first results. Environ Pollut 157:1721–1726
Mo WY, Chen Z, Leung HM, Leung AOW (2015) Application of veterinary antibiotics in China's aquaculture industry and their potential human health risks. Environ Sci Pollut Res:1–12
Monteiro SC, Boxall ABA (2010) Occurrence and fate of human pharmaceuticals in the environment. Rev Environ Contam Toxicol 202(202):53–154
Munir M, Xagoraraki I (2011) Levels of antibiotic resistance genes in manure, biosolids, and fertilized soil. J Environ Qual 40:248–255
Nieto A, Borrull F, Pocurull E, Marce RM (2010) Occurrence of pharmaceuticals and hormones in sewage sludge. Environ Toxicol Chem 29:1484–1489
Nikolaou A, Meric S, Fatta D (2007) Occurrence patterns of pharmaceuticals in water and wastewater environments. Anal Bioanal Chem 387:1225–1234
Noguera-Oviedo K, Aga DS (2016) Lessons learned from more than two decades of research on emerging contaminants in the environment. J Hazard Mater
OECD (2018) OECD.Stat—pharmaceutical market. https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_PHMC. Accessed 16 Sep 2019
Onesios K, Yu J, Bouwer E (2009) Biodegradation and removal of pharmaceuticals and personal care products in treatment systems: a review. Biodegradation 20:441–466
Patel M, Kumar R, Kishor K, Mlsna T, Pittman CU, Mohan D (2019) Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chem Rev 119:3510–3673
Pei M, Zhang B, He Y, Su J, Gin K, Lev O, Shen G, Hu S (2019) State of the art of tertiary treatment technologies for controlling antibiotic resistance in wastewater treatment plants. Environ Int 131:105026
Petrie B, Barden R, Kasprzyk-Hordern B (2015) A review on emerging contaminants in wastewaters and the environment: current knowledge, understudied areas and recommendations for future monitoring. Water Res 72:3–27
Petrovic M, Barceló D (2007) Analysis, fate and removal of pharmaceuticals in the water cycle. Elsevier, Amsterdam
Picó Y, Andreu V (2007) Fluoroquinolones in soil—risks and challenges. Anal Bioanal Chem 387:1287–1299

Postigo C, Richardson SD (2014) Transformation of pharmaceuticals during oxidation/disinfection processes in drinking water treatment. J Hazard Mater 279:461–475

Prosser RS, Trapp S, Sibley PK (2014) Modeling uptake of selected pharmaceuticals and personal care products into food crops from biosolids-amended soil. Environ Sci Technol 48:11397–11404

Radjenovic J, Petrovic M, Barceló D (2009) Fate and distribution of pharmaceuticals in wastewater and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor (MBR) treatment. Water Res 43:831–841

Ramakrishnan A, Blaney L, Kao J, Tyagi RD, Zhang TC, Surampalli RY (2015) Emerging contaminants in landfill leachate and their sustainable management. Environ Earth Sci 73: 1357–1368

Reyes-Contreras C, Hijosa-Valsero M, Sidrach-Cardona R, Bayona JM, Bécares E (2012) Temporal evolution in PPCP removal from urban wastewater by constructed wetlands of different configuration: a medium-term study. Chemosphere 88:161–167

Riaz L, Mahmood T, Khalid A, Rashid A, Ahmed Siddique MB, Kamal A, Coyne MS (2018) Fluoroquinolones (FQs) in the environment: a review on their abundance, sorption and toxicity in soil. Chemosphere 191:704–720

Rico A, Van den Brink PJ (2014) Probabilistic risk assessment of veterinary medicines applied to four major aquaculture species produced in Asia. Sci Total Environ 468–469:630–641

Rizzo L, Fiorentino A, Grassi M, Attanasio D, Guida M (2015) Advanced treatment of urban wastewater by sand filtration and graphene adsorption for wastewater reuse: effect on a mixture of pharmaceuticals and toxicity. J Environ Chem Eng 3:122–128

Rodriguez-Mozaz S, Ricart M, Kock-Schulmeyer M, Guasch H, Bonnineau C, Proia L, de Alda ML, Sabater S, Barcelo D (2015) Pharmaceuticals and pesticides in reclaimed water: efficiency assessment of a microfiltration-reverse osmosis (MF-RO) pilot plant. J Hazard Mater 282:165–173

Rosal R, Rodriguez A, Perdigon-Melon JA, Petre A, Garcia-Calvo E, Gomez MJ, Aguera A, Fernandez-Alba AR (2010) Occurrence of emerging pollutants in urban wastewater and their removal through biological treatment followed by ozonation. Water Res 44:578–588

Sabourin L, Beck A, Duenk PW, Kleywegt S, Lapen DR, Li H, Metcalfe CD, Payne M, Topp E (2009) Runoff of pharmaceuticals and personal care products following application of dewatered municipal biosolids to an agricultural field. Sci Total Environ 407:4596–4604

Shao S, Hu Y, Cheng J, Chen Y (2018) Research progress on distribution, migration, transformation of antibiotics and antibiotic resistance genes (ARGs) in aquatic environment. Crit Rev Biotechnol 38:1195–1208

Silva BF, Jelic A, López-Serna R, Mozeto AA, Petrovic M, Barceló D (2011) Occurrence and distribution of pharmaceuticals in surface water, suspended solids and sediments of the Ebro river basin, Spain. Chemosphere 85:1331–1339

Sim WJ, Lee JW, Lee ES, Shin SK, Hwang SR, Oh JE (2011) Occurrence and distribution of pharmaceuticals in wastewater from households, livestock farms, hospitals and pharmaceutical manufactures. Chemosphere 82:179–186

Singer AC, Shaw H, Rhodes V, Hart A (2016) Review of antimicrobial resistance in the environment and its relevance to environmental regulators. Front Microbiol 7:1728

Snyder SA, Adham S, Redding AM, Cannon FS, DeCarolis J, Oppenheimer J, Wert EC, Yoon Y (2007) Role of membranes and activated carbon in the removal of endocrine disruptors and pharmaceuticals. Desalination 202:156–181

Stottmeister U, Wiessner A, Kuschk P, Kappelmeyer U, Kastner M, Bederski O, Muller RA, Moormann H (2003) Effects of plants and microorganisms in constructed wetlands for wastewater treatment. Biotechnol Adv 22:93–117

Sui Q, Cao X, Lu S, Zhao W, Qiu Z, Yu G (2015) Occurrence, sources and fate of pharmaceuticals and personal care products in the groundwater: a review. Emerg Contam 1:14–24

Sundaravadivel M, Vigneswaran S (2001) Constructed wetlands for wastewater treatment. Crit Rev Environ Sci Technol 31:351–409

Tahar A, Choubert JM, Coquery M (2013) Xenobiotics removal by adsorption in the context of tertiary treatment: a mini review. Environ Sci Pollut Res 20:5085–5095
Tanoue R, Sato Y, Motoyama M, Nakagawa S, Shinohara R, Nomiyama K (2012) Plant uptake of pharmaceutical chemicals detected in recycled organic manure and reclaimed wastewater. J Agric Food Chem 60:10203–10211
Tasho RP, Cho JY (2016) Veterinary antibiotics in animal waste, its distribution in soil and uptake by plants: a review. Sci Total Environ 563–564:366–376
Ternes TA, Herrmann N, Bonerz M, Knacker T, Siegrist H, Joss A (2004) A rapid method to measure the solid-water distribution coefficient (Kd) for pharmaceuticals and musk fragrances in sewage sludge. Water Res 38:4075–4084
Tijani JO, Fatoba OO, Petrik LF (2013) A review of pharmaceuticals and endocrine-disrupting compounds: sources, effects, removal, and detections. Water Air Soil Pollut:224
Topp E, Larsson DGJ, Miller DN, Van den Eede C, Virta MPJ (2017) Antimicrobial resistance and the environment: assessment of advances, gaps and recommendations for agriculture, aquaculture and pharmaceutical manufacturing. FEMS Microbiol Ecol 94
Tran NH, Reinhard M, Gin KY-H (2018) Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions—a review. Water Res 133:182–207
Truu M, Juhanson J, Truu J (2009) Microbial biomass, activity and community composition in constructed wetlands. Sci Total Environ 407:3958–3971
Urase T, Kikuta T (2005) Separate estimation of adsorption and degradation of pharmaceutical substances and estrogens in the activated sludge process. Water Res 39:1289–1300
Velagaleti R (1997) Behavior of pharmaceutical drugs (human and animal health) in the environment. Drug Inf J 31:715–722
Verlicchi P, Zambello E (2014) How efficient are constructed wetlands in removing pharmaceuticals from untreated and treated urban wastewaters? A review. Sci Total Environ 470–471:1281–1306
Verlicchi P, Al Aukidy M, Galletti A, Petrovic M, Barceló D (2012a) Hospital effluent: investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment. Sci Total Environ 430:109–118
Verlicchi P, Al Aukidy M, Zambello E (2012b) Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment—a review. Sci Total Environ 429:123–155
Vieno N, Sillanpää M (2014) Fate of diclofenac in municipal wastewater treatment plant—a review. Environ Int 69:28–39
Vo HN-P, Bui XT, Nguyen TM-H, Koottatep T, Bandyopadhyay A (2018) Insights of the removal mechanisms of pharmaceutical and personal care products in constructed wetlands. Curr Pollut Rep 4:93–103
Vymazal J, Brix H, Cooper PF, Green MB, Haberl R (1998) Constructed wetlands for wastewater treatment in Europe. Backhuys Publishers, Leiden
Vymazal J, Dvoráková Brezinová T, Koželuh M, Kule L (2017) Occurrence and removal of pharmaceuticals in four full-scale constructed wetlands in the Czech Republic—the first year of monitoring. Ecol Eng 98:354–364
Wang XH, Lin AY-C (2014) Is the phototransformation of pharmaceuticals a natural purification process that decreases ecological and human health risks? Environ Pollut 186:203–215
Wang J, Wang S (2016) Removal of pharmaceuticals and personal care products (PPCPs) from wastewater: a review. J Environ Manage 182:620–640
Watkinson AJ, Murby EJ, Costanzo SD (2007) Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling. Water Res 41:4164–4176
Wilkinson J, Hooda PS, Barker J, Barton S, Swinden J (2017) Occurrence, fate and transformation of emerging contaminants in water: an overarching review of the field. Environ Pollut 231:954–970

Wu C, Spongberg AL, Witter JD, Fang M, Czajkowski KP (2010) Uptake of pharmaceutical and personal care products by soybean plants from soils applied with biosolids and irrigated with contaminated water. Environ Sci Technol 44:6157–6161

Wu H, Zhang J, Ngo HH, Guo W, Hu Z, Liang S, Fan J, Liu H (2015) A review on the sustainability of constructed wetlands for wastewater treatment: design and operation. Bioresour Technol 175: 594–601

Xie WY, Shen Q, Zhao FJ (2018) Antibiotics and antibiotic resistance from animal manures to soil: a review. Eur J Soil Sci 69:181–195

Yan Q, Feng G, Gao X, Sun C, Guo Js, Zhu Z (2016) Removal of pharmaceutically active compounds (PhACs) and toxicological response of Cyperus alternifolius exposed to PhACs in microcosm constructed wetlands. J Hazard Mater 301:566–575

Yang SF, Lin CF, Wu CJ, Ng KK, Lin AYC, Hong PKA (2012) Fate of sulfonamide antibiotics in contact with activated sludge—sorption and biodegradation. Water Res 46:1301–1308

Yang Y, Ok YS, Kim KH, Kwon EE, Tsang YF (2017) Occurrences and removal of pharmaceuticals and personal care products (PPCPs) in drinking water and water/sewage treatment plants: a review. Sci Total Environ 596–597:303–320

Yu YY, Huang QX, Cui JL, Zhang K, Tang CM, Peng XZ (2011) Determination of pharmaceuticals, steroid hormones, and endocrine-disrupting personal care products in sewage sludge by ultra-high-performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 399:891–902

Zarate J, Schulwitz SE, Stevens KJ, Venables BJ (2012) Bioconcentration of triclosan, methyl-triclosan, and triclocarban in the plants and sediments of a constructed wetland. Chemosphere 88:323–329

Zhai J, Rahaman M, Ji J, Luo Z, Wang Q, Xiao H, Wang K (2016) Plant uptake of diclofenac in a mesocosm-scale free water surface constructed wetland by Cyperus alternlifolius. Water Sci, Technol

Zhang Y, Geißen SU, Gal C (2008) Carbamazepine and diclofenac: removal in wastewater treatment plants and occurrence in water bodies. Chemosphere 73:1151–1161

Zhang BY, Zheng JS, Sharp RG (2010) Phytoremediation in engineered wetlands: mechanisms and applications. Proc Environ Sci 2:1315–1325

Zhang DQ, Hua T, Gersberg RM, Zhu J, Ng WJ, Tan SK (2012) Fate of diclofenac in wetland mesocosms planted with Scirpus validus. Ecol Eng 49:59–64

Zhang DQ, Gersberg RM, Hua T, Zhu J, Ng WJ, Tan SK (2013a) Assessment of plant-driven uptake and translocation of clofibric acid by Scirpus validus. Environ Sci Pollut Res 20:4612–4620

Zhang DQ, Hua T, Gersberg RM, Zhu J, Ng WJ, Tan SK (2013b) Carbamazepine and naproxen: fate in wetland mesocosms planted with Scirpus validus. Chemosphere 91:14–21

Zhang D, Gersberg RM, Ng WJ, Tan SK (2014) Removal of pharmaceuticals and personal care products in aquatic plant-based systems: a review. Environ Pollut 184:620–639

Zhang L, Lyu T, Ramírez Vargas CA, Arias CA, Carvalho PN, Brix H (2018a) New insights into the effects of support matrix on the removal of organic micro-pollutants and the microbial community in constructed wetlands. Environ Pollut 240:699–708

Zhang X, Jing R, Feng X, Dai Y, Tao R, Vymazal J, Cai N, Yang Y (2018b) Removal of acidic pharmaceuticals by small-scale constructed wetlands using different design configurations. Sci Total Environ 639:640–647

Zhou XF, Zhang YL, Shi L, Chen JB, Qiang ZM, Zhang TC (2013) Partitioning of fluoroquinolones on wastewater sludge. Clean-Soil Air Water 41:820–827