Chapter 1
Green Technologies for the Treatment of Pharmaceutical Contaminants in Wastewaters

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Abstract The remarkable worldwide increase in the production and use of several pharmaceuticals, on one hand, brings advantages to modern society and, on the other hand, represents a hazardous risk to natural ecosystems. Pharmaceuticals are considered emerging contaminants of great environmental concern since its continuous disposal in the environment and high persistency can affect ecosystems and human life quality. In this context, the scientific community has addressed this problematic in several fronts investigating incidence, toxicological effects, and detection techniques to determine the real impact of the increase of its release as one of the challenges of the new millennia. The present chapter approaches the occurrence, and deleterious effects of these contaminants, as well as the alternative treatments developed to adequately remove them from natural water bodies and water streams.

Keywords Wastewaters · Pharmaceutical contaminants · Hazardous risks · Green technologies · Treatment

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1.1 Introduction

Emerging contaminants have no proper definition, being hard to describe and classify (Tijani et al. 2016). The US Geological Society defines the emerging contaminants as synthetic or naturally occurring chemicals, microorganisms, or metabolites that are not monitored but have the potential to cause adverse ecological and/or human health effects (USGS 2014). Recent research shows that the use of pharmaceuticals will globally reach 4500 billion doses by 2020, approximately 24% more than in 2015; at the same time, 50% of the world population will be able to consume more than one dose per person per day. Compared to consumption, global spending for pharmaceuticals is mostly driven by the USA, EU (Germany, the UK, Italy, France, Spain), Japan, Canada, South Korea, and Australia (QuintilesI MS Health, 2015, 2016), with an overall market of $1400 billion by 2020 (Mezzelani et al. 2018).

The development of analytical techniques such as high-performance liquid chromatography-mass spectrometry (HPLC-MS) allowed the detection of several compounds in complex matrixes identifying and quantifying the compounds in concentrations as low as nanograms per liter. Considering their high toxicity and the ability to move along the food chain, most times even nano-level of contaminations is enough to see deleterious effects promoted from contact with pharmaceuticals (Rivera-Utrilla et al. 2013; Yadav et al. 2016a; Comber et al. 2018). Attempts like the Stockholm Convention, also known as the Persistent Organic Pollutants Treaty of 2001, and the Berlaymont Declaration of 2013 have been made seeking to control the level of these contaminants in the environment, without success.

Among the emerging contaminants, pharmaceuticals are classified according to their uses adding to up to 24 classifications, of which four are predominantly found in water and are known as nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antibiotics, and lipid regulators (Tijani et al. 2016). The first reports of pharmaceuticals as environmental contaminants were only found when ethinylestradiol (birth control substance) was directly related to neurological impairment found in fishes back in 1994 (Gautam et al. 2017; Purdom et al. 1994), but their effects on the environmental balance vary from disrupting key bacterial cycles (nitrification/denitrification) to impairments in soil fertility (Watkinson et al. 2009). With the increase in human and animal use of these drugs, and due to the incomplete metabolization of these compounds, an increase in volume detected in the environment has been seen in recent years. Although most of the pharmaceuticals reach the wastewater treatment plants after being somewhat digested by human and animal organisms, there is still a great amount of the contaminants that reach the systems as purchased due to inadequate disposal of these compounds (Pereira et al. 2017).

This problem is accentuated when considering that conventional wastewater treatment plants do not reach complete mineralization of these compounds, which several times exits the system unchanged (Yadav et al. 2016b; Zhang et al. 2018). The scenario is more problematic when considering practices of water reuse, especially adopted in areas where the resource is scarce. For instance, Kleywegt et al.

(2011) detected more than 30 different pharmaceuticals in drinking water across the world.

Endocrine disruption, chronic toxicity, and increase in bacterial strain resistance to these drugs are the main side effects already spread worldwide. Hence, pharmaceuticals and several emerging contaminants are being even more frequently the focus on research and investments in order to better understand their incidence and their fate in natural environments. In this sense, UNESCO-IHP initiative funded by the Swedish International and Developed Cooperation Agency (Sida) just invested in studies in 17 different countries (Australia, Brazil, China, Ethiopia, India, Kenya, Kuwait, Mexico, Mongolia, Nigeria, Norway, Rwanda, Saint Lucia, Thailand, Tunisia, Ukraine, and Vietnam).

Notably, efforts from various entities are starting to promote awareness of the problem and address possible solutions and research on the topic. However, pharmaceutical pollution control protocols involve both political and cultural changes demanding intensive and direct participation of the standard home user. With this background, this chapter presents a critical review of the recent scientific development on the issue of presenting environmentally friendly options for pharmaceutical removal from the environment. In addition, a summary of the main pharmaceuticals found in the environment and the latest detection methods is presented. Finally, the uses of environmentally friendly technologies named green technologies for the elimination of these compounds from the environment are also discussed.

1.2 Occurrence of Pharmaceuticals Worldwide

The presence of pharmaceutical contaminants in the wastewater is directly related to human activity and, as such, is highly unpredictable. Partly, this is because these contaminants can enter the environment from several sources (Fig. 1.1). However, household wastewater is one of the main sources for pharmaceuticals found in the environment (Pereira et al. 2017). Additionally, pharmaceuticals used in veterinary applications are commonly excreted directly into soils or superficial waters without proper treatment, which increases the complexity of emission estimation (Bielen et al. 2017).

Due to their physical-chemical properties, high stability, and chemical persistence, pharmaceuticals are generally hard to naturally degrade. In a more concerning scenario, their chemical structures can present specific affinities that lead them to bond, rearrange, and develop synergistic effects resulting in a more bioactive compound than their metabolic precursor (Luo et al. 2014; Zainith et al. 2019). Various routes by which the pharmaceuticals enter the environment can be seen in Fig. 1.1 (Tijani et al. 2016; Verlicchi et al. 2012; Ding et al. 2010; Yang et al. 2017a; Scott et al. 2018).

Therefore, it is no surprise that pharmaceuticals have been found in both influent and effluent waters from wastewater treatment plants (WWTP) (Comber et al. 2018; Verlicchi et al. 2012; Cotillas et al. 2016; Guedes-alonso et al. 2013), surface water

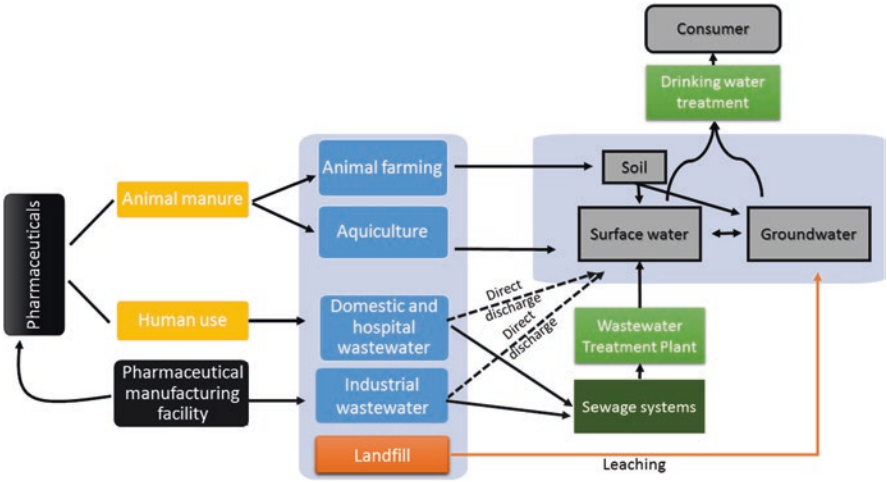

Fig. 1.1 Schematic pathways of pharmaceutical contaminants from sources to receptors (gray) (Adapted from Stuart et al. (2012))

Table 1.1 Pharmaceutical classes and representative compounds intensely consumed worldwide according to its use

Classes	Representative compound
Antibiotic	Erythromycin; sulfamethoxazole
Antimicrobial	Oxytetracycline, trimethoprim
Anti-inflammatory	Acetylsalicylic acid; ibuprofen; diclofenac
Analgesic	Paracetamol
Antidepressants	Benzodiazepines
Antiepileptics	Carbamazepine
Lipid-lowering drugs	Fibrates
β-Blockers	Atenolol, propranolol, and metoprolol
Antiulcer drugs and antihistamines	Ranitidine and famotidine
Other substances	Cocaine, barbiturates, methadone, amphetamines, opiates, heroin, and other narcotics

(Bielen et al. 2017; Marsik et al. 2017; Mandaric et al. 2017), groundwater (Yao et al. 2017; Sui et al. 2015), and even drinking water (Machado et al. 2016; Saxena et al. 2015; Leung et al. 2013; Mompelat et al. 2009). Among the several compounds found in literature, a brief summary of the most frequent classes of pharmaceuticals and representative compounds is displayed in Table 1.1 (Kümmerer 2001; Balakrishna et al. 2017; Puckowski et al. 2016).

In countries like China, known as the largest producer and consumer of pharmaceuticals in the world, amounts of over 90,000 tons of antibiotics were estimated to be consumed, of which 53,800 tons entered the environment through WWTP (Zhang

et al. 2018). The loadings vary according to the season, sporadic events, intra- and inter-day variation, and spatial distribution, which all contribute to the difficulty to properly predict the amounts of contaminants found in the environment (Petrie et al. 2014). Further, urban and anthropic variables, such as tourism and collective vacation periods, have been found to significantly alter the incidence of pharmaceuticals in the environment (Mandaric et al. 2017). For example, studies developed by Mandaric et al. (2017), analyzing the incidence of 80 different pharmaceutical compounds in the Adige river basin (Italy), found that the overall presence of the compounds was higher in winter than in summer.

However, considering the distribution throughout over 400 km of the river and 12 different sampling points, it was proven that this difference is related to both the larger dilution seen in summer, due to the snow melting and the higher presence of tourists during winter. Similarly, Azzouz and Ballesteros (2013) and Pereira et al. (2015) analyzed the influence of environmental conditions on the concentration of pharmaceuticals, hormones, and personal care products in samples of raw water received by a WWTP in southeastern Spain. The research focused on determining the presence of compounds most resistant to removal by conventional wastewater treatment. Higher levels of these contaminants were observed in colder periods than in warm periods (spring and summer), which was mainly attributed to the biodegradation being favored by high temperatures and solar irradiance. On the other hand, carbamazepine in raw water presented only little change between periods, which suggests that this pharmaceutical is resistant to changes in temperature and solar irradiance.

Finally, the efficiency with which these contaminants are removed by a conventional water treatment plant operating by means of peroxidation with potassium permanganate and chlorination with sodium hypochlorite in the presence of highly concentrated ammonia was evaluated (Saxena et al. 2015; Bharagava et al. 2018). As result, it was found that water treated in the colder periods still contained small amounts of ibuprofen and carbamazepine (0.09–0.50 ng L^{-1}), these values being less than 0.2% of their initial concentrations at the WWTP intake.

On the other hand, Marsik et al. (2017) analyzed the concentration of five of the most common nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, diclofenac, naproxen, ketoprofen, and indomethacin) collected in 29 sites, including urban and rural areas, water streams, and main water supply points in the Elba river in Czech Republic. Although the amount of NSAID varied according to the sampling point, in general, their concentrations increase during the months of spring and autumn. In this study, ibuprofen was the most abundant compound found (3.210 ng L^{-1}), followed by naproxen, diclofenac, and ketoprofen (1.4238 ng L^{-1}, 1.080 ng L^{-1}, and 929 ng L^{-1}, respectively). Additionally, factors like flow rates also influenced the concentration of all compounds showing a significant increase in creeks, probably associated with the proximity to the contamination source.

Kot-Wasik et al. (2016) investigated the occurrence and efficiency of removing 25 pharmaceuticals during water and wastewater treatment analyzing the seasonal variation noted throughout the year. The compounds found more frequently were carbamazepine (100% of the samples) and ibuprofen (98% of the samples). Still,

pharmaceutical concentrations were higher in winter, especially for the nonsteroidal anti-inflammatory drugs (NSAIDs) and caffeine, probably due to degradation inhibition related to low temperatures and limited sunlight. Carbamazepine was once again found as the most resistant to natural degradation, and its concentration was uniform throughout the year.

Therefore, complex studies like these, which seek to understand the anthropogenic effect on the concentration of pharmaceuticals throughout the year, promote a better knowledge of the various routes in which population density can affect contamination rates and aid in developing adequate protocols to suit various environments. Nowadays, an increasing concern on the presence of these contaminants in drinking water is seen, especially in governmental studies. Kleywegt et al. (2011) reported a survey carried out by the Ontario Ministry of the Environment (MOE), analyzing 258 field samples, collected through the timespan of 16 months. Incidence of pharmaceuticals and other emerging contaminants is widely reported in drinking water samples in this study, highlighting the need for improvements in the treatment used to remove these specific compounds.

Moreover, the amounts in which these compounds are found have become an alarming problem. Kay et al. (2017) analyzed the Aire and Calder catchment in West Yorkshire (UK), which receive 105 WWTP effluents being the most populated area of the UK with close to 1.5 million people. For analysis, only five of the most commonly found compounds were analyzed in the samples gathered, which were 121 WWTP effluents, 185 receiving waters, and 14 combined sewer outflows. The compounds analyzed were diclofenac, erythromycin, ibuprofen, mefenamic acid, and propranolol. After thorough analysis, the pharmaceuticals chosen were found in 51–94% of the samples in concentrations up to tens of hundreds of ng L^{-1}, many times exceeding the permissible values found in legislation. Although the variety of products found in effluents and surface waters is endless, studies can have a range as wide as hundreds of compounds and still not effectively characterize all the compounds found in samples collected. Worldwide the number of contaminants identified in these studies is continuously increasing. Table 1.2 shows the latest studies highlighting the analysis method applied and the water matrix chosen in each case.

When brought to light, the incidence in which contaminants are found in natural water bodies only reinforces the need to improve the WWTP. Studies developed in South Korea frequently detected incomplete removal of 25 compounds from the total of 26 analyzed by the WWTP, even in systems relying on membrane filtration, membrane bioreactor, nanofiltration, reverse osmosis, and ultraviolet irradiation (Kim et al. 2018; Chowdhary et al. 2018). Further, this situation is even more worrisome in countries with poor environmental protection laws. In such places, the contamination occurs notably by poor understanding from the population, disposing pharmaceuticals directly into toilets and water bodies, combined with limited contamination control measurement adopted by hospitals, treatment centers, and even industries (Visanji et al. 2018).

In countries like India, fiscal incentives and low employee costs will drive the pharmaceutical industry to produce $45 billion a year by 2020, where sewage treatment is so deficient that from 1.3 billion people attended, only 31% of the sewage

Table 1.2 Reports on pharmaceutical compounds found in natural waters worldwide

Country	Number of contaminants identified	Environment analyzed	Analysis method	Year	References
South Korea	26	Effluents, surface waters, drinking water	LC-MS/MS	2007	Kim et al. (2007)
Canada	48	Surface waters, drinking water	Q-trap MS LC-MS/MS	2011	Kleywegt et al. (2011)
Australia	28	Hospital wastewaters, WWTP effluent, surface waters, drinking waters	HPLC-MS/MS	2006	Watkinson et al. (2009)
Italy	80	Surface waters	UPLC-QLIT-MS^2	2017	Mandaric et al. (2017)
China	14	Ground water and surface water	HPLC-MS/MS	2017	Yao et al. (2017)
Spain	13	Wastewater	HPLC-MS/MS and UHPLC-MS/MS	2013	Guedes-alonso et al. (2013)
Spain	23	WWTP	LC-MS/MS	2017	Afonso-Olivares et al. (2017)
Spain	19	Wastewater	UPLC-Qtrap-MS	2017	Hom-Diaz et al. (2017)
India	67	Wastewater, hospital effluent, river water, ground water		2017	Balakrishna et al. (2017)
China	37	WWTP	HPLC-MS	2018	Zhang et al. (2018)
China	39	Advanced drinking water treatment plant	HPLC-MS/MS and LC/MS/MS	2016	Lin et al. (2016)
South Africa	90	WWTP, surface waters	UPLC-TQD-MS	2017	Archer et al. (2017)
Kenya	21	Rivers	UPLC	2018	K'oreje et al. (2018)

(38.254 million liters per day) is actually treated (Balakrishna et al. 2017). Although proper treatment methods and adequate environmental policies are still in development in these countries, an increase in studies focusing on the detection and quantification of pharmaceuticals in the environment has been noted (Gogoi et al. 2018).

Yao et al. (2017) investigated the occurrence of 14 antibiotics (fluoroquinolones, tetracyclines, macrolides, and sulfonamides) in groundwater and water bodies in the fields of Jianghan in China, during three seasons. Total concentrations of target compounds in water samples were higher in spring than in summer and winter, mostly associated with veterinary use and the higher incidence of diseases in this period. Erythromycin was the antibiotic found mostly in superficial waters with an

average concentration of 1.60 μg L^{-1}, 0.772 μg L^{-1}, and 0.546 μg L^{-1}, respectively, in spring, summer, and winter.

Matongo et al. (2015) investigated the presence of pharmaceuticals, such as sulfamethazine, sulfamethoxazole, erythromycin, metronidazole, trimethoprim, acetaminophen, caffeine, carbamazepine, clozapine, and ibuprofen in the Umgeni River, in the Durban city in KwaZulu-Natal, South Africa. Clozapine was found in higher concentrations (78.33 μg L^{-1}) followed by ibuprofen (62.0 μg L^{-1}).

Machado et al. (2016) investigated the presence of emerging contaminants of different classes in 100 samples of potable water in 22 Brazilian capitals, and seven water sources from most populated areas in the country. The samples were collected between June and September of 2011 and again in the same period of 2012. Among the emerging contaminants, caffeine was the substance most commonly found, detected in 93% of the potable water samples, and in 100% of the surface waters. Caffeine concentration in potable water varied from 1.8 ng L^{-1} to 2 μg L^{-1}, while in water sources, the concentrations varied from 40 ng L^{-1} to about 19 μg L^{-1}. The fact that caffeine is found in potable water indicates that there is still reminiscent of domestic wastewater contamination in potable water distribution since this is typically an anthropogenic compound. Similar results were found in studies carried out in China (Leung et al. 2013) and Spain (Boleda et al. 2011).

On the other hand, Watkinson et al. (2009) analyzed the presence of 28 antibiotics in hospital wastewaters, WWTP effluent, surface waters, and drinking waters and found that although the presence of antibiotics was seen in every sample, including surface water used as drinking water extraction sites, none of the antibiotics analyzed were found in drinking water samples. Thus, the samples collected from 81 different surface water and 20 different drinking water sites within South-East Queensland (Australia) pointed out that the treatment applied to the drinking water supplied to the population was satisfactory for antibiotic removal, which represents hopes in developing adequate treatment and distribution protocol for the critical areas.

The most delicate part of these studies relies on identifying adequately the presence of the compounds on the intake and output of the WWTP. In this sense, an innovative research developed by Sgroi et al. (2017) used fluorescence data of three-dimensional excitation—emission matrixes (EEM) to analyze treatment efficiency of 10 WWTP facilities in Sicily (Italy) using 11 target compounds. These WWTP presented secondary treatments varying from activated sludge units with nitrification and denitrification processes, activated sludge units without nitrification and rotating biological contactors, or even extended aeration activated sludge unit (Kumari et al. 2016; Saxena et al. 2017). All compounds were removed in a range from 28 to 82%; however, due to treatment efficiencies varying among the WWTPs proposed, the development of rapid, low-cost, and highly specific studies like these enable the tailoring of systems more adequately addressing the influent for every matrix it presents.

Finally, all the studies mentioned contamination found in untreated wastewater and/or the persistent contamination found after the effluent exits the WWTP. However,

considering that, for example, one in four households in the United States relies on septic systems for wastewater disposal, further investigation on the direct influence of this route is also necessary. Yang et al. (2017b) studied the fate of pharmaceuticals in septic systems considering drain fields of drip dispersal, gravel trench, and advanced system. Although the septic systems can treat partially the compounds analyzed, it also serves as an accumulation point for their byproducts. Additionally, these accumulation points infiltrate to groundwater contaminating the water source, which was confirmed in this study by identifying seven markers directly below the septic systems studied.

1.3 Ecotoxicological Effects

Other than toxicological effects related to direct exposure to pharmaceuticals, a concerning process occurring is the increase in microbial resistance normally caused by interaction with human and animal bacterial species, exposure to bacteria present in hospital, farms and home care, and finally interaction with bacteria present in sewage and biological wastes (Mishra and Bharagava 2016; Pereira et al. 2017; Gavrilescu et al. 2015).

Analyzing pharmaceutical ecotoxicological effect is normally carried out in laboratorial environment based on acute toxicity tests to a certain compound. The most commonly used organisms are fishes *Danio rerio* and *Pimephales promelas* and the crustaceous *Daphnia magna*, using standard methods measuring the concentrations that cause oxidative stress and/or mortality to the organism tested. One of the most common methods used is the effect concentration 50% (EC_{50}), which determines the concentration in which adverse effect is noted in 50% of the individuals (Petrie et al. 2014; Galus et al. 2013). Therefore, a compound is considered harmful when its EC_{50} is between 10 and 100 mg L^{-1}, toxic at 1–10 g L^{-1}, and highly toxic when <1 mg L^{-1} (Petrie et al. 2014). However, data comparison in literature is very complicated due to the specific compounds and species tested, as well as the variety of toxicological endpoints studied. Table 1.3 shows the EC_{50} found for a group of compounds tested using organisms *D. magna, V. fischeri, A. flos-aque, P. subcapitata, S. vacuolatus, and S. obliquus*.

Various factors affect the toxicity of certain compounds, and due to the sensitive nature of the species analyzed, variables such as temperature, pH, salinity, and turbidity, need to be considered as well (Yadav et al. 2019; Mani and Bharagava 2016). Mostly, for pharmaceutical contamination, the main factor affected is the pH of the water bodies. Recent studies by Liu et al. (2016) analyzed the toxicity of sulfadiazine to *Daphnia magna*, in various pH presenting toxicity increments up to 15-folds in EC50, when pH reduced from 8.5 to 6.0. Similar results had been previously reported by Anskjær et al. (2013), finding 11-fold increment in EC50 with the same pH variation, relating the specific transformation from its neutral form at pH 6.0 to its negatively charged form at pH 8.5.

Table 1.3 Estimations of the effective concentration (EC_{50}) for several organisms exposed to a variety of pharmaceutical compounds

Compound tested	Organism tested	Endpoint	Toxicity (mg L^{-1})	References
Sulfadiazine	*D. magna*	24 h EC_{50}	48.89	Liu et al. (2016)
		48 h EC_{50}	11.93	
Diclofenac	*D. magna*	24 h EC_{50}	3.18	Czech et al. (2014)
	V. fischeri	48 h EC_{50}	2.69	
	D. magna	14.04	14.04	
Chloramphenicol	*V. fischeri*	24 h EC_{50}	5	
	D. magna	48 h EC_{50}	5	
		27.06	27.06	
Metoprolol	*V. fischeri*	24 h EC_{50}	2.59	
		48 h EC_{50}	2.59	
		14.48	14.48	
Oxytetracycline	*Anabaena flos-aque*	72 h ErC_{50}	2.7	Kolar et al. (2014)
	Pseudokirchneriella subcapitata	72 h ErC_{10}	1.5	
	Daphnia magna	72 h ErC_{50}	1.04	
		72 h ErC_{10}	0.47	
Trimethoprim	*Anabaena flos-aque*	48 h EC_{50}	669[a]	
	Pseudokirchneriella subcapitata	48 h EC_{10}	197	
	Daphnia magna	72 h ErC_{50}	253	
		72 h ErC_{10}	26	
		72 h ErC_{50}	129	
		72 h ErC_{10}	65	
		48 h EC_{50}	100	
		48 h EC_{10}	66	

(continued)

Table 1.3 (continued)

Compound tested	Organism tested	Endpoint	Toxicity (mg L^{-1})	References
Sulfamethoxazole + sulfamethazine	*Scenedesmus vacuolatus*	72 h EC_{50}	19.52	Xiong et al. (2018)
	Scenedesmus obliquus	96 h EC_{50}	0.108	
Diclofenac	*D. magna*	24 h EC_{50}	82.3	Du et al. (2016)
		48 h EC_{50}	18.1	
		72 h EC_{50}	6.23	
Ibuprofen	*D. magna*	24 h EC_{50}	116	
		48 h EC_{50}	23.5	
		72 h EC_{50}	8.33	

[a]Value exceeded water solubility

Additionally, it is common to find that the by-product formed after degradation of the original pharmaceutical is many times more toxic for the studied organism than its previous form. For example, Dirany et al. (2012) analyzed the degradation of sulfachloropyridazine by electro-Fenton treatment and further analyzed the toxicity of the target compound and two of its oxidation by-products, namely amino-6-chloropyridazine and *p*-benzoquinone. Analyzing the toxicity in *V. fischeri*, they found EC_{50} of 1.96 mg L^{-1} for sulfachloropyridazine and <0.01 mg L^{-1} for *p*-benzoquinone and over 250 mg L^{-1} for 6-chloropyridazine. Considering the degradation chain follows the sequence sulfachloropyridazine > 6-chloropyridazine > *p*-benzoquinone, a sharp increase in toxicity is seen in an intermediary step of the treatment, which is a common finding when treating pharmaceuticals (Coledam et al. 2017).

Nevertheless, study on bioaccumulation of pharmaceuticals and their effects on the health of the species exposed to them is still a field to be widely researched. Cheng et al. (2017) reported the bioaccumulation of sulfadiazine in Chinese mitten crab (*E. sinensis*), finding rates of <3 ng/g, not dose-dependent. These researches increase the understanding of the secondary effects promoted by the environmental contamination of these compounds and aid in the development of new treatment protocols and risk identification.

Another particularly interesting study was developed by Mohd Zanuri et al. (2017) analyzing the effects of short-term exposure to realistic values of ibuprofen, diclofenac, and sildenafil citrate of selected specimens: echinoderms (*Asterias rubens* and *Psammechinus miliaris*) and a polychaete worm *Arenicola marina*. From the compounds analyzed, diclofenac was more toxic than the others reducing sperm swimming speed and fertilization success in *A. rubens*. Exposure to sildenafil

citrate (commercially known as Viagra®) actually enhanced sperm motility, which increased fertilization success in the echinoderms, which also did not present toxicity effects for this organism. Case studies like these are important to highlight the various toxic effects possible in environmental conditions.

Additionally, one of the main problems in estimating the toxicity of real effluents is that in many processes and in urban scenarios, the organisms are exposed to a complex mixture of compounds, and it is difficult to estimate EC_{50} for the compounds found. For example, Bielen et al. (2017) studied the effluents from two pharmaceutical companies in Croatia, collecting samples in four different periods throughout the year, analyzing seasonal effects. Sample one contained mostly azithromycin and erythromycin, while sample two contained sulfonamides, fluoroquinolones, tetracyclines, and β-lactams. *D. rerio* specimens were exposed to the effluent as in loco (after undergoing a membrane reactor treatment) and 2× diluted and 4× diluted. Mortality rates for the effluent from Company 1 as in loco were 100%, showing improvement to as low as 20% only after a 4× dilution. Meanwhile, the specimens exposed to effluent from Company 2 varied from under 10% mortality to no mortality after dilution. Studies like these highlight the complexity of ecotoxicity tests in case of pharmaceutical contamination supporting the need for Predicted No Effect Concentrations (PNECs) for all compounds being emitted in the environment.

1.4 Alternative Treatments

1.4.1 Microalgal

Studies developed in Spain by Hom-Diaz et al. (2017) analyzed the effectiveness of a tubular microalgae reactor for toilet wastewater treatment system for pharmaceutical removal. The system consisted of 1200 L microtubular tanks and a constant stirring velocity of 0.13 m s^{-1}, analyzing the system efficiency in two periods of the year (period 1: September 14 to October 16; period 2: October 20 to December 22), in order to analyze both seasonal effects and possible variations in population's consumption of pharmaceuticals. These studies also analyzed two hydraulic retention times of 8 and 12 days. In general, the system was able to remove 98% of the anti-inflammatory drugs, 48% of antibiotics, and between 30 and 57% of the psychiatric drugs, proving effectiveness for this proposed system to remove pharmaceuticals present in natural wastewaters.

Furthermore, extensive research has been carried out by Xiong et al. (2018) gathering the latest studies on microalgae used to remove pharmaceuticals from water sources in microalgae-mediated bioremediation, highlighting the possibility of solar energy use, eco-friendliness, and its low cost. The research classified microalgae treatment in bioadsorption, bioaccumulation, and biodegradation. Bioadsorption is highly recommended for pharmaceuticals with cationic groups that are actively attracted to the microalgae surface due to electrostatic interaction. Bioaccumulation

that is the uptake of substrates has been proven successful with specific pharmaceuticals like carbamazepine (Xiong et al. 2016). Finally, biodegradation was found to be the most common route for pharmaceutical removal by microalgae treatment, finding removal rates of up to 80% of active compounds according to the literature (Xiong et al. 2018).

When considering microalgae removal rates, a series of factors come into play, as seen in recent studies developed by Xiong et al. (2019), where sulfamethoxazole and sulfamethazine were combined at various concentrations and submitted to microalgae degradation with *S. obliquus*. While seeking to understand the degradation route of the compounds studied, it was possible to note that the degradation of sulfamethazine was considerably improved with the addition of sulfamethoxazole. By determining the degradation routes present, it was confirmed that *S. obliquus* was able to promote hydroxylation, methylation, deamination, and bond cleavage, all of which could contribute to the understanding and determination of the potential applications of this specific organism.

Microalgae is, therefore, one of the proposed solutions for pharmaceuticals removal from water bodies and various wastewaters. Mostly, the recent trends involve combined processes where the system is optimized by a previous or posterior microalgae treatment. In this sense, studies on integrating microalgae with advanced oxidation processes (AOPS) (Keen et al. 2012), constructed wetlands (Ding et al. 2016), and microbial fuel cells (Li et al. 2014) are being performed.

1.4.2 Advanced Oxidation Processes (AOP)

Contamination with certain pharmaceuticals due to their specific properties and high stability are typically hard to address. In this sense, the AOPs are known to be an effective indiscriminate method to strongly oxidase the most organic compounds. Furthermore, even in cases where the target compound is not totally degraded, the addition of hydroxyl groups to the parent molecule facilitates ring opening by certain catechol dioxygenase enzymes produced by heterotrophic bacteria being a critical step in biotransformation of aromatic compounds (Keen et al. 2012).

Ozonation, UV, photocatalysis, and Fenton reaction have been used for the treatment of potable water and to a lesser extent in wastewater disinfection. It has been reported that WWTPs equipped with AOPs were capable of eliminating pharmaceutical compounds, such as caffeine and sulfamethoxazole, at efficiencies of 89.5% and 92.2%, respectively (Lin et al. 2016).

Among the AOPs available, UV treatment is used as one of the main disinfection techniques in European Wastewater Treatment Plants considering its high disinfection capacity with no addition of chemicals required (Song et al. 2016). In a sense, the treatment efficiencies in WWTP have not been thoroughly addressed due to variations in environmental concentrations and specific operatiing conditions that are typically difficult to simulate in lab-scale reactors. However, Paredes et al. (2018) researched the fate of 12 different pharmaceuticals, analyzing UV dose, temperature, and water

matrix in order to determine the real applicability of the UV treatment. The effluents tested were collected from four different WWTP in Spain, UV dose varied from 12 to 44 mJ/cm^2, and contaminant concentration was spiked at environmentally relevant concentrations (10 μg L^{-1}). Phototransformation was seen in most compounds in rates varying from 60 to 92%, with a considerable increase in degradation when the temperature was altered from 15 to 25 °C.

Although Paredes et al. (2018) found high rates of degradation for recalcitrant compounds (such as diclofenac and diazepam), the phototransformation of the pharmaceuticals in full-scale system is almost negligible due to the low doses of UV applied in the system, also impaired by variables such as total suspended solids, dissolved organic matter, and nitrate concentration. These results suggest that the UV method, once it is present in most WWTP as a disinfection procedure, could be a viable route to improve the removal rates of pharmaceuticals if combined with catalytical processes.

In this sense, Keen et al. (2012) analyzed the degradation of carbamazepine, a well-known and very persistent drug prescribed for epilepsy and other mental disorders, by combining UV/H_2O_2 and biodegradation. Their study determined that the initial UV/H_2O_2 attacking the compound with the hydroxyls formed and leading to the formation of assimilable organic carbon (AOC) enables the biofilm growth. Additionally, the UV/H_2O_2 coupled with a traditional WWTP could also provide higher levels of disinfection, possibly even removing the need for that additional final step from the process.

1.4.3 Adsorption

Basically, considering a physical treatment approach, adsorption is well known for being highly efficient, low cost, and easy operation and presents no risk of formation of toxic products. It can be applied as a batch process or in the form of fixed-bed columns that is easily scaled up (Ahmed and Hameed 2018).

Improvements in the physical structures of adsorbents are another approach to increase their effectiveness when treating effluents contaminated with pharmaceuticals. In that sense, Shan et al. (2017) supported graphene oxide (compound widely known for its adsorptive features) onto rigid fluorine-containing molecules (TFT or DFB) analyzing its capacity to adsorb carbamazepine, sulfamethoxazole, sulfadiazine, ibuprofen, paracetamol, and phenacetin solutions. The enhancements proposed by doping the graphene oxide on the DFB structure can increase the adsorption capacity by 1.0–15 times, highlighting the potential for the use of this technology efficiently adsorbing these molecules from water bodies.

Further, since adsorption is mostly dependent on particle size, other improvements can be done to enhance the adsorption rates, especially when treating nanoparticles. In this sense, procedures such as coagulation would ensure the separation of larger particles allowing the use of filtration systems with smaller pores. Thus, Sheng et al. (2016) combined an ultrafiltration system with coagulation and

powdered activated carbon pretreatment to address samples containing acetaminophen, bezafibrate, caffeine, carbamazepine, cotinine, diclofenac, gemfibrozil, ibuprofen, metoprolol, naproxen, sulfadimethoxine, sulfamethazine, sulfamethoxazole, sulfathiazole, triclosan, and trimethoprim. By developing this procedure, they noted that pharmaceuticals would bond to the activated carbon by weak Van der Walls attraction forces, which would be retained in the ultrafiltration system blocking the passage of further pharmaceuticals.

Sheng et al. (2016) studied the effects of coagulation, activated carbon, and ultrafiltration alone and combined, finding that for the individual technologies, rates of 50, 29, and 7% removal were found for the activated carbon, ultrafiltration, and coagulation alone, respectively. As for the proposed combined process of ultrafiltration with coagulation pretreatment showed an improvement of only 4% in removal rates. Finally, rates of 90.3% removal were found when combining ultrafiltration with activated carbon use.

When focusing on adsorption using activated carbon, researchers have found good removal rates, but due to the high cost of activated carbon, the reuse of these materials is of great concern. In this sense, Marques et al. (2017) analyzed the thermal regeneration of activated carbon in granular, powdered, and cloth forms studying the retention of chlorofibric acid and paracetamol. The materials were tested for absorption capacity and then submitted to thermal regeneration in 400 and 600 °C. The procedure was repeated after every adsorption experiment for four cycles. Among the materials tested, carbon felt presented the highest regeneration capacity maintaining its activity over 50% up to the second reuse, decreasing to fewer than 20% at the fourth reuse in both the temperature conditions. Although the results in these tests are interesting, the need to develop efficient recovering systems is one of the main limiting factors for the industrial application of adsorption as a route for pharmaceutical removal from effluents.

1.4.4 Enzymatic Bioreactor

Based on the enzymatic capacity to degrade certain chemicals, enzymatic bioreactors are controlled by pH, temperature, and enzyme innate features. Enzymes such as laccases are well known for degrading a wide variety of compounds and their ability to sustain drastic changes in pH. Taking into account the advantages of this degradation route, Asif et al. (2017) proposed the integration of laccase-based bioreactor with high retention membranes coupling the two systems and working with *Aspergillus oryzae (A. oryzae)* and *Trametes versicolor (T. versicolor)*, analyzing degradation and retention of sulfamethoxazole, carbamazepine, diclofenac, oxybenzone, and a pesticide (atrazine). Since degradation by laccase occurs due to the nature of functional groups present in the compounds (e.g., electron-donating capacities) and the relative redox potential of the laccase and the compounds, the findings were particularly analyzed for each compound studied. Considering the

combined treatment of membrane filtering and the enzymatic attack by the laccase use, all compounds were removed in rates varying from 50 to 100%.

Likewise, Ba et al. (2018) studied the efficiency of a hybrid bioreactor (HBR) of a combined cross-linked tyrosinase and laccase aggregates and hollow fiber microfiltration (MF) membrane to remove a mixture of 14 pharmaceuticals from municipal wastewater in concentrations at 10 μg L^{-1}. They reported that after a 5-day continuous operation, the HBR achieved >90% efficiency for the elimination of the 14 selected pharmaceuticals at environmental concentration. This outstanding result was attributed to a synergistic action between insolubilized enzymes and membranes. Moreover, the biocatalyst retained nearly 70% of its initial enzymatic activity over the treatment period. In this sense, HBR was proven as an adequate method to treat these compounds inviting the scientific community to further investigate its applicability for the continuous treatment of wastewater.

1.5 Conclusion

To date, discussions on the environmental and human risk of exposure to pharmaceutical contaminants are still in serious debate. It is safe to say that although many studies developing toxicity tests have proven that many pharmaceuticals in low concentration do not impose a risk for human health, in long-term exposure the effective risk of these compounds is still to be properly assessed. Finally, as our understanding of pharmaceutical contamination increases, it becomes clear that certain measurements should be considered. First, the parent compounds are found in the environment mostly due to inadequate disposal of the products; however, their metabolites occur as a natural process of the incomplete consumption by the organism and are frequently as physiologically active as their parent compound. Therefore, special attention should be given to these compounds as well focusing on applying for the advances in wastewater treatment to ensure environmental safety for the following years as the use of pharmaceuticals increases.

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References

Afonso-Olivares C, Sosa-Ferrera Z, Santana-Rodrígues JJ (2017) Occurrence and environmental impact of pharmaceutical residues from conventional and natural wastewater treatment plants in Gran Canaria (Spain). Sci Total Environ 559–600:934–943

Ahmed MJ, Hameed BH (2018) Removal of emerging pharmaceutical contaminants by adsorption in a fixed-bed column: a review. Ecotoxicol Environ Saf 149:257–266

Anskjær GG, Rendal C, Kusk KO (2013) Effect of pH on the toxicity and bioconcentration of sulfadiazine on Daphnia magna. Chemosphere 91:1183–1188

Archer E, Petrie B, Kasprzyk-Hordern B et al (2017) The fate of pharmaceuticals and personal care products (PPCPs), endocrine disrupting contaminants (EDCs), metabolites and illicit drugs in a WWTW and environmental waters. Chemosphere 174:437–446

Asif MB, Nguyen LN, Hai FI et al (2017) Integration of an enzymatic bioreactor with membrane distillation for enhanced biodegradation of trace organic contaminants. Int Biodeterior Biodegrad 124:73–81

Azzouz A, Ballesteros E (2013) Influence of seasonal climate differences on the pharmaceutical, hormone and personal care product removal efficiency of a drinking water treatment plant. Chemosphere 93:2046–2054

Ba S, Jones JP, Cabana H (2018) A hybrid bioreactor based on insolubilized tyrosinase and laccase catalysis and micro filtration membrane remove pharmaceuticals from wastewater. Chemosphere 201:749–755

Balakrishna K, Rath A, Praveenkumarreddy Y et al (2017) A review of the occurrence of pharmaceuticals and personal care products in Indian water bodies. Ecotoxicol Environ Saf 137:113–120

Bharagava RN, Saxena G, Mulla SI, Patel DK (2018) Characterization and identification of recalcitrant organic pollutants (ROPs) in tannery wastewater and its phytotoxicity evaluation for environmental safety. Arch Environ Contam Toxicol 75(2):259–272

Bielen A, Šimatović A, Kosić-Vukšić J et al (2017) Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. Water Res 126:79–87

Boleda MR, Huerta-fontela M, Ventura F et al (2011) Evaluation of the presence of drugs of abuse in tap waters. Chemosphere 84:1601–1607

Cheng L, Chen Y, Zheng YY et al (2017) Bioaccumulation of sulfadiazine and subsequent enzymatic activities in Chinese mitten crab (Eriocheir sinensis). Mar Pollut Bull 121:176–182

Chowdhary P, Raj A, Bharagava RN (2018) Environmental pollution and health hazards from distillery wastewater and treatment approaches to combat the environmental threats: a review. Chemosphere 194:229–246

Coledam DAC, Pupo MMDS, Silva BF et al (2017) Electrochemical mineralization of cephalexin using a conductive diamond anode: a mechanistic and toxicity investigation. Chemosphere 168:638–647

Comber S, Gardner M, Sörme P et al (2018) Active pharmaceutical ingredients entering the aquatic environment from wastewater treatment works: a cause for concern ? Sci Total Environ 613–614:538–547

Cotillas S, de Vidales MJ, Llanos J et al (2016) Electrolytic and electro-irradiated processes with diamond anodes for the oxidation of persistent pollutants and disinfection of urban treated wastewater. J Hazard Mater 319:93–101

Czech B, Jo I, Oleszczuk P (2014) Ecotoxicological evaluation of selected pharmaceuticals to *Vibrio fischeri* and *Daphnia magna* before and after photooxidation process. Ecotoxicol Environ Saf 104:247–253

Ding H-Y, Feng Y-J, Lu J-W (2010) Study on the service life and deactivation mechanism of Ti/SnO2-Sb electrode by physical and electrochemical methods. Russ J Electrochem 46:72–76

Ding Y, Wang W, Liu X et al (2016) Intensified nitrogen removal of constructed wetland by novel integration of high rate algal pond biotechnology. Bioresour Technol 219:757–761

Dirany A, Sirés I, Oturan N et al (2012) Electrochemical treatment of the antibiotic sulfachloropyridazine: kinetics, reaction pathways, and toxicity evolution. Environ Sci Technol 46:4074–4082

Du J, Mei CF, Ying GG et al (2016) Toxicity thresholds for diclofenac, acetaminophen and ibuprofen in the water flea Daphnia magna. Bull Environ Contam Toxicol 97:84–90

Galus M, Kirischian N, Higgins S et al (2013) Chronic, low concentration exposure to pharmaceuticals impacts multiple organ systems in zebrafish. Aquat Toxicol 132–133:200–211

Gautam S, Kaithwas G, Bharagava RN, Saxena G (2017) Pollutants in tannery wastewater, their pharmacological effects and bioremediation approaches for human health protection and

environmental safety. In: Bharagava RN (ed) Environmental pollutants and their bioremediation approaches. CRC Press, Taylor & Francis Group, Boca Raton, pp 369–396
Gavrilescu M, Katerina D, Aamand J et al (2015) Emerging pollutants in the environment: present and future challenges in biomonitoring, ecological risks and bioremediation. N Biotechnol 32:147–156
Gogoi A, Mazumder P, Tyagi VK et al (2018) Occurrence and fate of emerging contaminants in water environment: a review. Groundw Sustain Dev 6:169–180
Guedes-alonso R, Afonso-olivares C, Montesdeoca-esponda S, et al (2013) An assessment of the concentrations of pharmaceutical compounds in wastewater treatment plants on the island of Gran Canaria 2:1–8
Hom-Diaz A, Jaén-Gil A, Bello-Laserna I et al (2017) Performance of a microalgal photobioreactor treating toilet wastewater: pharmaceutically active compound removal and biomass harvesting. Sci Total Environ 592:1–11
K'oreje KO, Kandie FJ, Vergeynst L et al (2018) Occurrence, fate and removal of pharmaceuticals, personal care products and pesticides in wastewater stabilization ponds and receiving rivers in the Nzoia Basin, Kenya. Sci Total Environ 637–638:336–348
Kay P, Hughes SR, Ault JR et al (2017) Widespread, routine occurrence of pharmaceuticals in sewage effluent, combined sewer overflows and receiving waters. Environ Pollut 220:1447–1455
Keen OS, Baik S, Linden KG et al (2012) Enhanced biodegradation of carbamazepine after UV/H2O2 advanced oxidation. Environ Sci Technol 46:6222–6227
Kim SD, Cho J, Kim IS et al (2007) Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. Water Res 41:1013–1021
Kim S, Chu KH, Al-Hamadani YAJ et al (2018) Removal of contaminants of emerging concern by membranes in water and wastewater: a review. Chem Eng J 335:896–914
Kleywegt S, Pileggi V, Yang P et al (2011) Pharmaceuticals, hormones and bisphenol A in untreated source and finished drinking water in Ontario, Canada—occurrence and treatment efficiency. Sci Total Environ 409:1481–1488
Kolar B, Arnuš L, Jeretin B et al (2014) The toxic effect of oxytetracycline and trimethoprim in the aquatic environment. Chemosphere 115:75–80
Kot-Wasik A, Jakimska A, Śliwka-Kaszynska M (2016) Occurrence and seasonal variations of 25 pharmaceutical residues in wastewater and drinking water treatment plants. Environ Monit Assess 188:661
Kumari V, Yadav A, Haq I, Kumar S, Bharagava RN, Singh SK, Raj A (2016) Genotoxicity evaluation of tannery effluent treated with newly isolated hexavalent chromium reducing Bacillus cereus. J Environ Manag 183:204–211
Kümmerer K (2001) Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources—a review. Chemosphere 45:957–969
Leung HW, Jin L, Wei S et al (2013) Pharmaceuticals in tap water: human health risk assessment and proposed monitoring framework in China. Environ Health Perspect 121:839–846
Li W-W, Yu H-Q, He Z (2014) Towards sustainable wastewater treatment by using microbial fuel cells-centered technologies. Energy Environ Sci 7(3):911–924
Lin T, Yu S, Chen W (2016) Occurrence, removal and risk assessment of pharmaceutical and personal care products (PPCPs) in an advanced drinking water treatment plant (ADWTP) around Taihu Lake in China. Chemosphere 152:1–9
Liu K, Xu S, Zhang M et al (2016) Estimation of the toxicity of sulfadiazine to Daphnia magna using negligible depletion hollow-fiber liquid-phase microextraction independent of ambient pH. Sci Rep 6:4–11
Luo Y, Guo W, Ngo HH et al (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
Machado KC, Tadeu M, Vidal C et al (2016) A preliminary nationwide survey of the presence of emerging contaminants in drinking and source waters in Brazil. Sci Total Environ 572:138–146
Mandaric L, Diamantini E, Stella E et al (2017) Contamination sources and distribution patterns of pharmaceuticals and personal care products in Alpine rivers strongly affected by tourism. Sci Total Environ 590–591:484–494

Mani S, Bharagava RN (2016) Exposure to crystal violet, its toxic, genotoxic and carcinogenic effects on environment and its degradation and detoxification for environmental safety. Rev Environ Contam Toxicol 237:71–104

Marques SCR, Marcuzzo JM, Baldan MR et al (2017) Pharmaceuticals removal by activated carbons: role of morphology on cyclic thermal regeneration. Chem Eng J 321:233–244

Marsik P, Rezek J, Zidkov M et al (2017) Non-steroidal anti-inflammatory drugs in the watercourses of Elbe basin in Czech Republic. Chemosphere 171:97–105

Matongo S, Birungi G, Moodley B (2015) Occurrence of selected pharmaceuticals in water and sediment of Umgeni River, KwaZulu-Natal, South Africa. Environ Sci Pollut Res Int 22(13):10298–10308

Mezzelani M, Gorbi S, Regoli F (2018) Pharmaceuticals in the aquatic environments: evidence of emerged threat and future challenges for marine organisms. Mar Environ Res 140:41–60

Mishra S, Bharagava RN (2016) Toxic and genotoxic effects of hexavalent chromium in environment and its bioremediation strategies. J Environ Sci Health C 34(1):1–32

Mohd Zanuri NB, Bentley MG, Caldwell GS (2017) Assessing the impact of diclofenac, ibuprofen and sildenafil citrate (Viagra®) on the fertilisation biology of broadcast spawning marine invertebrates. Mar Environ Res 127:126–136

Mompelat S, Le Bot B, Thomas O (2009) Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water. Environ Int 35:803–814

Paredes L, Omil F, Lema JM et al (2018) What happens with organic micropollutants during UV disinfection in WWTPs? A global perspective from laboratory to full-scale. J Hazard Mater 342:670–678

Pereira AMPT, Silva LJG, Meisel LM et al (2015) Environmental impact of pharmaceuticals from Portuguese wastewaters: geographical and seasonal occurrence, removal and risk assessment. Environ Res 136:108–119

Pereira AL, de Vasconcelos Barros RT, Pereira SR (2017) Pharmacopollution and Household Waste Medicine (HWM): how reverse logistics is environmentally important to Brazil. Environ Sci Pollut Res 24:24061–24075

Petrie B, Barden R, Kasprzyk-Hordern B (2014) A review on emerging contaminants in wastewaters and the environment: current knowledge, understudied areas and recommendations for future monitoring. Water Res 72:1–25

Puckowski A, Mioduszewska K, Łukaszewicz P et al (2016) Bioaccumulation and analytics of pharmaceutical residues in the environment: a review. J Pharm Biomed Anal 127:232–255. http://linkinghub.elsevier.com/retrieve/pii/S073170851630111X

Purdom CE, Hardiman PA, Bye VJ et al (1994) Estrogenic effects of effluents from sewage treatment works. Chem Ecol 8:275–285

Rivera-Utrilla J, Sánchez-Polo M, Ferro-García MÁ et al (2013) Pharmaceuticals as emerging contaminants and their removal from water. A review. Chemosphere 93(7):1268–1287

Saxena G, Bharagava RN, Kaithwas G, Raj A (2015) Microbial indicators, pathogens and methods for their monitoring in water environment. J Water Health 13(2):319–339

Saxena G, Chandra R, Bharagava RN (2017) Environmental pollution, toxicity profile and treatment approaches for tannery wastewater and its chemical pollutants. Rev Environ Contam Toxicol 240:31–69

Scott T, Phillips PJ, Kolpin DW et al (2018) Pharmaceutical manufacturing facility discharges can substantially increase the pharmaceutical load to U.S. wastewaters. Sci Total Environ 636:69–79

Sgroi M, Roccaro P, Korshin GV et al (2017) Use of fluorescence EEM to monitor the removal of emerging contaminants in full scale wastewater treatment plants. J Hazard Mater 323:367–376

Shan D, Deng S, Li J et al (2017) Preparation of porous graphene oxide by chemically intercalating a rigid molecule for enhanced removal of typical pharmaceuticals. Carbon 119:101–109

Sheng C, Nnanna AGA, Liu Y et al (2016) Removal of Trace Pharmaceuticals from Water using coagulation and powdered activated carbon as pretreatment to ultrafiltration membrane system. Sci Total Environ 550:1075–1083

Song K, Mohseni M, Taghipour F (2016) Application of ultraviolet light-emitting diodes (UV-LEDs) for water disinfection: a review. Water Res 94:341–349

Stuart M, Lapworth D, Crane E et al (2012) Review of risk from potential emerging contaminants in UK groundwater. Sci Total Environ 416:1–21

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

Tijani JO, Fatoba OO, Babajide OO et al (2016) Pharmaceuticals, endocrine disruptors, personal care products, nanomaterials and perfluorinated pollutants: a review. Environ Chem Lett 14:27–49

USGS, Survey UG (2014) Emerging contaminants in the environment. http://toxics.usgs.gov/regional/emc/

Verlicchi P, Al Aukidy M, Zambello E (2012) 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

Visanji Z, Sadr SMK, Memon FA (2018) An implementation of a decision support tool to assess treatment of emerging contaminants in India. J Water Resour Prot 10:422–440

Watkinson AJ, Murby EJ, Kolpin DW et al (2009) The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. Sci Total Environ 407:2711–2723

Xiong JQ, Kurade MB, Abou-Shanab RAI et al (2016) Biodegradation of carbamazepine using freshwater microalgae Chlamydomonas mexicana and Scenedesmus obliquus and the determination of its metabolic fate. Bioresour Technol 205:183–190

Xiong JQ, Kurade MB, Jeon BH (2018) Can microalgae remove pharmaceutical contaminants from water? Trends Biotechnol 36:30–44

Xiong JQ, Kim SJ, Kurade MB et al (2019) Combined effects of sulfamethazine and sulfamethoxazole on a freshwater microalga, Scenedesmus obliquus: toxicity, biodegradation, and metabolic fate. J Hazard Mater 370:138–146

Yadav A, Mishra S, Kaithwas G, Raj A, Bharagava RN (2016a) Organic pollutants and pathogenic bacteria in tannery wastewater and their removal strategies. In: Singh JS, Singh DP (eds) Microbes and environmental management. Studium Press (India) Pvt. Ltd, New Delhi, pp 104–130

Yadav A, Raj A, Bharagava RN (2016b) Detection and characterization of a multidrug and multimetal resistant Enterobacterium Pantoea sp. from tannery wastewater after secondary treatment process. Int J Plant Environ 1(2):37–41

Yadav A, Raj A, Purchase D, Ferreira LFR, Saratale GD, Bharagava RN (2019) Phytotoxicity, cytotoxicity and genotoxicity evaluation of organic and inorganic pollutants rich tannery wastewater from a Common Effluent Treatment Plant (CETP) in Unnao district, India using Vigna radiata and Allium cepa. Chemosphere 224:324–332

Yang Y, Ok YS, Kim K-H et al (2017a) 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

Yang YY, Toor GS, Wilson PC et al (2017b) Micropollutants in groundwater from septic systems: transformations, transport mechanisms, and human health risk assessment. Water Res 123:258–267

Yao L, Wang Y, Tong L et al (2017) Occurrence and risk assessment of antibiotics in surface water and groundwater from different depths of aquifers: a case study at Jianghan Plain, central China. Ecotoxicol Environ Saf 135:236–242

Zainith S, Purchase D, Saratale GD, Ferreira LFR, Bilal M, Bharagava RN (2019) Isolation and characterization of lignin-degrading bacterium Bacillus aryabhattai from pulp and paper mill wastewater and evaluation of its lignin-degrading potential. 3 Biotech 9(3):92

Zhang Y, Wang B, Cagnetta G et al (2018) Typical pharmaceuticals in major WWTPs in Beijing, China: occurrence, load pattern and calculation reliability. Water Res 140:291–300