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Environmental impact and biological removal processes of pharmaceutically active compounds: The particular case of sulfonamides, anticonvulsants and steroid estrogens

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ABSTRACT

Pharmaceutically active compounds (PhACs) have recently received wide attention in the scientific community due to their extensive consumption for human health and consequent discharge to the environment. Release of PhACs into the environment, even in trace amounts, can cause serious environmental damage. This has become a major concern and their removal from water sources is a priority. Although a few PhACs are efficiently removed in wastewater treatment plants (WWTPs), others remain recalcitrant, and their release is causing damage. In this review, the current state of the art on the biological removal processes of sulfonamide sulfamethoxazole (SMX), the anticonvulsant carbamazepine (CBZ), and steroid estrogens 17β-estradiol (E2) and 17α-ethinylestradiol (EE2) are discussed, along with their environmental impact. Other systems beyond activated sludge, such as membrane bioreactors, enzymatic membrane reactors, fungi treatments and hybrid systems are also becoming of major interest and are being evaluated for the removal of these compounds. Future perspectives are addressed.

1. Introduction

PhACs are an emerging concern worldwide. The European Union (EU) is the second biggest consumer in the World, with 24% of the total consumption, just a little less than the United States of America. Consumption per capita in EU ranges from 50 to 150 g year^{-1} for human medical products (Mugdal et al., 2013). About 4000 PhACs are used around the World for many purposes, with production rates reaching up to 100,000 tons year^{-1} for a number of them (IWW, 2014).

Regarding the particular case of the anticonvulsant, carbamazepine (CBZ), the world's annual consumption is estimated at 1,014 tons (Zhang, Geißen, & Gal, 2008). With respect to the total amount of discharged natural steroid estrogens (estrone – E1, estriol – E2 and 17β-estradiol – E3), it is estimated in 29.5 tons year^{-1} (considering the world's population of 6.7 billion inhabitants). Moreover, 720 kg year^{-1} of synthetic estrogens (17α-ethinylestradiol – EE2) are also released solely by contraceptive pills used (Combalbert & Hernandez-Raquet, 2010). Antibiotics consumption increased 65% between 2000 and 2015, from 21.1 to 34.8 billion daily doses (DDDs) and the consumption rate also increased 39% (from 11.3 to 13.7 DDDs inhabitant^{-1} day^{-1}; Klein et al., 2018). The total amount of antibiotics is estimated between 100,000 and 200,000 ton year^{-1} with approximatively 50% used for veterinary medicine and as growth promoters (Kümmerer, 2003; Danner, Robertson, Behrends, & Reiss, 2019), sulfonamides being one of the most commonly used for veterinary purposes (Sarmah, Meyer, & Boxall, 2006a).

1.1. PhACs in wastewaters

PhACs are commonly present in domestic sewages largely because of human excretion. Indeed, some of these compounds are not completely metabolized during their therapeutic use and are excreted unchanged (Mohapatra, Brar, Tyagi, Picard, & Surampalli, 2014). PhACs are nowadays considered as an emerging environmental problem due to their continuous release into and persistence in the aquatic ecosystem, even at low concentrations (Carabin, Drogui, & Robert, 2015). Concern about this release in recent decades is growing; the extent of their effects remains relatively unknown, due to lack of standard methods of quantification. This is considered a major challenge in water resources management (Geissen et al., 2015).

The interest of studying PhACs in full-scale wastewater treatment plants (WWTPs) has been increasing over the last decades, mainly due to the large amounts of PhACs that can be present. Although some of these compounds can mostly be removed, a few cannot, causing a number of serious environmental and human health problems due to their recalcitrance. In this sense, sulfonamide antibiotics, anticonvulsants, and steroid estrogens are 3 major PhACs classes of particular interest and concern due to their extensive use in human health.

1.2. PhACs metabolism in the human body

The most common antibiotics found in WWTPs cover a wide range of classes, such as β-lactams, quinolones, lincosamides, macrolides, tetracyclines, polyether ionophores, polypeptides, sulfonamides and others (Watkinson,

Murby, & Costanzo, 2007). The sulfonamide sulfamethoxazole (SMX) is widely applied as a broad-spectrum bacteriostatic drug because it interferes with folic acid synthesis in susceptible bacteria. SMX is used all over the world for the treatment of bronchitis, prostatitis and urinary tract infections (Lipman, 1993; Cavallucci, 2007). It should also be stressed that SMX is usually used in combination with trimethoprim for increased reduction of tetrahydrofolic acid synthesis (Drugbank, 2016b). The mechanism of action of SMX involves the inhibition of the bacterial synthesis of dihydrofolic acid, thus decreasing the synthesis of bacterial nucleotides and DNA. It inhibits the enzymatic conversion of pteridine and p-aminobenzoic acid (PABA) to dihydropteroic acid by competing with PABA for binding to dihydrofolate synthetase. As a result, it inhibits the tetrahydrofolic acid synthesis required for purines and deoxythymidine monophosphate (dTMP) synthesis, thus affecting bacterial growth.

The metabolism of SMX in the human body is largely hepatic and occurs predominately by N4-acetylation (N4-acetyl-SMX), although glucorination (SMX-N1-Glu, SMX-2-Glu) also occurs (Drugbank, 2016b). Significant amounts (45–75%) of ingested sulfonamides are excreted by the human body within 24 h, thus entering WWTPs through the sewage systems and being found in surface waters (Calamari, Zuccato, Castiglioni, Bagnati, & Fanelli, 2003; Radke, Lauwigi, Heinkele, MüRdter, & Letzel, 2009). Regarding the specific case of SMX, it should be stressed also that 15 to 30% is excreted unaltered from humans (Hirsch, Ternes, Haberer, & Kratz, 1999, RxList, 2016b).

Anticonvulsants are a class of PhACs that act by reducing abnormal activity in the brain, and are applied in the treatment of mental illnesses, depression, post-traumatic stress disorders, and drug and alcohol dependencies, among others (Mohapatra et al., 2014). One of the most frequently detected anticonvulsant in water bodies is carbamazepine (CBZ) (Zhang et al., 2008), usually employed in the treatment of epilepsy, seizures, trigeminal neuralgia, diabetic neuropathy, bipolar disorder, and drug and alcohol dependencies, among others (RxList, 2016a; Drugbank, 2016a). The mechanism of action of CBZ involves inhibiting sustained repetitive firing by blocking use-dependent sodium channels, norepinephrine release, synaptic transmission in the trigeminal nucleus, and reduction of post-tetanic potentiation on the spinal cord synaptic transmission. It is also believed to possess anticholinergic, antidiuretic, antiarrhythmic, and antidepressant activity, thus acting as a muscle relaxant and sedative (Drugbank, 2016a).

The metabolism of CBZ in the human body leads to the formation of 10,11-epoxycarbamazepine (EP-CBZ) and 10,11-dihydro-10,11-trans-dihydroxycarbamazepine (DiOH-CBZ). The CBZ is transformed by the cytochrome P450 3A4 (CYP3A4) in the liver and possibly undergoes

glucuronidation by UDP-glucuronosyltransferase-2B7 (UGT2B7) isoenzyme. Only 3% of CBZ remains unchanged when excreted, and is mainly found in the urine, whereas their (mono)hydroxylated and conjugated metabolites can be found in the feces (RxList, 2016a; INCHEM, 2016; Toxnet, 2016).

Steroid hormones are a group of biologically active compounds synthesized from cholesterol and with a common cyclopentane-perhydro phenanthrene ring (Ying, Kookana, & Ru, 2002). Four of the estrogens most commonly found in wastewater include 3 natural steroids (17β-estradiol (E2), estrone (E1) and estriol (E3)) and one synthetic compound (17α-ethinylestradiol (EE2)) (Racz & Goel, 2010). E2 is a naturally occurring steroid hormone, being the major female sex hormone, and is essential factor in the regulation of the menstrual cycle, in the development of puberty and in secondary female sex characteristics. E2 can also be present in hormone therapy products, such as reduced estrogen production (menopausal and peri-menopausal symptoms), treatment of hypoestrogenism, palliative treatment of breast and prostate cancer, as well as for transgender hormone therapy (Drugbank, 2016c). EE2 is used mainly for the treatment of vasomotor symptoms associated with the menopause, female hypogonadism, prostatic carcinoma-palliative therapy, treatment of breast cancer, and contraceptive purposes (Drugbank, 2016d).

The mechanism of action of estrogens is based on the interaction with a protein receptor on the cells of the female reproductive tract, mammary glands, hypothalamus and pituitary gland. This leads to an increased synthesis of sex hormones binding globulins in the liver, thyroid-binding globulins and serum proteins, as well as the suppression of the follicle-stimulating hormone. Metabolism of estrogens in the human body is largely hepatic, mainly by aromatic hydroxylation (for both synthetic and natural estrogens); for instance, E2 is excreted in the urine along with glucuronide and sulfate conjugates. While glucuronide conjugates can be mostly removed, or transformed back to the original compounds, sulfate conjugates are likely found in treated wastewaters due their lower deconjugation rates.

With respect to the toxicity of E2 conjugates, more studies are needed to confirm the effect of these compounds in aquatic organisms (Drugbank, 2016c; Liu, Lu, Yin, Dang, & Rittmann, 2015, Zhang, Zhao, & Fent, 2017). E2 is one of 3 naturally occurring steroid estrogens produced by the human body. Females excrete on average more E2 than males (2.9 and 1.6 μg day^{-1}, respectively), with menstruating (3.5 μg day^{-1}) and pregnant (259 μg day^{-1}) women excreting particularly large amounts of this natural estrogenic compound (Johnson, Belfroid, & Di Corcia, 2000; Wise, O'Brien, & Woodruff, 2011). Regarding EE2, the main metabolite is 2-hydroxy-

ethinylestradiol, but a number of other hydroxylated and methoxylated metabolites can also be found in the free form or as sulfates and conjugated glucuronides (Drugbank, 2016d). The major source of EE2 excretion is urine, in contrast with feces where large *E. coli* populations are able to deconjugate EE2 metabolites due to their β-glucuronidase and sulfatase activities (Dray, Dray, & Ullmann, 1972; Desbrow, Routledge, Brighty, Sumpter, & Waldock, 1998).

This review outlines the importance, strategies, and efficiency of the removal processes of the sulfonamide SMX, the anticonvulsant CBZ, and the estrogens E2 and EE2 in biological wastewater treatment (WWT) systems. With the concerns discussed above, accordingly SMX, CBZ, E2 and EE2 have in particular been addressed in this review, covering the main sources of these PhACs, and their impacts in soils, surface waters, aquatic biota and human health. Furthermore, the impact of PhACs on microbial communities in the WWTPs is far from negligible and, for that reason, this topic will be also discussed.

Several studies have already shown that conventional activated sludge (CAS) treatment in WWTPs is inefficient for the removal of a large number of PhACs (Hirsch et al., 1999; Joss et al. 2006). Based on this information, different technologies have been studied and applied to obtain a sustainable removal of PhACs, including membrane reactors (MBR), enzymatic membrane reactors (EMR) and hybrid systems (HS), among others (Salgado et al., 2012; Mohapatra et al., 2014; Petrie, Barden, & Kasprzyk-Hordern., 2015; Grandclément et al., 2017; Tiwari et al., 2017; Besha et al., 2017; Ahmed et al., 2017). Although knowledge of the relationship between the WWTPs operational conditions and the removal efficiencies of PhACs has been increasing, further information on the cost-benefit aspects of these technologies are of major interest to achieve full-scale implementation. Therefore, we will also be discussed herein the future perspectives and challenges regarding the sustainable removal of these compounds.

2. Sources and environmental impact assessment of PhACs

SMX, CBZ, E2 and EE2 can flow into WWTPs from hospital activities, clinical analysis laboratories and industrial activities such as pills production in the pharmaceutical industry (Cui, Ji, & Ren, 2006; Avberšek, Šömen, & Heath, 2011; Zhou, Zha, Xu, Lei, & Wang, 2012). Moreover, the surface waters distributed to the urban environment, even when treated in water treatment plants (WTP), may contain considerable amounts of these PhACs (Ting & Praveena, 2017), which later contaminate soils and aquifers. Figure 1 shows the main sources of SMX, CBZ, E2 and EE2 flowing into a WWTP, as well as the dissemination of these compounds in different
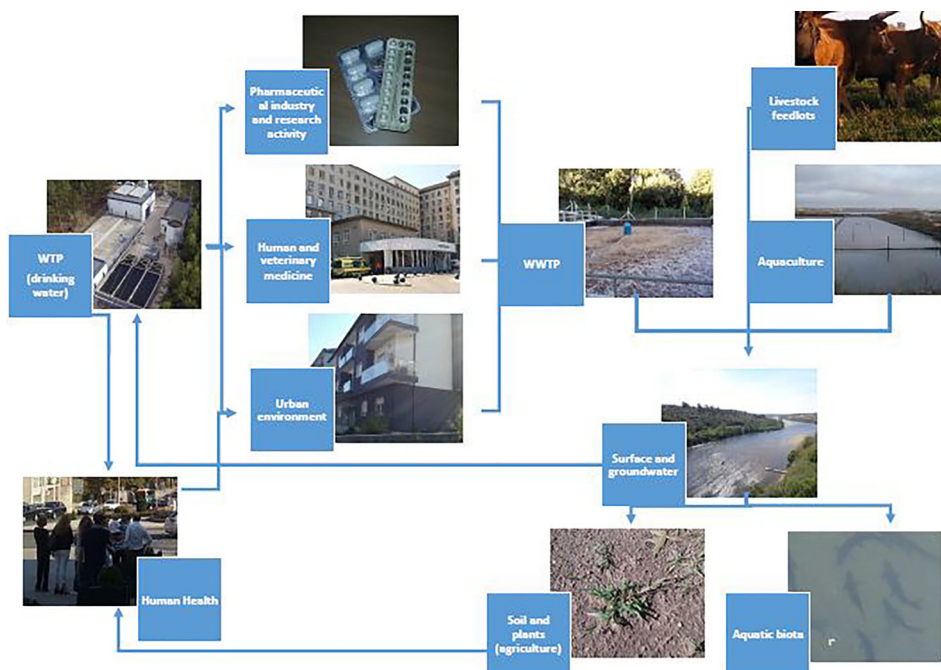
Figure 1. SMX, CBZ, E2 and EE2 in different environmental compartments (Ting & Praveena, 2017).

environmental compartments, including water, wastewater, soils and aquatic biota.

PhACs are been commonly found in ground waters, surface waters, treated wastewaters, and even drinking waters, in concentrations up to tens of nanograms per liter for E2, hundreds of nanograms per liter regarding SMX, up to $1\,\mathrm{mg\,L^{-1}}$ for EE2, and even $>1\,\mathrm{mg\,L^{-1}}$ for CBZ. The concentrations SMX, CBZ, E2 and EE2 in aquatic systems reported by others are given in Table 1. Furthermore, a wide variety of PhAC conjugated metabolites may undergo deconjugation in the environment, being transformed back to their original forms (Celiz, Tso, & Aga, 2009).

The ecotoxicity of PhACs is usually assessed by means of the Lowest Observed Effect Concentration (LOEC) and Predicted No-Effect Concentration (PNEC). Table 2 gives further information about the PNEC and the LOEC for the toxicity assessment of SMX, CBZ, E2 and EE2. CBZ had LOEC values ranging from hundreds of micrograms per liter in arthropods and rotifers and up to tens of milligrams per liter in fish (Ferrari, Paxéus, Lo Giudice, Pollio, & Garric, 2003). With respect to the PNEC, values as low as a few nanograms per liter for E2 (Anderson et al., 2012), and even lower for EE2 (Laurenson, Bloom, Page, & Sadrieh, 2014), were found in aquatic life. Ma and Yates (2018) found that 17ß-estradiol-3-sulfate (E2-3S) conjugate is more persistent in rivers and streams than 17ß-estradiol-3-glucuronide (E2-3G) conjugate. However, since the ecotoxicity of these

Table 1. Concentrations of SMX, CBZ, E2 and EE2 in aquatic systems.

Compound	Concentration	Type of water	References
SMX	Around 410 ng L^{-1}	Ground water	Sacher, Lange, Brauch, and Blankenhorn (2001)
	Around 480 ng L^{-1}	Surface water	Hirsch et al. (1999)
	Around 66 ng L^{-1}	Drinking water	Mückter (2006)
CBZ	390 ng L^{-1} (max)	Ground water	Loos et al. (2010)
	Above 1 µg L^{-1}	Surface water	Wiegel et al. (2004)
	0.060 µg L^{-1}		Thill (2005)
	1075 ng L^{-1}		Heberer et al. (2002)
	0.650 ng L^{-1} (max)		Metcalfe et al. (2003b)
	30 ng L^{-1}	Drinking water	Ternes (1998)
	6.3 mg L^{-1}	WWTPs effluents	Ternes (1998)
	2.3 µg L^{-1} (max)	Discharged wastewater	Metcalfe et al. (2003)
E2	1 to 22 ng L^{-1}	WWTPs	Pal, Gin, Lin, and Reinhard (2010)
	0 to 4.5 ng L^{-1}	River streams	Pal et al. (2010)
EE2	0 to 9 µg L^{-1}	Treated wastewater	Baronti et al. (2000)
	831 µg L^{-1} (max.) and 73 µg L^{-1} (avg.)	Stream water	Kolpin et al. (2002)

Table 2. PNEC and LOEC regarding SMX, CBZ, E2, and EE2 toxicity assessment.

Compound	LOEC	PNEC	References
SMX	n.a	0.59 µg L^{-1} for aquatic life	Straub (2016)
	n.a	0.89 µg L^{-1} for aquatic life	Huang et al. (2018)
	1.97 nmol L^{-1} for river biofilms communities	n.a	Yergeau, Lawrence, Waiser, Korber, and Greer (2010); Yergeau et al. (2012)
Avetyl-SMX	n.a	28 ng L^{-1} for Vidu bay in lake Geneva	Bonvin, Chevre, Rutler, and Kohn (2012)
SMX-Glu	n.a	28 ng L^{-1} for Vidu bay in lake Geneva	Bonvin et al. (2012)
CBZ	100 µg L^{-1}, 754 µg L^{-1} and 50 mg L^{-1} for C. dubia, B. calyciflorus and D. rerio respectively	n.a	Ferrari et al. (2003)
	n.a	6.359 µg L^{-1} for daphnids	Jones, Voulvoulis, and Lester (2002)
EP-CBZ	n.a	2500 ng L^{-1} for Vidu bay in lake Geneva	Bonvin et al. (2012)
DiOH-CBZ	n.a	2500 ng L^{-1} for Vidu bay in lake Geneva	Bonvin et al. (2012)
Acridone	1.44–3.07 mg L^{-1} and 1.09 mg L^{-1} for V. fischeri and P. subcapitata respectively	n.a	Donner et al. (2013)
E2	n.a	5 ng L^{-1} (short term on fish)	Anderson et al. (2012)
	n.a	2 ng L^{-1} (long term on fish)	Anderson et al. (2012)
	Below 8.94 ng L^{-1}, below 28.8 ng L^{-1} and below 85.9 ng L^{-1} for medaka, fathead minnow, and zebrafish respectively	n.a	Seki, Fujishima, Nozaka, Maeda, and Kobayashi (2006)
	n.a	2 ng L^{-1}	Caldwell, Mastrocco, Anderson, Lange, and Sumpter (2012)
EE2	n.a	0.1 ng L^{-1} for aquatic life	Pawlowski, Van Aerle, Tyler, and Braunbeck (2004); Laurenson et al. (2014)
	1 ng L^{-1} for fathead minnow	n.a	Pawlowski et al. (2004)

n.a – Not available

compounds remains unknown, further studies are needed. SMX also has low PNEC values, <1 microgram per liter, for aquatic life (Straub, 2016). However, the toxicity values of PhACs reported in the literature should be carefully analyzed since the results are strongly dependent on the species involved, and whether *in vitro* or *in vivo* assays are used (Laurenson et al., 2014).

2.1. Sulfonamides

Sulfonamides, including SMX, are widely prescribed and used to treat animals and humans all over the world with its acetylated and conjugated compounds posing an environmental risk (Hruska & Franek, 2012). Although Andreozzi, Raffaele, and Nicklas (2003) report that direct and indirect photodegradation can be an important process for the elimination of SMX, these compounds are only partially degraded in the environment; as a result, they are likely to accumulate in water bodies such as ground waters, surface waters and drinking waters in amounts up to hundreds of nanograms per liter (Table 1). On the other hand, acetylsulfamethoxazole, a SMX metabolite that may be transformed back to the parent form, has been detected at concentrations approaching 100 ng L^{-1} in WWTPs effluents and river streams (Göbel, McArdell, Suter, & Giger, 2004; Ashton, Hilton, & Thomas, 2004). Moreover, the concentrations of these antibiotics in WWTPs varies according to the consumption patterns, as well as the treatment methodology (Michael et al., 2013).

The effects of SMX in aquatic life remains poorly understood, and lacks information of the potential consequences of this antibiotic in the environment due to waste water discharge or reuse (Watkinson et al., 2007). Lin, Chen, and Chen (2013) showed the toxic effects of sulfonamides (including SMX), even at low concentrations, on the spontaneous movements, heartbeats and malfunctions of zebra fish embryos and larvae. SMX exposure can also lead to changes on the zebra fish liver (Madureira et al., 2012). Exposure of zebra fish to sulfonamides (including SMX) has also been related to pericardial edema, York sac edema hemagglutination, tail deformation and swim-bladder defects (Lin et al., 2013). SMX and SMX-transformation products (SMX-TP) resulting from the SMX biodegradation, photolysis or hydrolysis in the aquatic environment can also have acute effects on *Vibrio fischeri*, leading to inhibition of luminescence. However, the effects of SMX-TP seem to be lower than their parent compound (Majewsky et al., 2014). On the other hand, Osorio et al. (2016) showed that SMX had no individual acute toxicity on *V. fischeri* and *Daphnia magna* (using standardized acute toxicity tests), although synergic effects were determined with *Diclofenac* and nitro *Diclofenac* derivatives. However,

the mechanism behind these effects is poorly understood. Bisphenol A, humic acid and E2 also have a synergistic interaction with SMX leading to an increase of estrogenicity in water bodies by up to 5-fold (Ali, 2014).

The long-term persistence of antibiotics (at low concentrations) in the environment can promote the proliferation of antibiotic resistant bacteria in river streams and, thus stimulate microorganism drug resistance (Martinez, 2008; Watkinson, Murby, Kolpin, & Costanzo, 2009). Detection of sulfonamide resistance genes in river microorganisms and aquatic biofilm communities (Luo et al., 2010; Koczura, Mokracka, Taraszewska, & Łopacinska, 2016; Aubertheau et al., 2017), alongside the prevalence of SMX-resistant bacteria in aquaculture environments (Gao et al., 2012), have been correlated to the total SMX concentration, among other sulfonamides, in those environments. On the other hand, some investigations have shown that the bacterial resistance develops more slowly when trimethoprim and sulfamethoxazole are combined rather than when they are used alone (Drugbank, 2016b; Vilchèze & Jacobs, 2012). The fact that TMP and SMX target successive steps of the folate biosynthesis pathway can be the reason for this behavior. Whereas SMX inhibits dihydropteroate synthase TMP targets dihydrofolate reductase in the bacterial *de novo* folate synthesis pathway (Vilchèze & Jacobs, 2012).

Besides their impact in aquatic biota, SMX, among others sulfonamides, were also found in soil (Wang et al., 2015), with their sorption behavior being related to soil properties, such as the presence of manure or organic carbon source, and to the pH. In agricultural runoff waters resulting from biosolids introduction in soils, SMX deconjugation can also lead to increased concentrations of the SMX parent form with time (Topp et al., 2008). Another important issue that is closely related to the presence of SMX in soils is the effect of this compound in their microbial community. In this sense, Demoling, Bååth, Greve, Wouterse, and Schmitt (2009) showed that SMX initially decreased growth rates of sensitive bacterial species in the soil (assessed by leucine incorporation). SMX showed also an apparent correlation with the soil microbial diversity, measured by the Shannon-Winner index, the Pielou's evenness index and Simpson's index of diversity (Wang et al., 2016). Simpson's index of diversity indicates the probability of 2 individuals from an infinitely large community belonging to the same species, with higher values showing the predominance of fewer species, and consequently lower biodiversity. The Shannon-Winner index increases with biodiversity, attributing a higher importance to rare than to common species (Magurran, 2004).

Different SMX effects in soil-plant systems have already been detected, for instance their higher rate accumulation in radish than in packoi cultures, and an apparent correlation with seed germination and up-ground

plant growth (Wang et al., 2016). According to Liu et al. (2009), root elongation was sensitive to SMX (and sulfamethazine) during plant germination and growth. These antibiotics also inhibited soil phosphatase activity, as well as affecting temporal changes on soil respiration. However, these authors also considered that the expected effects regarding plant growth and soil microbial activities may be mild, and show a quick recovery due to loss and/or binding of SMX on to soil components. On the other hand, Brain, Ramirez, Fulton, Chambliss, and Brooks (2008) showed that SMX could disrupt the synthesis of folate and the substrate of dihydropteroate synthase in *Lemma giba*, using p-aminobenzoic acid as a biomarker. Due to its properties, SMX dissolves in cell membranes and is released into the cytosol in plants (Goldstein, Shenker, & Chefetz, 2014). More recently, Christou et al. (2019) has proved that tomatoes can uptake and accumulate SMX in hydroponic conditions, increasing their carbohydrate content. However, different results were obtained by Wu, Conkle, Ernst, and Gan (2014), who did not detect SMX in plant tissues, or in fields irrigated with treated wastewater. Despite the amount of information in the literature, further research is needed to address the effects of SMX in plants.

Regarding human health as a result of chronic exposure to environmental antibiotics, Hamscher, Pawelzick, Sczesny, Nau, and Hartung (2003) have stresed that a large number of antibiotics can give rise to allergic risks. Indeed, with respect to sulfonamides, a number of investigations have reported these allergic effects of sulfamethazine (Hjorth & Roed-Petersen, 1980; Choquet-Kastylevsky, Vial, & Descotes, 2002). Although no SMX effects alone have been thoroughly reported, Pomati et al. (2006) refer to the inhibition of human embryonic kidney cells at concentrations of nanograms per liter for a mixture of antibiotics containing sulfamethoxazole. On the other hand, Straub (2016) stated that no risk is apparent for indirect human exposure to SMX through drinking water and food, whereas Uslu, Jasim, Arvai, Bewtra, and Biswas (2013) came to the same conclusion regarding water bodies. However, this is not the case for sulfamethazine, which has the potential to increase thyroid gland follicular adenoma (Leung et al., 2013).

2.2. Anticonvulsants

As already mentioned, CBZ is widely applied as an anticonvulsant in epilepsy and in the treatment of drug and alcohol dependencies, among others applications. In the environment, CBZ can undergo a slow process of photodegradation (estimated half-life ∼100 days) in waters free of salt and organic compounds (Andreozzi et al., 2003). In WWTPs, the photolysis step of UV treatment can also lead to a mixture of different carbamazepine

transformation products, such as acridine and acridone (Donner et al., 2013); however, biotransformation has been recognized as the main elimination mechanism of CBZ, though retransformation from its conjugated metabolites can impair this process (Polesel, Andersen, Trapp, & Plósz, 2016).

Several studies have shown that conventional biological WWT systems are ineffective in removing CBZ (Bahlmann, Weller, Panne, & Schneider, 2009; Bahlmann, Brack, Schneider, & Krauss, 2014; Kruglova et al., 2014); for this reason, CBZ is the most common PhAC found in aquatic systems, including surface and ground waters (Clara, Strenn, & Kreuzinger, 2004) (Table 1). In fact, according to Ternes (1998) and Heberer, Reddersen, and Mechlinski (2002), CBZ has been detected at up to 6.3 mg L^{-1} in WWTPs effluents (Ternes, 1998), above 1 µg L^{-1} in surface waters (Wiegel et al., 2004), up to 390 ng L^{-1} in ground waters (Loos et al., 2010) and up to 30 ng L^{-1} in drinking waters (Ternes, 1998). On the other hand, metabolites such as EP-CBZ, carbamazepine-10,11-dihydrodiol, 2-hydroxycarbamazepine and 3-hydroxycarbamazepine can be present in concentrations exceeding 1 µg L^{-1} in treated wastewaters, and up to 2 ng L^{-1} in surface waters (Miao & Metcalfe, 2003).

CBZ can be potentially harmful, even toxic, to aquatic life at concentrations below 100 mg L^{-1}. However, toxicity levels are quite dependent on the test organisms (Fent, Weston, & Caminada, 2006). Assessment of the ecotoxicological impact of CBZ in aquatic biota showed decreases in *D. magna* mobility and *V. fischeri* bioluminescence (Jos et al., 2003). Moreover, *Allium cepa* and *Chlorella vulgaris* have been affected by CBZ exposure (at up to 1000 µmol L^{-1} of CBZ), with their growth decreasing with contact time and CBZ concentration (Jos et al., 2003). Similar results have also been found by others regarding the CBZ toxic effect in fish liver tissue (Madureira et al., 2012) and in embryos. van den Brandhof and Montforts (2010) showed a clear negative effect on *Danio rerio* growth at concentrations >30.6 mg L^{-1}.

Regarding the ecotoxicity of CBZ's main metabolites, EP-CBZ was significantly more toxic (LC$_{50}$ of 0.20 mg Kg^{-1}) to *Chironomus riparius* than CBZ (LC$_{50}$ of 1.20 mg Kg^{-1}), assessed by the 40-day sediment full life-cycle test. With respect to the EP-CBZ metabolite and its transformation products, fetal malformations in mice have also been described (Bennett et al., 1996). In addition, the decrease of *V. fischeri* bioluminescence, the inhibition of *Pseudokirchneriella subcapitata* growth and the decrease of *D. magna* mobility have also been reported for acridine and acridone, resulting from the photolysis step of UV treatment (Donner et al., 2013). On the contrary, no toxic effects have been reported so far for DiOH-CBZ (Heye et al., 2016).

Bioassays of ecotoxicity have also run on bacteria, algae, microcrustaceans and fish to estimate their PNEC and assess risk. Ferrari et al., (2003) concluded that CBZ seems to be more hazardous than the other PhACs, which is further emphasized considering that CBZ was the sole PhAC appearing in all of the WWTPs that were examined.

Regarding chronic effects, most of the data so far refers to those of CBZ on the hormonal and nervous systems in lower vertebrates and invertebrates (Ferrari et al., 2003; Thill, 2005). Others have shown that chronic effects (lasting over generations), as well as synergic effects with other chemicals, cannot be excluded (Jos et al., 2003; Lamichhane, Garcia, Huggett, Deangelis, & La Point, 2013). In fact, Ferrari et al. (2003) determined a LOEC of $100 \, \mu g \, L^{-1}$ for *Ceriodaphnia dubia,* $754 \, \mu g \, L^{-1}$ for *Brachionus calyciflorus* and $50 \, mg \, L^{-1}$ for *D. rerio*. Indeed, WWTPs discharges containing CBZ can have a profound effect on aquatic biofilms communities through fixation of this compound (Aubertheau et al., 2017). Furthermore, several effects can occur (even over generations) when CBZ is released into the environment, including fixation in sediments and profound effects in insects (such as Chironomids) affecting food webs. In this sense, life-cycle tests are quite fundamental in minimizing CBZ risks to the environment (Nentwig, Oetken, & Oehlmann, 2004).

CBZ is also one of the most studied PhACs in soils, with many researches trying to understand its behavior (including the interactions with organic materials) in several types of soils (Stein, Ramil, Fink, Sander, & Ternes, 2008; Navon, Hernandez-Ruiz, Chorover, & Chefetz, 2011; Fenet et al., 2012; Foolad, Hu, Tran, & Ong, 2016; Paz et al., 2016). CBZ has a lower sorption affinity and a higher diffusion in soils compared to the parent compounds, EP-CBZ and DiOH-CBZ, and it can be easily transported from soil surfaces to aquifers (Paz et al., 2016). In fact, similar results were obtained when treated wastewater was used for the irrigation of soils and recharging of artificial aquifers (Fenet et al., 2012).

Regarding the effect of the chronic exposure to CBZ in water and food products on the human health, Uslu et al. (2013), among others, have suggested no apparent risks regarding the concentrations of CBZ found in these sources. On the other hand, the 2-hydroxycarbamazepine metabolite may lead to the formation of 2-hydroxyiminostilbene, and later to iminoquinone, which, ultimately, can be responsible for carbamazepine-mediated adverse drug reactions in humans (Ju & Uetrecht, 1999).

2.3. Steroid estrogens

Estrogens present in the environment in concentrations up to hundreds of micrograms per liter can have a large impact on human and animal health

(Stumpe & Marschner, 2007). Since human excretion is a major source of the estrogens found in domestic wastewaters, the amount of estrogens, and namely EE2, depends of several factors, including gender, hormonal and menstrual state, pregnancy and contraceptive use (Johnson & Sumpter, 2001).

WWTPs effluents could be seen as one of the major sources of E2 and EE2 in surface and ground waters (Table 1) due to its inefficient removal (Braga, Smythe, Schäfer, & Feitz, 2005), alongside livestock manure and aquaculture (Sarmah, Meyer, et al., 2006b; Kolodziej, Harter, & Sedlak, 2004). In fact, several studies have shown that a considerable fraction of the polar metabolites of E2 and EE2 can be cleaved in WWTPs, resulting in discharge of the initial compounds (Panter, Thompson, Beresford, & Sumpter, 1999; Ternes et al., 1999; D'Ascenzo et al., 2003). On the other hand, Temes, Andersen, Gilberg, and Bonerz (2002) stressed that adsorption to sludge is important role in their removal from wastewaters. Consequently, the disposal of animal manure, wastewater, and sewage sludge to agricultural land can lead to the transfer of steroid hormones, including E2 and EE2, into soils, surface and ground waters (Stumpe & Marschner, 2007). Another major source of steroid estrogens comes from the urban environment, mainly from human excretion, being released into WWT systems in either conjugated or unconjugated forms at micrograms per person and day levels (Johnson & Sumpter, 2001; Johnson & Williams, 2004).

Although the excreted estrogen conjugates are mostly considered to be biologically inactive, they may be converted back to their parent estrogens in the environment (Celiz et al., 2009). For instance, Ternes et al. (1999b) have already reported the deconjugation of 17β-estradiol-17β-D-glucuronide and 17β-estradiol-3β-D-glucuronide in activated sludge slurries, with increases in E1 and E2 concentrations. Glucuronide metabolite deconjugation in domestic wastewaters also occurs (D'Ascenzo et al., 2003). β-glucuronidase and arylsulfatase enzymes of *E. coli* (abundant in activated sludge) can deconjugate glucuronide and sulfate conjugates back to their active estrogen forms (Ternes et al., 1999; Matejicek, Houserova, & Kuban, 2007).

Investigation of the effect of E2 in soils shows that its mineralization occurs co-metabolically and is limited by sorption, whereas testosterone seems to be utilized directly by soil microorganisms (Stumpe & Marschner, 2007). Stumpe and Marschner (2007) found that E2 is more strongly sorbed into the soil matrix than testosterone. Regarding the biodegradation of E2 and EE2 in soils, it has been found that, despite their structural similarities, bacteria can cause E2 mineralization whereas EE2 seems to be mineralized by white-rot fungi (Stumpe & Marschner, 2009).

Several environmental impacts could be related to exposure to E2 and EE2 affecting aquatic biota, soils, surface and ground waters (among

others). Indeed, bodies of water with high estrogen levels, including downstream WWTPs effluents, may have a pronounced effect on aquatic species, leading to fish being feminized (McAvoy, 2008). Estrogens can deregulate and interfere with normal biological responses by mimicking natural hormones and disrupting signal pathways, like endocrine disrupters. Chronic exposure of fathead minnows (*Pimephales promelas*) to low E2 concentrations (5 to 6 ng L^{-1}) feminize males through the production of vitellogenin (VTG) mRNA (evidenced by intersex changes in males), impact on gonadal development, and altered oogenesis in females (Kidd et al., 2007). EE2 also had the same effect (Bila & Dezotti, 2007). Moreover, estrogens (including E2 and EE2) and their mimics can cause severe damage to fish populations, as shown by the rapid decrease fish stocks in contaminated lakes (Bila & Dezotti, 2007; Kidd et al., 2007). Furthermore, fish reproductive rate can be reduced over 3 generations (Cripe et al., 2009), and Bila and Dezotti (2007) stated that E2 can affect egg production in turtles, as well as inducing blood VTG content.

Concerning the effect of the chronic exposure to contaminant estrogens in water and food products on humans, Swan, Liu, Overstreet, Brazil, and Skakkebaek (2007) found that hormones (used as growth promoters) were responsible for the reduction of the sperm count in the male offspring of women with a high red meat regime during gestation. Indeed, a number of studies have already shown that, over the past 60 years, the average sperm count in some countries has halved and the incidence of 33 malformations on the male reproductive system has doubled. Chronic exposure of adult males to estrogenic substances may result in breast growth and interference with the hypothalamus, pituitary and gonadal glandular systems, resulting in decreased libido, impotence, decreased androgen levels in the blood and decreased sperm count (Auger, Kunstmann, Czyglik, & Jouannet, 1995; Waring & Harris, 2005). Furthermore, contaminant estrogens, with relevance to EE2, are thought to induce some diseases, such as uterus, breast and prostate cancer, male fertility reduction, abnormal sexual development, abnormal thyroid glands, increased polycystic ovaries incidence, disturbances in ovarian functions, fertilization and pregnancy, endometriosis and neurobehavioral effects (Soto, Justicia, Wray, & Sonnenschein, 1991; Adeel, Song, Wang, Francis, & Yang, 2017; Verbinnen, Nunes, & Vieira, 2010; Birnbaum & Fenton, 2003; Coleman, Abdullah, Eggins, & Palmer, 2005; Solomon & Schettler, 2000; Gray, 1998; Daston et al., 1997). Finally, Sodré, Locatelli, Montagner, and Jardim (2007) emphasize that the embryonic stage is much more susceptible to estrogens compared to adults. Indeed, exposure at early stages of development can change developmental processes themselves, whereas at a more advanced stage they can solely interfere with reproduction or affect the offspring (Arcand-Hoy & Benson, 1998).

3. Impact of PhACs in the microbial communities of WWT systems

The main impacts of SMX, CBZ, E2, and EE2 in the microbial communities of biological WWT systems are discussed more fully in this section.

A few studies have already been conducted to understand the effect of SMX in microbial communities of WWTPs. Bacteria belonging to Betaproteobacteria and Gammaproteobacteria classes seemed to be the dominant species in WWT systems treating this compound (Cydzik-Kwiatkowska & Zielińska, 2016). Moreover, the disappearance of species belonging to the Sphingobacteria, Actinobacteria, Chloroflexi and Chlorobi classes suggests that these species are strongly affected by SMX in CAS systems (Collado et al., 2013). Similar results showed that bacteria belonging to Betaproteobacteria and Gammaproteobacteria were dominant in WWT systems with antibiotic removal using anoxic/oxic membrane biological reactor (A/O-MBR) processes. Indeed, monitoring *Thiothrix* spp. (Gammaproteobacteria) showed that the number of living cells increased due to its augmented antibiotic tolerance. However, in a different study (Novo, André, Viana, Nunes, & Manaia, 2013), the SMX concentration and the abundance of antibiotic resistant cultivable bacteria in raw wastewaters from full-scale WWTPs were positively correlated with the abundance of Epsilonproteobacteria in treated wastewater and negatively correlated with Gammaproteobacteria, Betaproteobacteria and Firmicutes.Guo, Pang, Dou, and Yin (2017) found that SMX and chemical oxygen demand (COD) could change the structures of bacterial community within a sequencing batch reactor (SBR). However, Simpson's index of diversity and the Shannon-Weiner index values showed no significant change in bacterial diversity by these compounds. The sludge retention time (SRT) significantly influences the relative numbers of nitrifying bacteria (Xia et al. 2012). These results suggest that SMX may affect removal of nitrogenous compounds from biological systems, reducing the efficiency of ammonia nitrogen disposal (Guo et al., 2017). Other data help in elucidating the fact that denitrification processes are more vulnerable than nitrification and carbon oxidization processes under SMX stress. Indeed, the relative abundance of denitrifiers decreased by 86% at a SMX concentration of $2000\,\mu g\,L^{-1}$ (Zhu et al., 2017).

Even though there is a significant lack of knowledge regarding the impact of anticonvulsants on microbial communities, according to Aubenneau, Tahar, Casellas, and Wisniewski (2010) some effects on both the respiratory activity of bacterial communities and on the bacterial agglomerate sizes could be related to CBZ exposure. And although no apparent inhibition occurs in the presence of $1\,\mu g\,L^{-1}$ of CBZ, the oxygen uptake rate (OUR) increased under endogenous conditions. A possible explanation lies in an increase in the maintenance requirements as a result

of CBZ-induced chemical stress. On the other hand, an OUR decrease was noted under exogenous conditions, which may be attributed to a change in the microbial community structure or the activity of individual species (Aubenneau et al., 2010). Cripe et al. (2009) found a negative effect of CBZ in the activity of the microbial communities of a MBR, leading to an initial OUR decrease, corresponding to the first CBZ dosing period. However, it was also noticed that from that moment onwards, the biomass behavior was quite similar with or without CBZ. Regarding the effect of CBZ in mixed microbial cultures (MMC) from full-scale WWTPs, growth inhibition was found relevant, being related to the CBZ concentration, especially under lower organic load conditions (Wang, Holzem, & Gunsch, 2008). These results suggest that further studies should be encompass the ecological impacts of CBZ in WWTPs with different biological systems.

Due to the persistence of EE2 in the environment, it is necessary to carefully identify the microorganisms able to degrade this compound, including metabolic processes involved (Cajthaml, Křesinová, Svobodová, Sigler, & Řezanka, 2009). Investigations are under way to better understand the effect of EE2 on activated sludge bacterial communities, and are showing that Firmicutes are negatively correlated with EE2 concentrations in a pilot scale reactor (Kruglova, Gonzalez-Martinez, Matilda Kråkström, Mikola, & Vahala, 2017). Other studies, conducted to understand the effect on activated sludge microbial communities caused by EE2 assimilation under both aerobic and anaerobic conditions showed that microbial diversity decreased (Wang, Tam, & Zhang, 2011). Furthermore, Proteobacteria were the predominant class (due to their EE2 biodegradation abilities), including *Pseudomonas thermotolerans, Rhodanobacter lindaniclasticus, Azonexus caeni* and *Rhodanobacter* sp. (Wang et al., 2011). As a result, EE2 biodegradation efficiencies were reported to be ~80% under both aerobic and anaerobic conditions.

Regarding the biodegradation ability of E2 and its effects on the microbial communities in WWT systems, Pholcan, Baptista, Davenport, Sloan, and Curtis (2013) showed that decreasing microbial diversity was associated with a decline in E2 removal.

Given the lack of further significant published research on the impact of sulfonamides (and other antibiotics), anticonvulsants, and steroid estrogens in the microbial communities of WWT systems, and particularly of full-scale systems, additional studies are needed on these points of major interest.

4. PhACs removal in biological WWT systems

The increasing concern about the environmental and human health risks of PhACs led to the development of several removal technologies for these

compounds, ranging from CAS, MBR and moving bed biofilm reactor (MBBR) systems to fungal and enzymatic treatments, among others (Badia-Fabregat, Oller, & Malato, 2017).

Among the most widely used, CAS and MBR systems have been 2 of the major options. In fact, MBR systems, which include biological degradation of organic matter coupled with membrane filtration, emerged during the last few years as a promising technology that surpass some of the limitations of the CAS treatment systems, such as limited SRT operational control and sludge settling (Radjenović et al., 2009). Taking this into consideration, the influence of operational and chemical parameters in CAS and MBR systems for PhACs removal will be addressed in the next section.

Knowledge of the PhACs key physicochemical properties seem to be relevant to the assessment of their removal efficiency in WWT systems (Stevens-Garmon, Drewes, Khan, McDonald, & Dickenson, 2011; Hyland, Dickenson, Drewes, & Higgins, 2012). Therefore, the most relevant physicochemical properties in this respect, including the water solubility and Log octanol-water coefficient (Log Kow) values for CBZ, SMX, E2 and EE2, are shown in the supplementary information (Tables 1–3). The Log Kow value has proved useful as a means of predicting biodegradation and sorption behavior (moderate sorption potential for organic compounds with Log Kow values between 2.5 and 4, and higher potential for values >4), for a number of different compounds (Martín, Camacho-Muñoz, Santos, Aparicio, & Alonso, 2012; Rogers, 1996).

PhACs removal from wastewaters is receiving more attention over the last few years mainly due to their large environmental impact in surface waters, aquatic biota and soils, due to their inefficient removal by traditional biological WWT systems. Several technologies have been used to remove PhACs, including CAS, MBR and EMR systems, hybrid technologies (involving a number of different systems, such as biofilms and suspended biomass), and treatment with the *Trametes versicolor* fungi, among others. Taking this into consideration, the main biological WWT technologies used for sulfonamides, anticonvulsants and steroid estrogens removal, both in pilot-scale reactors and full-scale plants, will be described below.

4.1. Full-scale WWTPs

A significant number of studies have tried to determine the removal efficiencies of PhACs on full-scale WWTPs. A literature survey of the main works encompassing SMX, CBZ, E2 and EE2 removal efficiencies in full-scale WWTPs is presented in Table 3.

Elimination of SMX has been investigated in full-scale WWTP with different biological WWT systems by Göbel, Thomsen, McArdell, Joss, and

Table 3. Studies encompassing SMX, CBZ, E2, and EE2 removal efficiencies in full-scale WWTPs.

Compound	Concentration	Load	Process type	Removal efficiency	References
SMX	Average of 430 ng L^{-1}	n.a.	AS	67%	Göbel et al. (2005)
	0.21 to 2.8 μg L^{-1}	n.a.	1 AS (two stage with a nitrification tank), 1 extended aeration, 1 RBC, 1 pure oxygen AS	48 to 75%	Batt, Kim, and Aga (2007)
	230 to 570 ng L^{-1}	n.a.	CAS / MBR* / FBR*	60–138%	Göbel et al. (2007)
	139 ng L^{-1}	n.a.	1 MBR*, 1 NF, 1 RO	>95% for NF and RO; MBR inefficient	Kim et al. (2007)
	n.a	40 mg day^{-1} per 1000 inhabitants	3 AS, 1 AS + UV	No removal	Zuccato, Castiglioni, Bagnati, Melis, and Fanelli (2010)
	Below 10^3 ng L^{-1}	n.a.	MBR	66%	Kim et al. (2014)
	4 to 8 to 3180 ng L^{-1}	Maximum load of 447 μg d^{-1} per person	2 A^2/O, 1 cyclic AS, 1 OD	7.5–61%	Yan et al. (2014)
	Maximum of 641 ng L^{-1}	n.a.	WWTP1 (OD + UV) WWTP2 (A^2/O-ClO$_2$-UV)	No removal in WWTP1 and 99% in WWTP2	Estrada-Arriaga et al. (2016)
	Below 5.3 μg L^{-1}	n.a.	AS	51-70%	de Jesus Gaffney et al. (2017)
	0.245 to 1.15 μg L^{-1} in CAS and 0.019 μg L^{-1} in CW**	n.a.	1 CAS, 1 CW	99.6–99.8% in CAS and negative (−100 %) removal in CW	Afonso-Olivares, Sosa-Ferrera, and Santana-Rodríguez (2017)
CBZ	n.a	n.a.	1 WWTP	Maximum of 8%	Heberer et al. (2002)
	0.7 μg L^{-1}	n.a.	1 WWTP with primary treatment 3 with tertiary treatment 10 with secondary treatment and 4 lagoons	<50 %	Metcalfe et al. (2003)
	226 ng L^{-1}	n.a.	1 MBR*, 1 NF, 1 RO	>95% for NF and RO; MBR inefficient	Kim et al. (2007)
	10 to 40 ng L^{-1}	n.a.	2 A^2/O, 1 cyclic AS, 1 OD	No removal in all WWTPs	Yan et al. (2014)
	20 μg L^{-1}	n.a.	1 WWTP and 1 SBR*	No biodegradation in all experiments	Kruglova et al. (2014)
	Above 500 ng L^{-1}	n.a.	MBR	28%	Kim et al. (2014)
	0 to 80 μg L^{-1}	n.a.	1 AS, 1 RBC, 1 CW, 1 WSP	Maxima of 10, 5, 37 and 73% in extended AS, RBC, CW and WSP, respectively	Matamoros, Rodríguez, and Albaigés (2016)
	Maximum of 167 ng L^{-1}	n.a.	WWTP1 (OD + UV) WWTP2 (A^2/O-ClO$_2$-UV)	No removal in WWTP1 and 33% in WWTP2	Estrada-Arriaga et al. (2016)
	0.82 to 6.5 μg L$^-$	n.a.	AS	51–70%	de Jesus Gaffney et al. (2017)
	0.284 to 0.763 μg L^{-1} in CAS and 0.281 to 3.03 μg L^{-1} in CW**	n.a.	1 CAS, 1 CW	7.0–58.4 % in CAS and 40% in CW	Afonso-Olivares et al. (2017)
E2	Maximum of 10.1 ng L^{-1}	n.a.	CAS	<20%	Martínez-Alcalà et al. (2017)
	1–30 ng L^{-1}.	n.a.	4 WWTPs with no biological treatment, 6 AS, 1 AS + biosorption, 3 TF, 1 biorotor, 2 AS + N removal, 1 TF/AS, 2 TF/AS + N removal	58–99% removal	Svenson, Allard, and Ek (2003)

Table 3. Continued.

Compound	Concentration	Load	Process type	Removal efficiency	References
	Above 1.0 ng L^{-1}	n.a.	1 MBR*, 1 NF, 1 RO	>95% for NF and RO; MBR inefficient	Kim et al. (2007)
	1.0–4.2 ng L^{-1}	n.a.	1 CAS, 2OD, 1 with bioreactors, 1 with aerobic lagoons	47–68%	Ying et al. (2008)
	Maximum of 1,1 ng L^{-1}	n.a.	1 AS N/D/P, 1 AS N/D	>90%	Koh et al. (2009)
	119 ng L^{-1}	n.a.	CAS	70–100%	Manickum and John (2014)
	Maximum of 44 ng L^{-1}	n.a.	WWTP1 (OD+UV) WWTP2 (A^2/O-ClO$_2$-UV)	99 and 100% in WWTP1 and WWTP2, respectively	Estrada-Arriaga et al. (2016)
EE2	0.003 µg L^{-1}	n.a.	AS	Maximum of 85 %	Baronti et al. (2000)
	1–30 ng L^{-1}	n.a.	4 WWTPs with no biological treatment, 6 AS, 1 AS+biosorption, 3 TF, 1 biorotor, 2 AS+N removal, 1 TF/AS, 2 TF/AS+N removal	58–99%	Svenson et al. (2003)
	1.3 ng L^{-1}	n.a.	1 MBR*, 1 NF, 1 RO	>95% for NF and RO; MBR inefficient	Kim et al. (2007)
	0.1–1.3 ng L^{-1}	n.a.	1 AS + 6 lagoons for tertiary treatment 1 with 2 OD+chlorination 1 AS+UV 1 with 10 anaerobic lagoons + 8 aerobic lagoons	No removal	Ying et al. (2008)
	Maximum of 0,2 ng L^{-1}	n.a.	1 AS N/D/P, 1 AS N/D	>90%	Koh et al. (2009)
	30 ng L^{-1}	n.a.	CAS	90%	Manickum and John (2014)

n.a. – not available; A^2/O – Anaerobic/anoxic/oxic reactor; FBR – Fixed bed reactor; RBC – Rotating biological contactor; WSP – Waste stabilization ponds; NF – Nanofiltration; RO – Reverse osmosis; *lab-scale; **concentrations data reported to sample points after grinding, for all WWTPs.

Giger (2005, Göbel, McArdell, Joss, Siegrist, & Giger, 2007) and Polesel et al. (2016) among others. Removal of SMX in full-scale WWTPs occurs mainly by biotransformation, though deconjugation of metabolites back to the parent form can have a negative effect on the removal efficiency (Polesel et al., 2016). In this sense, the most commonly studied conjugated metabolite of SMX in full-scale WWTPs is N4-acetyl-SMX (Göbel et al., 2007), and the sorption of this metabolite can be considered negligible due to its chemical properties (Polesel et al., 2016).

CBZ remains recalcitrant in full-scale WWTPs due to its high solubility and low distribution coefficient between wastewater and sludge (Kruglova et al., 2014; Odize et al., 2017; Clara et al., 2005). Moreover, similar results showing slight or no removal were obtained for CBZ and 5 of its metabolites (10,11-dihydro-10,11-dihydroxy-CBZ, 10,11-dihydro-10-hydroxy-CBZ, 10,11-epoxy-10,11-dihydro-CBZ, 2-hydroxy-CBZ and 3-hydroxy-CBZ) in German and Portuguese full-scale WWTPs (Bahlmann et al., 2014). On the other hand, full-scale constructed wetlands (CW) were useful for CBZ and SMX removal purposes (Gross, Montgomery-Brown, Naumann, & Reinhard, 2004; Matamoros, García, & Bayona, 2008; Hijosa-Valsero, Matamoros, Martín-Villacorta, Bécares, & Bayona, 2010; Anderson et al., 2013; Lee, Lee, Park, Kim, & Cho, 2013). Nevertheless, conflicting results have been reported by these authors, ranging from no effective removal of both compounds in a study conducted in Canada (Anderson et al., 2013), from 15 to 37% CBZ removal efficiencies in full-scale and surface flow CW reported in Spain (Hijosa-Valsero et al., 2010).

With respect to estrogens, removal efficiencies of >90% for E2 and EE2 in municipal WWTPs were obtained under both aerobic and anaerobic conditions (Joss, Andersen, Ternes, Richle, & Siegrist, 2004). However, whereas E2 was oxidized and further eliminated by a CAS system in a WWTP in Germany, EE2 remained mainly persistent according to Ternes et al. (1999). In addition, investigations evaluating different full-scale WWTPs technologies were crucial for a deeper understanding of the removal process of estrogens. Braga et al. (2005) found that the removal efficiencies of estrogens were higher in WWTPs with microfiltration (MF), reverse osmosis (RO) and chlorination/dichlorination compared to the WWTP with $FeCl_3$ addition. Taking into account the relatively low solids concentration in the enhanced primary treatment, the degree of estrogens partitioning in the organic fraction was thought to be responsible for the difference between the 2 plants. Miège et al., 2009 reported greater removal efficiencies for steroid estrogens in AS systems with nitrogen removal and membrane bioreactors. In addition, EE2 removal in fixed biomass reactors and waste stabilization ponds occurred predominantly in the liquid phase, under high solids retention time (SRT) conditions. Johnson et al. (2005)

compared the concentration of steroid estrogens (E1, E2 and EE2) in treated effluents from different WWTPs presenting diverse WWT technologies, finding that the lowest estrogen removals occurred in the WWTP with solely a primary chemical treatment, whereas higher efficiencies were seen in WWTPs with AS and oxidation ditch (OD) systems.

With the purpose of understanding the behavior and the removal efficiencies of estrogens in a full-scale WWTP in Australia, Ying, Kookana, and Kumar (2008) showed that the removal rates of estrogens were consistent with the biochemical oxygen demand (BOD), mixed liquor suspended solids (MLSS) and ammonia removal efficiencies. Higher BOD, MLSS and ammonia values resulted in lower removal efficiencies of estrogens. Moreover, this study pointed out that the least efficient studied WWTP consisted of a series of anaerobic and aerobic lagoons whereas the most efficient was in CAS and OD systems.

4.2. Influence of operational and chemical parameters in CAS and MBR systems

As previously mentioned, the sustainable removal of PhACs from wastewaters is nowadays of major interest, and an increasing number of reports relating to the operational conditions and their removal efficiencies. To this effect, the main studies encompassing SMX, CBZ, E2 and EE2 removal efficiencies in AS and MBR systems under different operation conditions are presented in Table 4.

Keeping the above in mind, and with respect to sulfonamides, SMX is only partially removed in the primary treatment of WWTPs (Pérez, Eichhorn, & Aga, 2005). On the other hand, Xia et al. (2012) showed that high SRT (>30 days) in the secondary treatment (using anoxic/aerobic membrane bioreactors – A/O-MBR) gave removal efficiencies >80% for a number of antibiotics, including SMX. Nevertheless, comparable removal efficiency results have been obtained using an MBR operated with 15 to 30 days of SRT (Kimura, Hara, & Watanabe, 2007; Tambosi et al., 2010), suggesting that the removal efficiency is not strictly related to this operational parameter. Given the dependency of SMX removal efficiencies under the SRT conditions, other reports were on the use of 2 MBR systems at different SRT (15 and 30 days), with SMX removal efficiencies of, respectively, 55 and 64% (Tambosi et al., 2010; Schröder et al., 2012). However, Suárez et al. (2010) showed that SMX degradation was independent of DO levels.

Regarding CAS systems, Yang et al. (2012) found that SMX was completely removed within 13 h. However, comparing the SMX removal in CAS and MBR systems, others have shown diverse SMX removal efficiencies. Indeed, MBR

Table 4. Studies encompassing SMX, CBZ, E2, and EE2 removal efficiencies in AS and MBR systems.

Compound	Concentration	Load	Process type	Scale	Removal efficiency	References
SMX	n.a	1.42 to 5.81 g day⁻¹	CAS / MBR	FS and LS respectively	60.5% and 55.6% in MBR and CAS, respectively	Radjenović et al., (2007)
	0.093 µg L⁻¹	n.a.	CAS / MBR	FS and LS respectively	removal larger in the MBR systems	Radjenović et al. (2009)
	100 µg L⁻¹	n.a.	A/O AS	Batch	9.9% to 17.1%	Li and Zhang (2010)
	100 µg L⁻¹	n.a.	CAS	LS	Complete removal after 11 to 13 days	Yang et al. (2012)
	50 µg L⁻¹*	50 µg L⁻¹ day⁻¹	2 MBR systems	LS	55% (15 days SRT) and 64% (30 days SRT)	Tambosi et al. (2010); Schröder et al. (2012)*
	173.4 ng L⁻¹	n.a.	CAS and nutrient biostimulation	LS	Below 20% after 17 h without bioaugmentation	Muter et al. (2017)
CBZ	n.a	1.44 to 6.71 g day⁻¹	CAS / MBR	FS and LS respectively	Below 10% in both systems	Radjenović et al. (2007)
	0.156 µg L⁻¹	n.a.	CAS/MBR	FS and LS respectively	No removal in both systems	Radjenović et al. (2009)
	10 µM	n.a.	SBR	LS	12.9%	Wang and Gunsch (2011)
	1.13 µg L⁻¹	n.a.	3 MBR systems	LS	No removal	Maeng et al. (2013)
	245.8 ng L⁻¹	n.a.	CAS and nutrient biostimulation	LS	Up to 30% after 17 h in bioaugmented WW	Muter et al. (2017)
E2	Maximum of 1000 ng L⁻¹	n.a.	CAS and OD	Batch	94 to 98% from the water phase within 5 minutes	Hashimoto and Murakami (2009)
	0.93 µg L⁻¹	n.a.	3 MBR systems	LS	90% when nitrification was inhibited	Maeng et al. (2013)
EE2	Maximum of 1000 ng L⁻¹	n.a.	CAS and O)	Batch	Complete removal after 24 h	Hashimoto and Murakami (2009)
	0.70 µg L⁻¹	n.a.	3 MBR systems	LS	10% when nitrification was inhibited	Maeng et al. (2013)

n.a. – Not available; FS – Full-scale; LS – Lab-scale; *concentration studied in the marked reference.

was for the most part more efficient for SMX removal than CAS systems (Radjenović, Petrovic, and Barceló, 2007; Radjenović et al., 2009).

A number of studies focusing on the use of CAS and MBR systems to remove CBZ have has given conflictive or even opposite results (Grandclément et al., 2017); these conflicting results are probably due to differences in the operating conditions of the CAS systems being compared, such as the SRT, hydraulic retention time (HRT) or MLSS, but also to the sludge and the wastewaters chemical composition (Grandclément et al., 2017). A number of other investigations have shown that CAS systems are largely inefficient for the removal of CBZ due to the deconjugation (during the WWT) of conjugates by hydrolysis, which could lead to an increase of the contaminant load. Indeed, the CBZ removal inefficiency is well known to be related to its chemical properties (Mohapatra et al., 2014).

Contrary to SMX, studies on the relationship between the operational conditions in a MBR reactor and CBZ removal efficiencies showed that this compound remains recalcitrant regardless of the SRT values (Bernhard, Müller, & Knepper, 2006; Maeng, Choi, Lee, & Song, 2013). Furthermore, and regarding the influence of the HRT (Gros, Petrović, Ginebreda, & Barceló, 2010) and pH (Tadkaew, Sivakumar, Khan, McDonald, & Nghiem, 2010), the CBZ removal efficiency also did not show any clear relationship between these parameters. Several other studies have compared removal efficiencies of several PhACs by CAS and MBR systems, including CBZ. According to Bernhard et al., (2006), MBR had higher removal efficiencies than CAS regarding a number of polar contaminants, whereas recalcitrant compounds, e.g. CBZ, were not eliminated.

Regarding the removal and biodegradation efficiencies of estrogens, reports include both pilot-scale reactors and full-scale plants; as a result, crucial knowledge about these compounds structures, their transformation pathways, and the relation between removal efficiencies and operational conditions has emerged (Cajthaml et al., 2009; Liu et al., 2015; Ting & Praveena, 2017). Regarding the temperature effect on the removal efficiencies of estrogens, a higher efficiency is found in summer (average 26.4 °C) than in winter (average 16.4 °C) (Nakada et al., 2006). However, Suárez et al. (2012) found higher removal efficiencies of EE2 in CAS systems in the temperature at 10–35 °C than above 45 °C.

Iit is well known that estrogens (e.g. E2 and EE2) removal can also be affected by other conditions, including SRT and HRT values and MLSS contents. Indeed, high SRT (especially from 20 to 24 days) leads to higher efficiencies of the removal on estrogens (Clara, Kreuzinger, Strenn, Gans, & Kroiss, 2005; Carballa, Omil, Ternes, & Lema, 2007; McAdam et al., 2010; Petrie, McAdam, Hassard, Stephenson, Lester, & Cartmell, 2014). With respect to the MLSS influence, there have been contradictory results; while Suzuki and

Maruyama, (2006) reported no differences in removal efficiencies in CAS systems, varying the MLSS from 1619 mg L^{-1} to 1921 mg L^{-1}, Chen and Hu (2009) and Li, Yuasa, Obara, and Mathews, (2005) showed increased efficiency in batch tests by varying the MLSS from 4 g L^{-1} to 12.5 g L^{-1}, and from 435 mg L^{-1} to 1750 mg L^{-1}, respectively. Suárez et al. (2010) showed that removal efficiencies of 99% for E2and 87% for EE2 with regard to the influence of HRT could be obtained with a 24 h HRT (for a MLVSS of 1.6 g L^{-1} and a temperature range from 16 to 20 °C) in CAS systems. These results suggest that other factors besides temperature, HRT, SRT and MLSS, e.g. the initial estrogens concentration, could play a major role in their removal processes. In fact, other operational conditions were found relevant in improving the biodegradation kinetics of EE2 in CAS processes, including the food to microorganism ratio (F/M). Ziels, Lust, Gough, Strand, and Stensel (2014) indicated that population selection, in low organic substrate concentrations, can improve EE2 biodegradation kinetics. Maeng et al. (2013) obtained better removal efficiencies for E2 than EE2 in MBR systems when nitrification was inhibited. In this sense, more work is needed to clarify the influence of the above parameters in E2 and EE2 removal efficiencies in WWTPs.

Although Hashimoto and Murakami (2009) showed that estrogens can be completely removed after 24 h in batch experiments using samples from CAS and OD full-scale WWTPs, Kim, Cho, Kim, Vanderford, and Snyder (2007) results suggest that MBR could be more efficient in hormones (estriol, testosterone, androstenedione) removal from wastewaters than CAS systems.

In comparing PhACs removal efficiencies between the CAS and MBR systems favoring the latter, it should be emphasized that these results could be partially explained by the differences in the operational conditions (e.g. SRT). Nonetheless, it is also known that the floc surface, per reactor volume, is 10 times higher in MBR than in CAS, suggesting that the contact between microorganisms and pollutants could be favored in MBR, thus stimulating enzymatic activity (Cirja, Ivashechkin, Schäffer, & Corvini, 2008). However, it should be noted that natural and human originated metabolites and PhACs by-products can be even more toxic than the parent compounds, such as chlorine by-products in disinfection (Buttiglieri & Knepper, 2008).

4.3. Fungi treatments, EMR and HS

In the last few years, a number of different WWT methodologies, e.g. fungi treatments, EMR and HS, have been examined regarding the removal of PhACs from wastewaters. To this effect, the major reports encompassing SMX, CBZ, E2 and EE2 removal efficiencies using these systems are presented in Table 5. Rodarte-Morales, Feijoo, Moreira, and Lema (2011)

Table 5. Studies encompassing SMX, CBZ, E2, and EE2 removal efficiencies using hybrid systems.

Compound	Concentration	Load	Process type	Removal efficiency	Reference
SMX	0.5 and 0.25 mg L⁻¹	1660 and 830 µg L⁻¹ day⁻¹	EMR	25%	Nguyen et al. (2014)
	14 µg L⁻¹	n.a.	Hybrid biofilm and CAS	30% (biodegradation)	Escolà Casas et al. (2015)
	100 µg L⁻¹	n.a. .	UASB and hybrid MBR	>90%	Alvarino, Suárez, Garrido, Lema, and Omil (2016)
	0,5 and 0,25 mg L⁻¹	1660 and 830 µg L⁻¹ day⁻¹	Packed-bed enzyme reactor	Maximum of 60% biodegradation and 40% adsorption	Nguyen et al. (2016)
CBZ	1 µg L⁻¹	n.a.	Hybrid biofilm-AS	No removal	Falås et al. (2013)
	5 µg L⁻¹	n.a.	UV oxidation and hybrid MBR	30 and 96%, respectively	Nguyen et al. (2013)
	100 µg L⁻¹	n.a.	MF and CLEA-Lac	99% from aqueous solution	Ba, Jones, and Cabana (2014)
	5 µg L⁻¹	n.a.	MBBR	26%	Luo et al. (2015)
	5 µg L⁻¹	n.a.	MBBR and MBR	30%	Luo et al. (2015)
	14 µg L⁻¹	n.a.	Hybrid biofilm and CAS	30% (biodegradation)	Escolà Casas et al. (2015)
	100 µg L⁻¹	n.a.	UASB and hybrid MBR	<40%	Alvarino et al. (2016)
	20 µM	n.a.	Hybrid MBR with *T. versicolor* laccase immobilized on TiO$_2$ nanoparticles	71%	Ji, Hou, Wang, Zhang, and Chen (2016)
E2	0.5 and 0.25 mg L⁻¹	1660 and 830 µg L⁻¹ day⁻¹	Packed-bed enzyme reactor	40% biodegradation and 50% adsorption	Nguyen et al. (2016)
	20 µg L⁻¹	n.a.	UASB and hybrid MBR	<20% in anaerobic conditions; highly biotransformed in aerobic conditions	Alvarino et al. (2016)
	5 µg L⁻¹ and 100 µg L⁻¹	n.a.	EMR	70% of removal	Nguyen et al. (2015)
	5 µg L⁻¹	n.a.	MBBR	96%	Luo et al. (2015)
	5 µg L⁻¹	n.a.	MBBR and MBR	96%	Luo et al. (2015)
EE2	20 µg L⁻¹	n.a.	UASB and hybrid MBR	Below 40%	Alvarino et al. (2016)
	5 µg L⁻¹ and 100 µg L⁻¹	n.a.	EMR	77%	Nguyen et al. (2015)
	5 µg L⁻¹	n.a.	MBBR	85%	Luo et al. (2015)
	5 µg L⁻¹	n.a.	MBBR and MBR	76%	Luo et al. (2015)

n.a. – Not available; CAS – conventional activated sludge; UASB – Upflow Anaerobic Sludge Blanket; MBR – Membrane bioreactor; MF – Microfiltration; CLEA-Lac – cross-linked enzymes aggregate of laccase; EMR – Enzymatic membrane reactor; MBBR – moving bed biofilm reactor.

focusing on the removal of SMX using white rot fungi, found complete degradation after 14 days of incubation with the 3 fungal strains (an anamorph species of *Bjerkandera* sp. R1, *Bjerkandera adusta* and *Phanerochaete chrysosporium*). Fungi were also of interest in the degradation of estrogens (E2 and EE2), including the use of laccase from *T. versicolor* (Auriol, Filali-Meknassi, Tyagi, & Adams, 2007) and other enzymatic solutions. In fact, *MnP* solutions produced by *P. ostreatus* gave an 80% EE2 removal efficiency (Cajthaml et al., 2009; Suzuki, Hirai, Murata, & Nishida, 2003). Others showed that enzymatic reactions mediated by vanillin, p-coumaric acid or ferulic acid achieved EE2 removal percentages ranging from 80 to 100% after 24 h (Nguyen, Hai, Kang, Price, & Nghiem, 2013).

Significant research has also been developed to achieve CBZ removal using fungi treatments. One of the most employed organisms in CBZ removal from aqueous media is *T. versicolor;* Jelic et al. (2012) reported a high removal efficiency (96%) using an air-pulsed fluidized bed bioreactor operated under batch conditions. On the contrary, Cruz-Morató et al. (2013) found that the deconjugation of CBZ intermediates led to increased CBZ in a fluidized bed bioreactor treating real wastewater with *T. versicolor*. Others have also exploited the potential of commercial fungi (e.g. *T. versicolor*) based enzymes; Tran, Urase, and Kusakabe (2010) reported CBZ removal efficiencies just under 40% with commercial laccase. *Phanerochaete chrysosporium* fungi has also been used to evaluate *in vitro* degradation of CBZ. Zhang and Geissen (2010) batch experiments yielded poor (mostly <10%) to no CBZ removal abilities using *P. chrysosporium* lignin peroxidase (*LiP*). On the contrary, the use of manganese peroxidase (*MnP*) solutions produced by *Pleurotus ostreatus* degraded 98% of CBZ (Zhang & Geissen, 2010; Golan-Rozen, Chefetz, Ben-Ari, Geva, & Hadar, 2011).

However, there have been conflicting results regarding a wider range of PhACs removal strategies. Thus, the interest in studying HS by combining one or more treatment processes for this purpose has been increasing. Tang et al. (2017) found poor removal SMX efficiencies (∼10%) and CBZ recalcitrance in a polishing MBBR. In fact, poor removal CBZ efficiencies had been reported beforehand in a hybrid biofilm-activated sludge process and in a MBBR (Falås et al., 2013; Luo et al., 2014). On the contrary, 80% of CBZ removal was obtained in an integrated fixed-film activated sludge membrane bioreactor (IFAS-MBR) (De La Torre et al., 2015). In another study, a hybrid biofilm and activated sludge system (Hybas^{TM}) has been used for hospital wastewater (containing SMX and CBZ) treatment, obtaining ∼30% in removal efficiency for both compounds (Escolà Casas et al. 2015). Regarding steroid estrogens removal in hybrid systems, De la Torre et al. (2015) achieved complete (100%) E2 and EE2 removal in an IFAS-

MBR, whereas removal efficiencies >80% were obtained by Luo et al. (2014) using a sponge-based MBBR.

5. Concluding remarks and future perspectives

PhACs, including sulfonamides, anticonvulsants and estrogens, are widely present in municipal sewage, largely due to human excretion, causing serious environmental damage. Although a number of different biological WWT systems can be found in WWTPs, AS and MBR systems remain the most widely operated. However, these systems have shown - for the most part - inefficiency in the removal of these compounds, with serious consequences to aquatic life and human health. With this in mind, concern over the development of new sustainable removal technologies is increasing, including EMR, fungi treatments and HS. Therefore, the main commonly employed biological WWT systems for PhACs removal, particularly sulfonamides (SMX), anticonvulsionants (CBZ) and steroid estrogens (E2 and EE2) are being addressed, as well as their main environmental impacts, mainly in terms of aquatic biota, soil and human health.

Although AS systems (including CAS, SBR, OD and other configurations) are frequently inefficient in the removal of PhACs (including CBZ, SMX, E2, and EE2), a number of different investigations focusing on the removal efficiencies of these systems have been published. In fact, several factors have been thoroughly studied, including different PhAC concentrations, system configurations, and diverse chemical and operational conditions. Furthermore, it has also been found that MBR systems are more suitable and efficient than CAS systems. That being the case, more research is required to enlighten and corroborate these previous findings.

Despite the undertaken efforts regarding CAS and MBR systems, it should be pointed out that some PhACs, e.g. CBZ, remain recalcitrant in these systems; thus, the development of EMR, fungi treatments and HS removal methodologies is a major focus of interest. Again, a number of different strategies for the removal of SMX, CBZ, E2 and EE2 for such technologies have been published, although with varying removal efficiencies being reported.

The evaluation of the above technologies in terms of cost-benefit should also be exploited to achieve sustainable implementation in full-scale WWTPs. In this sense, future studies encompassing the use of alternative technologies (e.g. aerobic granular sludge) for PhACs removal are needed. Further investigation should also address the problem of improving the ability of these technologies to achieve sustainable removal of PhACs, and to understand the relationships between the operational parameters and correspondent removal efficiencies. Moreover, long-term exposure

(chronic) effects of products resulting from PhACs degradation should be also investigated in future studies.

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