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Performance of secondary wastewater treatment methods for the removal of contaminants of emerging concern implicated in crop uptake and antibiotic resistance spread: a review

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Abstract

Contaminants of emerging concern (CEC) discharged in effluents of wastewater treatment plants (WWTPs), not specifically designed for their removal, pose serious hazards to human health and ecosystems. Their impact is of particular relevance to wastewater disposal and re-use in agricultural settings due to CEC uptake and accumulation in food crops and consequent diffusion into the food-chain, thus determining unintentional human exposure. This is the reason why the chemical CEC discussed in this review have been selected considering, besides recalcitrance, frequency of detection and entity of potential hazards, their relevance for crop uptake. Antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) have been also included as microbial CEC because of the potential of secondary wastewater treatment to offer conditions favourable to the survival and proliferation of ARB, as well as dissemination of ARGs. Given the adverse effects of chemical and microbial CEC, their removal is being considered as an additional design criterion, which highlights the necessity of upgrading of conventional WWTPs through the inclusion of more effective technologies. In this review, the performance of the currently applied biological treatment methods for secondary wastewater treatment is analysed. To this end, technological solutions including conventional activated sludge (CAS), membrane bioreactors (MBRs), moving bed biofilm reactors (MBBRs), and nature-based solutions such as constructed wetlands (CWs) are compared for the achievable removal efficiencies of the selected CEC and their potential of acting as reservoirs of ARB&ARGs. With the aim of giving a picture of real systems, this review focuses on data from full-scale and pilot-scale plants treating real urban wastewater. To achieve an integrated assessment, technologies are compared considering also other relevant evaluation parameters of general validity, such as investment and management costs, complexity of layout and management, present scale of application and need of a post-treatment. The results of their comparison allow the definition of design and operation strategies for the implementation of CEC removal in WWTPs, when agricultural reuse of effluents is planned.

Keywords: secondary wastewater treatment; biological processes; CEC removal; antibiotic resistance; EU Watch list; crop uptake;

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1. Introduction and objectives

A discussion on the performance of technologies applied in wastewater treatment plants (WWTPs) for secondary treatment cannot disregard the presence of contaminants of emerging concern (CEC) in wastewaters, when assessing hazards to human health and ecosystems. According to the NORMAN network (2017), a CEC is "*a substance currently not included in routine environmental monitoring programmes and may be candidate for future legislation due to its adverse effects and/or persistency"*. Also, according to the United States Geological Survey (USGS) CEC include: "*any synthetic or naturally occurring chemical or any microorganism that is not commonly monitored in the environment but has the potential to enter the environment and cause known or suspected adverse ecological and/or human health effects*" (Klaper and Welch 2011).

Currently, there is no standardized categorization of CEC, and generally, examined categories include among others, pharmaceuticals, personal care products, plasticizers, flame retardants, and pesticides.

The release of CEC to the aquatic environment has been occurring for a long time, but suitable detection methods were not available until recently. As a result, nowadays we are able to identify and quantify these compounds. The synthesis of new chemicals, or changes in use and disposal of existing chemicals can create new sources of CEC into aquatic environments.

Abbreviations: A^2O, anaerobic–anoxic–oxic; ACTM, Acetamiprid; ARB, antibiotic resistant bacteria; ARGs, antibiotic resistance genes; AZM, Azithromycin; BDL, below detection limit; BHT, 2,6-Ditert-butyl-4-methylphenol; BOD, biochemical oxygen demand; BTA, Benzotriazole; CAS, conventional activated sludge; CBZ, Carbamazepine; CEC, contaminants of emerging concern; CIP, Ciprofloxacin; COD, chemical oxygen demand; CW, constructed wetland; Da, dalton; DCF, Diclofenac; DO, dissolved oxygen; DOC, dissolved organic carbon; E1, Estrone; E2, 17-Beta-estradiol; EE2, 17-Alpha-ethynylestradiol; EDG, electron donating functional groups; EHMC, 2-Ethylhexyl 4-methoxycinnamate; ENR, Enrofloxacin; ERY, Erythromycin; EWG, electron withdrawing functional groups; EU, European Union; F/M, Food to microorganisms ratio; HBCD, Hexabromocyclododecane; HGT, horizontal gene transfer; HRT, hydraulic retention time; IntI1, class 1 integron; K_{biol}, kinetic reaction rate constant, L/g_{SS}.d; K_d, solid-water partition coefficient, L/kg_{SS}; K_{ow}, octanol-water partition coefficient; LCA, life cycle assessment; MBBR, moving bed biofilm reactor; MBR, membrane bioreactor; MDR, multi-drug resistance; MF, microfiltration; MLSS, mixed liquor suspended solids; MLVSS, mixed liquor volatile suspended solids; MRSA, methicillin-resistant Staphylococcus aureus; N.A., not available; NDMA, N-Nitrosodimethylamine; NEREUS, COST Action ES1403 'New and emerging challenges and opportunities in wastewater reuse'; NORMAN, Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances; NSAID, non-steroidal anti-inflammatory compound; PCPs, personal care products; PE, population equivalent; PFBA, Perfluorobutanoic acid; PFHxA, Perfluorohexanoic acid; PFPeA, Perfluoropentanoic acid; QMRA, quantitative microbial risk assessment; q-PCR, quantitative polymerase chain reaction; SF CW, surface flow CWs; SMX, Sulfamethoxazole; SRT, sludge retention time; SWWTP, small WWTP of < 5.000 PE; TBBPA, Tetrabromobisphenol A; TCS, Triclosan; TCEP, Tris(2-chloroethyl)phosphate; TMP, Trimethoprim; TPs, transformation products; TSS, total suspended solids; UF, ultrafiltration; USGS, United States Geological Survey; VRE, Vancomycin-resistant enterococci; WWTP, wastewater treatment plant.

In addition to the occurrence of chemical CEC in water environments, the widespread use and misuse of antibiotic residues and their uncontrolled emission in the environment was shown to contribute to the proliferation of antibiotic resistant bacteria (ARB) and their associated genes (antibiotic resistance genes, ARGs) (Berendonk et al., 2015), whose presence has been also detected in urban wastewater (Michael et al., 2013; Rizzo et al., 2013; Li et al., 2014a; Berglund et al., 2015; Xu et al., 2015). In this review, the latter are considered as microbial CEC. WWTPs can potentially reduce the emission of CEC including antibiotics. However, they also represent an important emission source of CEC to the receiving water bodies, due to the incomplete removal of a large number of these compounds. Moreover, WWTPs can act as collection points for ARB and antimicrobials from a variety of sources (i.e., hospitals, industries, households), consequently becoming point sources for environmental dissemination of antibiotic resistance (Pruden et al., 2013).

The above-mentioned aspects give an idea of the complexity of the issues arising from the presence of CEC in aquatic environments and antibiotic resistance-related problems. A wide spectrum of chemical and microbial contaminants with different physicochemical properties, toxicological characteristics and degree of potential risk must be managed, requiring suitable responses according to the applied treatment process. WWTPs are only partially effective in CEC removal or degradation, so these residual CEC are discharged into the environment with treated effluent and excess sludge. In an era of water scarcity, the presence of residual amounts of CEC in treated effluents is not only a problem for the environment but can also compromise treated wastewater reuse.

The fate of CEC highly depends on the type of treatment applied at a specific WWTP. There are many factors determining the removal of specific classes of contaminants in WWTPs: compound chemical properties, plant configuration, hydraulic retention time (HRT), operating conditions (i.e. pH, temperature, etc), presence of industrial wastewater, etc. Furthermore, WWTPs commonly need to operate on a broad and heterogeneous group of contaminants in a wide range of influent concentrations (varying from 0.001 to 1000 μg/L) [based on Table 2 data]. Therefore, there is a need for technological solutions effective for various contaminants and under different operating conditions.

The CEC have attracted the attention of the scientific community in the recent years, with many review papers addressing various aspects of CEC. These reviews were either focused on selected pharmaceutical compounds such as diclofenac, estrogens or antibiotics (Rivera-Utrilla et al., 2013; Vieno and Sillanpää 2014; Polesel et al., 2016; Schröder et al., 2016; Tiedeken et al., 2017) or on the selected treatment processes applied for CEC removal. Among these processes, membrane-based processes (Siegrist and Joss 2012; de Cazes et al., 2014; Li et al., 2015; Ojajuni et al., 2015; Shojaee Nasirabadi et al., 2016; Taheran et al., 2016; Kim et al., 2018), constructed wetlands (CWs) (Dordio and Carvalho 2013; Li et al., 2014b; Verlicchi and Zambello 2014; Zhang et al., 2014; Gorito et al., 2017), biological processes such as conventional activated sludge (CAS), membrane bioreactors (MBRs), and bioelectrochemical systems (Verlicchi et al., 2012; Rojas et al., 2013; Vieno and Sillanpää 2014; Besha et al., 2017; Cecconet et al., 2017; Grandclément et al., 2017; Tiwari et al., 2017), and various conventional and advanced processes such as advanced oxidation processes (AOPs) or activated carbon (Rivera-Utrilla et al., 2013; Luo et al., 2014; Barbosa et al., 2016; Bui et al., 2016; Hamza et al., 2016; Ahmed et al., 2017; Rodriguez-Narvaez et al., 2017; Tiedeken et al., 2017; Yang et al., 2017) were reviewed. In addition, aspects such as the use of hybrid systems (Grandclément et al., 2017), impact on membrane fouling (Besha et al., 2017) sorption and biotransformation (Alvarino et al., 2018), geographical distribution (Tran et al., 2018), and comprehensive strategies for managing CEC (Talib and Randhir 2017) were also reviewed.

The gaps that have been identified in these reviews were, among others, related to the significance and reliability of the collected CEC removal data being based on synthetic wastewater, small lab-scale systems, specific industrial wastewaters and/or unsuitable sampling (Taheran et al. 2016, Cecconet et al. 2017, Grandclément et al. 2017, Tran et al. 2018). In addition, the need of a cost-benefit evaluation of the different treatment technologies (Bui et al. 2016, Grandclément et al. 2017) and the lack of information on design for optimum performance (Ahmed et al. 2017) were also pointed out. Furthermore, the general lack of knowledge on the occurrence of CEC in WWTP effluents and on the efficiency of different treatment methods (Schröder et al. 2016) as well as the need for intensification of technology-focused studies for effective and efficient control measures of CEC (Tiedeken et al. 2017), have been reported. One of the processes listed was a biofilm process, such as the moving bed biofilm reactor (MBBR) (Tran et al. 2018). Finally, due to the increasing importance of wastewater reuse as well as to the concern for antibiotic resistance spread from WWTPs effluents, there is a clear need to review the microbial CEC, namely ARB&ARGs and relevant aspects related to crop uptake.

To this end, the aim of this review is to address these gaps and specifically: i) to give a picture of real applications by focusing on full-scale systems, ii) to analyse the performance of currently applied secondary biological treatment technologies (namely CAS, MBR and MBBR) and nature-based solutions (namely CWs) for the removal of CEC, iii) to summarize current knowledge on the occurrence of antibiotic resistance after biological treatment and on the potential for antibiotic resistance spread, and iv) to combine present findings on technical and economic considerations regarding the compared technologies as an attempt to provide input for a cost-benefit evaluation. Thus, the novelty of this paper predominantly lies in reviewing only full- and pilot-scale plants treating real urban wastewater, and including microbial CEC and crop uptake aspects, which are of relevance for wastewater reuse. Therefore, the performance of the investigated technologies is analysed for a group of target CEC relevant for wastewater reuse, including the compounds reported in the EU Watch list (Decision 2015/495/EU, (2015/495/EU) and others, which are relevant for crop uptake (Piña et al. 2018). This last factor is essential for reuse, because the CEC present in the treated wastewater that is used for irrigation, can accumulate in food crops, being the first link for CEC diffusion into the human food-chain, consequently being of relevance given the unintentional human exposure. The prevalence of antibiotic resistance after biological treatment is also analysed to search for common trends regions on WWTPs potential for antibiotic resistance spreading, in spite of variables that may influence the outcomes, e.g. the operating conditions, plant configuration or geographic regions.

2. Selection of CEC

A list of 33 CEC was compiled for investigation in the present review: compounds were selected according to their relevance to wastewater reuse, in particular for potential uptake by crops, public health issues and/or environmental safety implications. In addition to this list of organic micro-contaminants, also ARB&ARGs were included as CEC, an option that is justified by the critical relevance of these (micro)biological contaminants to public health and, above all, the recognized persistence and self-replication potential of these micro-contaminants in environmental compartments. The selection of specific organic and microbial CEC was based on the recommendations of the NEREUS COST Action ES 1403[1], a network of scientists and stakeholders interested in urban wastewater reuse from 42 countries. The NEREUS COST Action Working Group 2 activities, focused on 'Uptake and translocation of organic micro-contaminants and ARB&ARGs in crops' identified and indicated compounds relevant to crop uptake. This list was combined with a list of compounds from the EU Watch List, recommended by the NEREUS COST Action Working Group 4, whose activities focused on 'Technologies efficient/economically viable to meet the current wastewater reuse challenges', due to their environmental and health relevant aspects.

The following criteria reported in order of priority, were taken into account during the selection of the CEC for examination in this review.

i. **Uptake by crops.** Once in the agricultural environment, CEC have the potential to be taken up by fodder and edible crops. The uptake of pharmaceuticals has been demonstrated by various authors

[1] COST Action ES1403 New and emerging challenges and opportunities in wastewater reuse (NEREUS), http://www.nereus-cost.eu

(Calderón-Preciado et al., 2013; Goldstein et al., 2014; Malchi et al., 2014; Christou et al., 2017; Christou et al., 2018). More specifically in a study by Calderón-Preciado et al., (2013), the uptake of various CEC and metabolites by lettuce, carrots, potatoes, tomatoes, cucumbers and green beans irrigated with reclaimed water has been examined. The results of these studies showed that non-ionic pharmaceuticals such as carbamazepine are taken up at higher concentrations compared to ionic compounds, by the examined plants. Moreover, the presence of carbamazepine metabolites in the leaves of carrots and potatoes at higher concentrations than the parent compound, suggests the occurrence of uptake and metabolic breakdown of carbamazepine inside the crop plants.

ii. **Effects on crop production.** Plant exposure to CEC may affect plant development, either through direct contact and damage, or as the result of the action of pharmaceuticals on plant microbiota and soil microorganisms, so having a role in plant-microorganism symbioses and soil nutrient cycling (Peñuelas et al., 2013). Ferrari et al., (2003) investigated the effect of carbamazepine, diclofenac and clofibric acid residues found in irrigated wastewater on the microalga *Pseudokirchinella subcapitata*, demonstrating a reduction in growth in the algal nutrient solution in the presence of the CEC, at a concentration of 10 mg/L. In another study by Eggen et al., (2011), the effect of the uptake of metformin, ciprofloxacin and narasin (an anti-coccidial) in carrot and barley were investigated. The results showed negative effects on the growth of all plants investigated, when these were grown in soil, which contained a concentration of these CEC at 6 to 10 mg kg^{-1} dry weight.

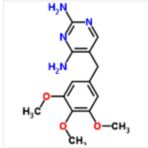
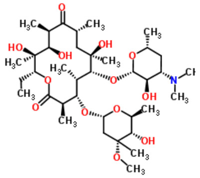
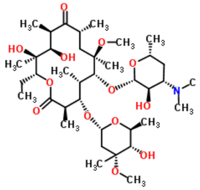
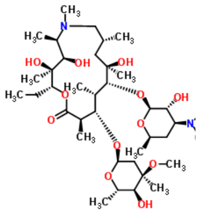
iii. **Environmental- and human-health concern.** The occurrence of CEC in environmental compartments has been often associated to a number of biological adverse effects, such as toxic effects, endocrine disruption and antibiotic resistance in microorganisms (Luo et al., 2014). Yet, the potential effects of CEC remain unclear and in need of further investigations (Ahmed et al., 2017). In 2015, the European Commission established the EU Watch List (Decision (2015/495/EU) of 17 substances for monitoring in water. Their inclusion has been justified by their potential to cause damage to aquatic environments and to pose a significant risk at European Union level, but for which monitoring data are insufficient to come to a conclusion regarding the actual posed risk. These compounds belong to various categories such as estrogenic hormones, non-steroidal anti-inflammatory compounds (NSAIDs), antibiotics, UV filters and antioxidant compounds, pesticides and herbicides.

iv. **Recalcitrance.** Recalcitrant compounds, which remain practically unaltered during wastewater treatment, require special attention, as they may accumulate in environments receiving treated wastewater, and may thus pose a hazard to environmental health. For instance, Jones et al., (2017) investigated recently the fate of 95 CEC in 3 full-scale WWTPs after trickling filter treatment followed by nitrification, or after activated sludge treatment. Their results indicated that a group of compounds were recalcitrant to both treatments, as their removal varied from -58% to 14%. Azithromycin (total average removal of 14%), carbamazepine (1%) and estrone (13%) were among the recalcitrant CEC. Moreover, the antibiotic erythromycin was found to be recalcitrant during biological treatment according to various studies conducted in real wastewater effluents (Yang et al., 2011; Guerra et al., 2014; Kim et al., 2014; Pasquini et al., 2014), indicating the importance of antibiotic monitoring in treated effluent receiving environments.

v. **Frequency of detection.** Frequency of detection is an indicator of persistence and tolerance to biological treatment. For example, compounds like sulfamethoxazole, carbamazepine, diclofenac, estrone and estradiol showed high frequency of detection being present in all treated wastewater samples (n=16) of four WWTPs in southern California (Vidal-Dorsch et al., 2012). Loos et al., (2013) found similar results in an EU-wide monitoring survey assessing the occurrence of polar chemical contaminants in effluents of 90 WWTPs. Carbamazepine and ciprofloxacin showed a frequency of 90%, and sulfamethoxazole and diclofenac were detected with a frequency of 83 and 89% respectively. Metformin and benzotriazole were also detected in high concentrations exceeding 1μg/L in the effluent during the screening of the Swiss WWTPs (Margot et al., 2013).

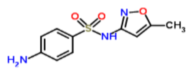
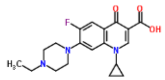
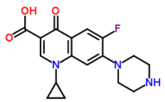
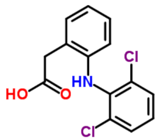
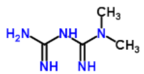
The list of the compounds examined in this review, based on the above selection criteria, is shown in Table 1.

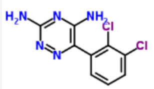
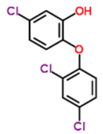
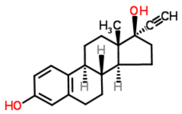
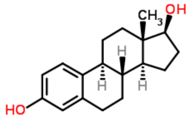
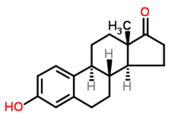
Table 1. Properties, function of selected compounds and justification of their selection for the purposes of this review.

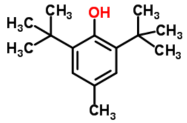
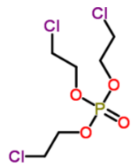
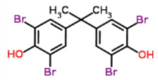
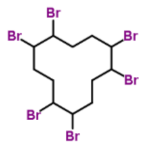
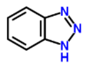
Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log Kow	Molecular weight [g/mol]	Function	Justification[3]
Pyrimidine inhibitor antibiotic	Trimethoprim	TMP		738-70-5	0.91	290.32	Antibiotic	Relevance for crop uptake
Macrolide antibiotics	Erythromycin	ERY		114-07-8	2.48-3.06	733.93	Antibiotic	EU Watch List (Decision 2015/495/EU)
	Clarithromycin	CLR		81103-11-9	3.16	747.95	Antibiotic	EU Watch List (Decision 2015/495/EU)
	Azithromycin	AZM		83905-01-5	4.02	748.98	Antibiotic	EU Watch List (Decision 2015/495/EU)

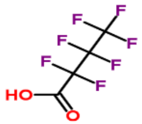
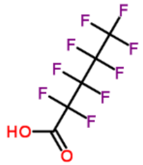
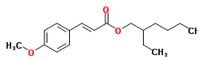
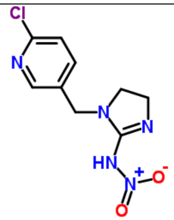
[2] http://www.chemspider.com

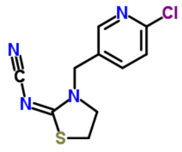
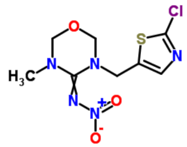
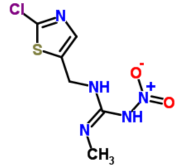
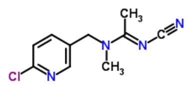
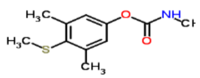
[3] Selected compounds are also indicators in Swiss water protection act to evaluate effectiveness of advanced treatment of wastewater (Carbamazepine, Clarithromycin, Diclofenac, Benzotriazole) or listed as priority hazardous substance in Norway (TCEP, TBBPA, HBCD, Triclosan).

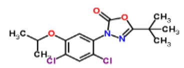
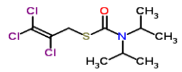
Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log Kow	Molecular weight [g/mol]	Function	Justification[3]
Sulfonamide antibiotics	Sulfamethoxazole	SMX		723-46-6	0.89-0.91	253.28	Antibiotic	Relevance for crop uptake
Quinolone antibiotics	Enrofloxacin	ENR		93106-60-6	1.1	359.39	Antibiotic	Relevance for crop uptake
	Ciprofloxacin	CIP		85721-33-1	0.28-0.40	331.34	Antibiotic	Relevance for crop uptake
Pharmaceuticals	Diclofenac	DCF		15307-86-5	4-4.5	296.15	Non-steroidal anti-inflammatory agent	EU Watch List (Decision 2015/495/EU), relevance for crop uptake
	Metformin	MTF		657-24-9	-2.48	129.16	Antidiabetic drug	Relevance for crop uptake
	Carbamazepine	CBZ		298-46-4 85756-57-6	2.45	236.27	Antiepileptic drug	Relevance for crop uptake

Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log Kow	Molecular weight [g/mol]	Function	Justification[3]
Antimicrobial agent	Lamotrigine	LTG		84057-84-1	1.19-2.12	256.09	Anticonvulsant drug	Relevance for crop uptake
	Triclosan	TCS		3380-34-5	5.34	289.54	Antiseptic	Relevance for crop uptake
Estrogens	17-Alpha-ethynylestradiol	EE2		57-63-6	3.67-4.12-4.2	296.40	Synthetic hormone	EU Watch List (Decision 2015/495/EU), relevance for crop uptake
	17-Beta-estradiol	E2		50-28-2	3.94-4.01	272.38	Natural hormone	EU Watch List (Decision 2015/495/EU), relevance for crop uptake
	Estrone	E1		53-16-7	3.13-3.43	270.37	Natural hormone (breakdown product of E2)	EU Watch List (Decision 2015/495/EU)

Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log Kow	Molecular weight [g/mol]	Function	Justification[3]
Industrial chemicals	2,6-Ditert-butyl-4-methylphenol	BHT		128-37-0	3.5-5.1	220.35	Antioxidant (food additive)	EU Watch List (Decision 2015/495/EU)
	Tris(2-chloroethyl)phosphate	TCEP		115-96-8	1.44-1.6	285.49	Flame retardant, plasticizer	Relevance for crop uptake
	Tetrabromobisphenol A	TBBPA		79-94-7	5.3-5.9	543.87	Brominated flame retardant	Relevance for crop uptake
	Hexabromocyclododecane	HBCD		3194-55-6	5.07-5.47	641.69	Brominated flame retardant	Relevance for crop uptake
	Benzotriazole	BTA		95-14-7	1.44	119.13	Corrosion inhibitor	Relevance for crop uptake
	N-Nitrosodimethylamine (dimethylnitrosamine)	NDMA		62-75-9	-0.57	74.08	Industrial and chlorination by-product	Relevance for crop uptake

Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log Kow	Molecular weight [g/mol]	Function	Justification[3]
	Perfluorobutanoic acid	PFBA		375-22-4	2.82	214.04	Perfluorinated carboxylic acid (PFCA)	Relevance for crop uptake
	Perfluoropentanoic acid	PFPeA		2706-90-3	3.43	264.05	Perfluorinated carboxylic acid (PFCA)	Relevance for crop uptake
	Perfluorohexanoic acid	PFHxA		307-24-4	4.06	314.05	Perfluorinated carboxylic acid (PFCA)	Relevance for crop uptake
Personal care products (PCPs)	2-Ethylhexyl 4-methoxycinnamate	EHMC		5466-77-3	5.8	289.39 290.40	UV-filter/ stabilizer	EU Watch List (Decision 2015/495/EU)
Neonicotinoids	Imidacloprid	IMI		105827-78-9/138261-41-3	0.57	255.66	Pesticide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake

Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log Kow	Molecular weight [g/mol]	Function	Justification[3]
	Thiacloprid	THI		111988-49-9	0.73-1.26	252.72	Pesticide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake
	Thiamethoxam	TMX		153719-23-4	-0.13	291.71	Pesticide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake
	Clothianidin	CLO		210880-92-5	0.7	249.68	Pesticide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake
	Acetamiprid	ACTM		135410-20-7/160430-64-8	0.8	222.67	Pesticide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake
Pesticides	Methiocarb			2032-65-7	2.92	225.31	Pesticide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake

Group	Compound	Acronym	Structure[2]	CAS number	Partition coefficient, Log K_{OW}	Molecular weight [g/mol]	Function	Justification[3]
	Oxadiazon			19666-30-9	3.9-4.9	345.22	Herbicide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake
	Triallate			2303-17-5	4.6	304.66	Herbicide	EU Watch List (Decision 2015/495/EU) + relevance for crop uptake

3. Selection of secondary wastewater treatment technologies

3.1 Criteria for selection

The examined technologies applied in secondary wastewater treatment were selected according to their present level of application at full scale WWTPs, as well as to the state of knowledge of their performance for the removal of the selected CEC. The availability of reliable dataset for CEC was mandatory to this aim and, unfortunately, not so many data are available for technologies other than CAS and MBRs. Accordingly, the attention was mainly focused on these two treatment options. However, MBBRs, a potentially effective technology for CEC removal, and CWs, as a valid example of nature-based method characterized by easy installation and operation as well as good removal efficiencies for several CEC, were also introduced as potential promising alternatives to CAS and MBRs.

3.2 Removal mechanisms of CEC for the selected treatment technologies

For the CAS process, the main removal mechanisms of CEC are biodegradation (intended as complete mineralization of the compound) and sorption. Their occurrence and extent depend on the operating parameters of the plants i.e. SRT, Food to Microorganisms (F/M) ratio, presence of aerated and not aerated zones, pH and temperature. Previous studies found that long SRT have a positive effect on the removal of several compounds (Cirja et al., 2017), in particular on hormones and antibiotics, which are mainly removed by biodegradation (Strenn et al., 2004). This removal increase may be justified by the fact that long SRTs may promote growth of slow growing bacteria with various enzymes, which have been shown to have positive effects on removal of various CEC including diclofenac, erythromycin and 17α-ethynylestradiol (Suarez et al., 2010; Fernandez-Fontaina et al., 2012). In addition, varying composition of the solid matrix and different sorption capacities due to high SRTs in conjunction with reduced F/M ratio may also increase microbial diversity (Göbel et al., 2007). The influence of HRT has been a subject of discussion as it was reported to enhance some compounds degradation (Metcalfe et al., 2003; Gros et al., 2010) as well as to have negligible effect on removal of other compounds, e.g. diclofenac (Bernhard et al., 2006). Moreover, high biomass concentrations provide higher stability, persistence to shock loads, increased contact between microorganisms and pollutants, thus facilitating their biodegradation (Cirja et al., 2007; Verlicchi et al., 2012; Trinh et al., 2016a). This may also induce microorganisms metabolism of poorly degradable compounds due to relative shortages in biodegradable substances associated with reduced F/M ratio (Verlicchi et al., 2012). Suarez et al., (2010) classified CEC based on the removal potential under different biological conditions: i) highly removed under aerobic and anoxic conditions (e.g., ibuprofen, fluoxetine, natural estrogens); ii) highly removed under aerobic but persistent under anoxic conditions (e.g., diclofenac, 17α-ethynylestradiol, erythromycin), and iii) refractory to biological transformation (e.g., sulfamethoxazole, carbamazepine). Finally, temperature of wastewater as well as seasonal temperature changes play a role in the removal of CEC, as better removal is obtained at temperatures of 15–20°C compared to below 10°C (Vieno et al., 2005; Castiglioni et al., 2006).

Biodegradation and sorption are also the main CEC removal mechanisms in MBRs (Radjenović et al., 2008; Verlicchi et al., 2012; Luo et al., 2014; Li et al., 2015). This is because of the low molecular size of most CEC, typically below 1000 dalton, which leads to no direct physical retention on MF (microfiltration) and UF (ultrafiltration) membranes (retention size of ca. 10 000-500 000 Da). However, the sludge deposits formed on the membrane surface can act as an additional barrier contributing to the removal of CEC (Li et al., 2015). Furthermore, the hydrophobicity of CEC influences CEC sorption and removal. The removal is improved when the compound is significantly hydrophobic (log K_{ow}>3), such as the case of diclofenac, EE2, E2, EHMC, azithromycin, triallate and oxadiazon (Phan et al., 2014). Otherwise, sorption onto biosolids is limited and biodegradation is the dominant removal mechanism. Variable removal efficiencies have been reported in MBRs for persistent compounds, including diclofenac and carbamazepine, which have low k_{biol} and low K_d values (Wijekoon et al., 2013). Despite the agreement on the higher removal of hydrophobic compounds and containing electron donating functional groups (EDG) compared to the compounds with opposite characteristics by MBRs, there is still a lack of understanding on the complete causes of removal of CEC and their transformation products (TPs) in MBRs (Reif et al., 2013). Concerning the effect of the operating parameters on CEC removal in MBRs, similarly to CAS, Li et al., (2015) concluded that higher SRT, lower pH, higher nitrogen loading rate, and anoxic conditions favour removal of some pharmaceutical micropollutants in MBRs.

In CWs, a combination of physical, chemical, and biological processes may occur simultaneously and contribute to CEC removal. These include photodegradation, volatilization, phytoremediation, adsorption and sedimentation, as well as microbial biodegradation (Matamoros et al., 2005; Hijosa-Valsero et al., 2010a; Reyes-Contreras et al., 2012; Li et al., 2014b). First, photodegradation is an important removal pathway for CEC in CW systems with free water surface, i.e. surface flow CWs (Andreozzi et al., 2003). Seasonal variations leading to lower light availability, lower light intensity, or stronger light attenuation with increasing water depth will reduce photodegradation efficiency in aquatic systems (Buser et al., 1998; Matamoros et al., 2008). These parameters will also affect removal of compounds with high volatilization potential. Secondly, the plants in CWs can directly uptake and translocate CEC (Dordio et al., 2009; Dordio et al., 2010; Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011a; Carvalho et al., 2014). This uptake and translocation is most likely driven by diffusion, as no specific transporters exist within plants to move CEC into plant tissues (Dordio and Carvalho 2013). In addition, CEC can be transformed to less toxic compounds during metabolization in plants (Salt et al., 1998; He et al., 2017). Furthermore, the substrate of a CW (the CWs filling) can support growth of microorganisms and plants, and can adsorb different compounds, including CEC. Substrates with a greater adsorption capability for CEC can significantly enhance CEC removal (Dordio et al., 2007; Bui and Choi 2010; Conkle et al., 2010).

In MBBRs, the main removal mechanism is biodegradation. The amount of CEC eliminated with excess sludge withdrawal is lower than with CAS system as MBBRs work at a very low organic load. As mentioned in the CAS section above, SRT is as an important operational parameter for the removal of several micropollutants (Strenn et al., 2004). The agglomeration of bacteria as a biofilm and the retention of the support media for the attached growth process in the biological reactor results in long SRT. The geometry of the support media for bacterial growth allows the development of thin (~50 μm) or thick (> 200 μm) biofilms with different density, biodiversity composition, microbial activity and redox conditions (Torresi et al., 2017). Thin biofilms result in high nitrifying activities (enhancement of biotransformation kinetic of diclofenac, sulfamethoxazole, erythromycin, atenolol) while thick biofilms have a high bacterial biodiversity (more than 60% of target compounds showed higher biotransformation kinetics). Thus, combining the more suitable media and operational conditions lead the MBBR process to enhance specific or overall CEC elimination.

4. Effects of secondary treatments on chemical CEC fate

4.1 Influent characterization

To evaluate the performance of the analyzed technologies it is important to have information on the CEC concentrations present in WWTPs influents. These concentrations are relevant for the determination of the efficiency of the applied technology. Data available for the selected compounds are reported in supplementary material Table SM1, while the range of concentrations is reported in **Feil! Fant ikke referansekilden.**. A variable range, from a few ng/L to several μg/L, is observed, which makes necessary to evaluate, case by case, the effluent quality and the related CEC emissions.

Table 2. Concentration range of the selected CEC in municipal wastewater before treatment.

Category	Concentration range (ng/L)	Reference
Antibiotics		
Trimethoprim	13-6000	(Gobel et al., 2005; Perez et al., 2005; Leung et al., 2012; Senta et al., 2013; Guerra et al., 2014; Carvalho and Santos 2016; Botero-Coy et al., 2018)
Erythromycin	17-320	(Yang and Carlson 2004; Gobel et al., 2005; Gros et al., 2006; Papageorgiou et al., 2016; Botero-Coy et al., 2018)
Clarithromycin	BDL-8000	(Loganathan et al., 2009; Margot et al., 2013; Birošová et al., 2014; Guerra et al., 2014; Tran et al., 2018)
Azithromycin	BDL-6810	(Gobel et al., 2005; Loganathan et al., 2009; Margot et al., 2013; Senta et al., 2013; Botero-Coy et al., 2018)
Sulfamethoxazole	BDL-3100	(Gobel et al., 2005; Perez et al., 2005; Gros et al., 2006; Margot et al., 2013; Zhou et al., 2013; Guerra et al., 2014; Papageorgiou et al., 2016)
Enrofloxacin	3-100	(Watkinson et al., 2007; Ghosh et al., 2009; Birošová et al., 2014)
Ciprofloxacin	15-3350	(Watkinson et al., 2007; Margot et al., 2013; Zhou et al., 2013; He et al., 2015; Botero-Coy et al., 2018)
Other pharmaceuticals/antimicrobials		
Diclofenac	50-4114	(Clara et al., 2005b; Gros et al., 2006; Margot et al., 2013; Sari et al., 2014)
Metformin	BDL->10000	(Margot et al., 2013; Kosma et al., 2015)
Carbamazepine	54-1850	(Clara et al., 2005b; Nakada et al., 2006; Margot et al., 2013)
Lamotrigine	13-1110	(Bollmann et al., 2016; Zonja et al., 2016)
Triclosan	500- 6100	(Lindstrom et al., 2002; Singer et al., 2002; Halden and Paull 2005; Ying and Kookana 2007)
Industrial Chemicals		
2,6-Ditert-butyl-4-methylphenol(BHT)	2420	(Liu et al., 2015)
Tris(2-chloroethyl) phosphate (TCEP)	180-439	(Meyer and Bester 2004; Ryu et al., 2014; Zeng et al., 2015; Cristale et al., 2016)
Tetrabromobisphenol A	$1.22x10^{-4}$-41	(Morris et al., 2004; Potvin et al., 2012; Kim et al., 2016)
Hexabromocyclododecane	1.2-11	(Vieno and Toivikko 2014; De Guzman 2016)

(HBCD)		
Benzotriazole (BTA)	1119- 44000	(Reemtsma et al., 2010; Liu et al., 2012; Asimakopoulos et al., 2013)
N-Nitrosodimethylamine (dimethyl-nitrosamine)	183-8230	(Yoon et al., 2011; Wang L. 2014)
Perfluorobutanoic acid (PFBA)	0.05-265	(Zhang et al., 2013; Zhang et al., 2015a)
Perfluoropentanoic acid (PFPeA)	0.5- 1520	(Lin et al., 2010; Ma and Shih 2010; Pan et al., 2011; Kim et al., 2012; Zhang et al., 2013; Zhang et al., 2015a)
Perfluorohexanoic acid (PFHxA)	1-348	(Lin et al., 2010; Ma and Shih 2010; Kim et al., 2012; Zhang et al., 2013; Zhang et al., 2015a)
Estrogens		
Estrone (E1)	11.6-224	(Zhou et al., 2012; Margot et al., 2013; Ekpeghere et al., 2018)
17β-Estradiol (E2)	3.7-140	(Zhou et al., 2012; Margot et al., 2013; Ekpeghere et al., 2018)
17α-Ethynylestradiol (EE2)	BDL-330	(Zhou et al., 2012; Margot et al., 2013; Ekpeghere et al., 2018)
Personal care products		
2-Ethylhexyl ethoxycinnamate (EHMC)	23-1290	(Tsui et al., 2014; Ekpeghere et al., 2016)
Neonicotinoids		
Imidacloprid	54.7	(Sadaria et al., 2016)
Thiacloprid	BDL	(Sadaria et al., 2016)
Thiamethoxam	BDL	(Sadaria et al., 2016)
Clothianidin	149.7	(Sadaria et al., 2016)
Acetamiprid	3.7	(Sadaria et al., 2016)
Pesticides		
Methiocarb	N.A.	
Oxadiazon	N.A.	
Triallate	N.A.	

Legend: BDL - below detection limit; N.A. – not available.

4.2 Conventional activated sludge

Data available on the removal efficiencies detected for CAS are mainly related to pharmaceuticals (by far the most investigated class of CEC), personal care products and endocrine disruptor compounds.

The high concentrations especially for some pharmaceuticals reported in **Feil! Fant ikke referansekilden.** show that, even when high removal efficiencies are achieved, consistent residual amounts will remain in the effluent which can significantly impact the receiving water body or compromise treated wastewater reuse.

Table 3 shows an overview of the data on the removal efficiencies for the selected CEC in secondary treatment by CAS. Reported data are mainly referring to the last decade. A high variability in the removal efficiencies is observed, which can be explained with the seasonal variation of the plant performance and the variability of the CEC influent concentrations. Moreover, the presence of very low concentrations, which, in some cases, are close or below detection limits, makes the evaluation of a precise removal efficiency difficult. A more detailed and extended table (Table SM2) on the removal efficiencies is included in supplementary material.

According to the results of a Canadian survey of 18 WWTPs (Metcalfe et al., 2003), primary treatment resulted in minimal reductions of CEC, while better results were observed for the secondary. It is worth noting that in several cases negative removals were observed, which are indicative of formation of parent compounds e.g., through de-conjugation, or accumulation of the substances during treatment, especially if sampling was carried out during non-steady-state plant operation. In addition, effluent quality can be worsened by the formation of intermediate products in case of partial biodegradation.

Among the selected pharmaceuticals, the neutral drug carbamazepine was poorly removed by the secondary treatment. It resulted as one of the most critical compounds, among the monitored pharmaceuticals, in all countries. This behaviour may be due to its hydrophilic nature ($\log K_{ow} < 3$) and chemical stability (Nakada et al., 2006). Similar behaviour is observed for lamotrigine which, in two recent studies (Bollmann et al., 2016; Zonja et al., 2016), showed a consistent concentration increase in the effluent.

For the selected antibiotics, highest removal efficiencies were detected for ciprofloxacin and sulfamethoxazole, while the other antibiotics are characterized by quite low removals.

As regard as the estrogenic compounds, higher removal efficiencies were observed for the hormone 17β-estradiol than for estrone (Zhou et al., 2012). Secondary treatment can reach removal efficiencies ≥ 90% for estrogenic compounds but only in WWTPs performing nitrification or nitrogen removal (Andersen et al., 2003). This is because high HRT and SRT are required for efficient estrone removal, as it is confirmed by Margot et al., (2013) reporting the data of the Lausanne plant (operated without nitrification) where the removal of 17β-estradiol and estrone was 91% and 58±31%, respectively.

Not many data are available for EHMC removal and neonicotinoids in CAS. Tsui et al., (2014) for a WWTP operated with Modified Ludzack Ettinger configuration, reported low to moderate removal of EHMC, i.e., 30% in the wet season and 55% in the dry season, which was negatively affected by seasonal variation of the influent load and temperature during the wet season. As regard as neonicotinoids, Sadaria et al., (2016) in a recent study on a WWTP measured low removal efficiencies of 11-18% for the selected compounds except for thiacloprid and thiamethoxam showing negligible concentration (BDL) in the influent and effluent.

Pesticides are among the organic contaminants most investigated in the aquatic environment, but their occurrence and fate in WWTPs has been rarely investigated, perhaps because these compounds are of agricultural rather than of urban origin. In spite of this, wastewaters represent one of the main routes of pesticide contamination into the environment (Cahill et al., 2011) and several sources justifying the presence of pesticides in WWTPs were identified. They are extensively applied in grass-maintenance, in industrial vegetation control for electric utilities, roadways, railroads, pipelines, and in non-agricultural crops such as commercial forestry and horticulture (Barceló D 2003). For these reasons, to our best knowledge data on these specific compounds in the target list are not available in literature. In any case, it is worth noting that the reported removals of pesticides in full-scale WWTPs are generally poor with presence, in some cases, of increased concentrations in the effluent (Kock-Schulmeyer et al., 2013).

An extremely variable behaviour in WWTPs is observed for industrial chemicals with almost complete/good removal for instance for BHT, TBBP-A, BTA, and wide range of removal efficiency for other compounds such as PFCAs (PFBA, PFPeA, PFHxA) and NDMA. This finding is expected if we consider the diversity of the chemical structure, which as pointed out in the paragraph 4.1 consistently affects the removal mechanisms.

From the data analysis of CAS, we can conclude that CEC removal efficiency is strongly affected by HRT and SRT. To give a general idea of the limit values, according to Metcalfe et al., (2003), worst performance is observed in plants having HRT $\leq$ 7 hr and SRT $\leq$ 1.9 d.

Table 3. Range of the removal efficiencies of the selected CEC in CAS plants

Category	**Removal efficiency (%)**	**Reference**
Antibiotics		
Trimethoprim	31	(Gobel et al., 2005)
Erythromycin	(-14)-100	(Yang and Carlson 2004; Gobel et al., 2005; Gros et al., 2006)
Clarithromycin	37	(Margot et al., 2013)
Azithromycin	11-44	(Gobel et al., 2005; Loganathan et al., 2009; Margot et al., 2013)
Sulfamethoxazole	35-84	(Gobel et al., 2005; Margot et al., 2013; Zhou et al., 2013)
Enrofloxacin	~ 0	(Watkinson et al., 2007)
Ciprofloxacin	63-90	(Margot et al., 2013; Zhou et al., 2013)
Other pharmaceuticals/antimicrobials		
Diclofenac	<0-81	(Clara et al., 2005b; Margot et al., 2013; Luo et al., 2014; Sari et al., 2014)
Metformin	78-99	(Kosma et al., 2015)
Carbamazepine	(-90)-(-3)	(Metcalfe et al., 2003; Clara et al., 2005b; Nakada et al., 2006; Margot et al., 2013)
Lamotrigine	(-361)-(-38)	(Bollmann et al., 2016; Zonja et al., 2016)
Triclosan	34-99	(Lindstrom et al., 2002; Singer et al., 2002; Halden and Paull 2005; Ying and Kookana 2007)
Industrial Chemicals		
2,6-Ditert-butyl-4-methylphenol(BHT)	89	(Liu et al., 2015)
Tris(2-chloroethyl) phosphate (TCEP)	(-106)-0	(Meyer and Bester 2004; Ryu et al., 2014; Zeng et al., 2015; Cristale et al., 2016)
Tetrabromobisphenol A	10-100	(Potvin et al., 2012; Kim et al., 2016)
Hexabromocyclododecane (HBCD)	0-86	(Vieno and Toivikko 2014; De Guzman 2016)
Benzotriazole (BTA)	30-91	(Reemtsma et al., 2010; Liu et al., 2012; Asimakopoulos et al., 2013)
N-Nitrosodimethylamine (dimethyl-nitrosamine) (NDMA)*	5-84	(Yoon et al., 2011; Wang L. 2014)

Perfluorobutanoic acid (PFBA)	(-108)-65	(Zhang et al., 2013; Zhang et al., 2015a)
Perfluoropentanoic acid (PFPeA)	(-400)-50	(Pan et al., 2011; Kim et al., 2012; Zhang et al., 2013; Zhang et al., 2015a)
Perfluorohexanoic acid (PFHxA)	(-226)-39	(Kim et al., 2012; Zhang et al., 2013; Zhang et al., 2015a)
Estrogens		
Estrone (E1)	58-81	(Zhou et al., 2012; Margot et al., 2013)
17β-Estradiol (E2)	91-96	(Zhou et al., 2012; Margot et al., 2013)
17α-Ethynylestradiol (EE2)	>18-94	(Zhou et al., 2012; Margot et al., 2013)
Personal care products		
2-Ethylhexyl ethoxycinnamate (EHMC)	30-55	(Tsui et al., 2014)
Neonicotinoids		
Imidacloprid	11	(Sadaria et al., 2016)
Thiacloprid	BDL in/out	(Sadaria et al., 2016)
Thiamethoxam	BDL in/out	(Sadaria et al., 2016)
Clothianidin	13	(Sadaria et al., 2016)
Acetamiprid	18	(Sadaria et al., 2016)
Pesticides		
Methiocarb	N.A.	
Oxadiazon	N.A.	
Triallate	N.A.	

4.3 Membrane bioreactors

The MBR is a process that integrates biodegradation of contaminants by activated sludge, with direct solid-liquid separation by membrane filtration, i.e. through a MF or UF membrane. The MBR technology is currently widely accepted as an alternative key technology to CAS treatment utilised in urban WWTPs and water reuse applications. The wide use of MBRs has been attributed to its notable advantages, such as high quality of produced water, high biodegradation efficiency of contaminants, and an overall smaller footprint (Judd, 2015).

This technology permits bioreactor operation with considerably higher mixed liquor suspended solids (MLSS) concentration than CAS systems, which are limited by sludge settling phenomena. The process in MBRs is typically operated at MLSS in the range of 8–12 g/L, while CAS is operated in the range of 2–3 g/L (Melin et al. 2006), thus providing high biological activity per unit volume. This feature favours the generation of slow-growing bacteria, which have the ability to degrade certain biologically-recalcitrant organic and inorganic pollutants (Clouzot et al., 2011). Therefore, despite not been designed to remove organic and inorganic micropollutants, MBRs may provide effective removal of some of the CEC. Early studies reported improved CEC removal with MBRs compared to CAS, as MBRs operate at a higher SRT than CAS, thus enhancing contaminant biodegradability (Holbrook et al., 2002; Stephenson et al., 2007). However, when MBRs and CAS were compared under similar operating conditions (i.e., SRT, temperature) in the removal of CEC, no significant differences were observed (Joss et al., 2006; Bouju et al.m 2008; Weiss and Reemtsma, 2008; Abegglen et al., 2009). Therefore, it was postulated that MBRs and CAS systems may perform similar as long as the same operating conditions are provided, although MBRs may outperform CAS at higher SRT. This is because CEC are generally highly soluble and relatively small compounds, typically below 1000 Dalton, which can freely pass through the membranes used in MBR systems thereby indicating that those membranes have no direct impact on the removal of

CEC (Snyder et al., 2007). Others report that MBRs are able to effectively remove a wide spectrum of CEC including compounds that are not eliminated during CAS processes (Radjenović et al., 2009; Luo et al., 2014).

Overall, the potential to achieve slightly improved removal of CEC in MBRs compared to the CAS process, is attributed to: (1) complete retention of suspended and colloidal particles to which many of the CEC sorb or are entrapped at the cake layer developed on the membrane surface; (2) ability to operate under longer SRT providing additional biological transformation of CEC (via diversification of microorganisms metabolic activity in response to the lower sludge loading with bulk organics) and more diversified microbial community (e.g. nitrifying bacteria); and (3) higher biomass concentrations providing higher degradation rate. All of the aforementioned factors may provide additional removal mechanisms of CEC. On the other hand, the advantage of operating MBRs at very high SRT to promote the biodegradation of recalcitrant compounds is usually offset by the increased operating costs associated with the higher oxygen requirements of biomass. Hence, despite significant research attention in the past years, general consensus regarding the MBRs and CAS potential to remove CEC has not been reached yet.

Table 4 summarizes the removal efficiency of the selected CEC (Hernando et al., 2007; Onesios et al., 2008; Petrovic et al., 2009; Tambosi et al., 2010b; Verlicchi et al., 2012; Reif et al., 2013; Rojas et al., 2013; de Cazes et al., 2014; Luo et al., 2014; Eggen and Vogelsang 2015; Li et al., 2015). The overview excludes the experimental work carried out using lab-scale MBR systems fed with synthetic wastewater, and reports only results from full-scale MBRs or pilot-scale MBRs located at the premises of the WWTPs and fed with real wastewater. Until now, only a limited number of the studies were performed on full-scale MBR installations (Sui et al., 2011; Trinh et al., 2012b; Oosterhuis et al., 2013; Fenu et al., 2015; Trinh et al., 2016b).

A more detailed table including the operating conditions of the WWTPs and on the type of wastewater and sampling methods is reported in the supplementary material section (Table SM3).

Table 4. Range of the removal efficiencies of the selected CEC in MBRs

Category	Removal efficiency (%)	References
Antibiotics		
Trimethoprim	<0-99	(Göbel et al., 2007; Kim et al., 2007; Snyder et al., 2007; Tambosi et al., 2010a; Sahar et al., 2011a; Sahar et al., 2011b; Sahar et al., 2011c; Sui et al., 2011; Schröder et al., 2012; Trinh et al., 2012b; Qi et al., 2015; Arriaga et al., 2016; Tran et al., 2016; Trinh et al., 2016b; Arola et al., 2017; Park et al., 2017)
Erythromycin	4-99	(Kim et al., 2007; Radjenovic et al., 2007; Snyder et al., 2007; Barceló et al., 2009; Radjenovic et al., 2009; Xue et al., 2010; Sahar et al., 2011a; Sahar et al., 2011b; Sahar et al., 2011c; Dolar et al., 2012; Malpei et al., 2012; Kim et al., 2014; Qi et al., 2015; Arriaga et al., 2016; Mamo et al., 2016; Tran et al., 2016)
Clarithromycin	<0-99	(Göbel et al., 2007; Sahar et al., 2011a; Sahar et al., 2011b; Sahar et al., 2011c; Dolar et al., 2012; Malpei et al., 2012; Kim et al., 2014; Qi et al., 2015; Arriaga et al., 2016; Mamo et al., 2016; Tran et al., 2016; Park et al., 2017)
Azithromycin	5-90	(Göbel et al., 2007; Dolar et al., 2012; Kim et al., 2014; Mamo et al., 2016; Tran et al., 2016)
Sulfamethoxazole	0-90	(Kreuzinger et al., 2004; Clara et al., 2005b; Joss et al., 2005; Göbel et al., 2007; Kim et al., 2007; Radjenovic et al., 2007; Barceló et al., 2009; Radjenovic et al., 2009; Le-Minh et al., 2010:Snyder, 2007 #1635; Tambosi et al., 2010a; Sahar et al., 2011a; Sahar et al., 2011b; Sahar et al., 2011c; Dolar et al., 2012; García Galán et al., 2012; Schröder et al., 2012; Trinh et al., 2012b; Kim et al., 2014; Fenu et al., 2015; Phan et al., 2015; Qi et al., 2015; Tran et al., 2016; Trinh et al., 2016b; Park et al., 2017)
Enrofloxacin	<LOQ-56	(Baumgarten et al., 2007; Park et al., 2017)
Ciprofloxacin	15-94	(Baumgarten et al., 2007; Malpei et al., 2012; Kim et al., 2014; Tran et al., 2016; Park et al., 2017)
Other pharmaceuticals/antimicrobials		
Diclofenac	<0-87	(Clara et al., 2005a; Clara et al., 2005b; Kimura et al., 2005; Quintana et al., 2005; Bernhard et al., 2006; González et al., 2006; Kim et al., 2007; Kimura et al., 2007; Radjenovic et al., 2007; Snyder et al., 2007; Pérez and Barceló 2008; Barceló et al., 2009; Radjenovic et al., 2009; Xue et al., 2010; Sahar et al., 2011a; Sui et al., 2011; Lipp et al., 2012; Malpei et al., 2012; Trinh et al., 2012b; Cartagena et al., 2013; Oosterhuis et al., 2013; Phan et al., 2015; Qi et al., 2015; Arriaga et al., 2016; Trinh et al., 2016b; Arola et al., 2017; Park et al., 2017; Tran and Gin 2017)
Metformin	94-99	(Trinh et al., 2012b; Oosterhuis et al., 2013; Kim et al., 2014)
Carbamazepine	<0-96	(Kreuzinger et al., 2004; Clara et al., 2005a; Clara et al., 2005b; Joss et al., 2005; Bernhard et al., 2006; Kim et al., 2007; Radjenovic et al., 2007; Snyder et al., 2007; Barceló et al., 2009; Radjenovic et al., 2009; Xue et al., 2010; Sui et al., 2011; Dialynas and Diamadopoulos 2012; Dolar et al., 2012; Lipp et al., 2012; Malpei et al., 2012; Trinh et al., 2012b; Cartagena et al., 2013; Oosterhuis et al., 2013; Kim et al., 2014; Komesli et al., 2015; Phan et al., 2015; Qi et al., 2015; Arriaga et al., 2016; Arola et al., 2017; Park et al., 2017; Tran and Gin 2017)

Lamotrigine	0-84	(Bollmann et al., 2016)
Triclosan	41-96	(Kim et al., 2007; Snyder et al., 2007; Kantiani et al., 2008; Coleman et al., 2009; Trinh et al., 2012b; Cartagena et al., 2013; Tran et al., 2016; Trinh et al., 2016b)
Industrial Chemicals		
2,6-Ditert-butyl-4-methylphenol(BHT)	N.A.	
Tris(2-chloroethyl) phosphate (TCEP)	<0-37	(Bernhard et al., 2006; Kim et al., 2007)
Tetrabromobisphenol A	62-90	(Potvin et al., 2012)
Hexabromocyclododecane (HBCD)	N.A.	
Benzotriazole (BTA)	15-74	(Weiss and Reemtsma 2008; Sahar et al., 2011b; Qi et al., 2015; Arriaga et al., 2016)
N-Nitrosodimethylamine (dimethyl-nitrosamine) (NDMA)*	70-94	(Gerrity et al., 2015; Mamo et al., 2016)
Perfluorobutanoic acid (PFBA)	11	(Pan et al., 2016)
Perfluoropentanoic acid (PFPeA)	<0	(Pan et al., 2016)
Perfluorohexanoic acid (PFHxA)	<0	(Pan et al., 2016)
Estrogens		
Estrone (E1)	58-100	(Joss et al., 2004; Clara et al., 2005a; Joss et al., 2005; Zuehlke et al., 2006; Coleman et al., 2009; Le-Minh et al., 2010; Xue et al., 2010; Cases et al., 2011; Wu et al., 2011a; Trinh et al., 2012a; Trinh et al., 2012b; He et al., 2013; Phan et al., 2015; Trinh et al., 2016b)
17β-Estradiol (E2)	39-100	(Joss et al., 2004; Clara et al., 2005a; Zuehlke et al., 2006; Lee et al., 2008; Le-Minh et al., 2010; Xue et al., 2010; Wu et al., 2011a; Dialynas and Diamadopoulos 2012; Trinh et al., 2012a; Trinh et al., 2012b; He et al., 2013; Trinh et al., 2016b)
17α-Ethynylestradiol (EE2)	20-100	(Clara et al., 2004; Joss et al., 2004; Kreuzinger et al., 2004; Clara et al., 2005a; Zuehlke et al., 2006; Le-Minh et al., 2010; Xue et al., 2010; Wu et al., 2011b; Dialynas and Diamadopoulos 2012; He et al., 2013; Trinh et al., 2016b)
Personal care products		
2-Ethylhexyl ethoxycinnamate (EHMC)	N.A.	
Neonicotinoids		
Imidacloprid	N.A.	
Thiacloprid	N.A.	
Thiamethoxam	N.A.	
Clothianidin	N.A.	

Acetamiprid	N.A.
Pesticides	
Methiocarb	N.A.
Oxadiazon	N.A.
Triallate	N.A.

4.4 Constructed Wetlands

Constructed wetlands (CWs) are treatment systems that use natural processes involving wetland vegetation, soils, and their associated microbial assemblages. As nature-based solutions, CWs have the potential to address societal and economical challenges related to safe water reuse. If well designed and maintained, CWs may provide effluents suitable for water reuse (Rousseau et al., 2008).

CWs are mainly used to efficiently remove organic matter, suspended solids, nutrients, and some metals from wastewater, and in recent years, CWs have been used also to remove organic pollutants, such as pesticides (Matamoros and Salvadó 2012), hydrocarbons (Guittonny-Philippe et al., 2015) and a few CEC (Gorito et al., 2017). Currently, CWs are recognized as a reliable wastewater treatment technology, representing a suitable solution for the treatment of many types of wastewaters, such as municipal or domestic wastewaters, storm water, agricultural wastewaters and industrial wastewaters (such as petrochemicals, pulp and paper, food wastes and mining industries) (Vymazal 2011a). Furthermore, due to their simple set-up and low maintenance, CWs can be used in rural areas, where the treated water can be reused in agriculture.

CWs are applied as a secondary treatment of municipal wastewater in relatively small communities, i.e. up to 1000 population equivalent (PE), but can also be used for the treatment of wastewater from greater areas covering 2000 PE (or more) (Vymazal 2011b). A limitation of the use of CWs for large, urbanized areas is associated with the higher area demand for these systems in comparison to the techniques based on activated sludge. Various examples exist on the removal of CEC in secondary treatments (Table 5 and Table SM4), and only a few applications of CWs for removing CEC during the polishing of wastewater effluent as a tertiary treatment are reported (Dordio et al., 2007; Imfeld et al., 2009; Bui and Choi 2010; Bhatia and Goyal 2014; Garcia-Rodríguez et al., 2014).

The removal efficiencies of the tested CEC are seasonally variable, with higher removal percentages in summer compared to winter (Garcia-Rodríguez et al., 2014; Li et al., 2014b). Furthermore, different designs exist, such as surface flow CWs (SF CWs), and sub-surface flow CWs with horizontal (HF) and vertical (VF) flows (Vymazal 2011b). Higher removal rates were found in systems with sub-surface flow (horizontal) CWs to surface flow CWs (Imfeld et al., 2009; Berglund et al., 2014; Bhatia and Goyal 2014; Li et al., 2014b; Díaz-Cruz and Barceló 2015). Other important parameters are water depth, HRT, vegetation type, temperature (seasonality), and substrate (CWs filling) type (Verlicchi and Zambello 2014; Zhang et al., 2014).

In the literature, various CWs applications for CEC removal are described, and details for the selected compounds are given in Table 5 and Table SM4, and described below. Current literature focuses on measuring influent and effluent concentrations of CEC to evaluate the overall removal performance, rather than detailed studies on the actual fate of target compounds or their removal pathways. CWs have shown the potential to remove CEC from urban/domestic wastewaters, including diclofenac, metformin, carbamazepine, triclosan, trimethoprim, clarithromycin, erythromycin, sulfamethoxazole, estrone, 17β-estradiol, 17α-ethynylestradiol, and benzotriazole (see Table 5 and Table SM4 for details and percent removal efficiency). Diclofenac is the most studied CEC, described in almost 70% of the published studies on CEC removal in CWs (see Table 5). Other well-studied compounds are the pharmaceuticals carbamazepine and triclosan and the antibiotics trimethoprim and sulfamethoxazole.

In detail, many of the studied compounds showed removal up to 100%. Nevertheless, the removal percentage is dependent on the CWs operational parameters, e.g. surface flow or subsurface flow (either horizontal or vertical) as can be seen in Table SM4. For instance, benzotriazole and trimethoprim were more effectively removed in vertical subsurface flow CW that in a surface flow CW. Especially the vertical sub-surface flow CWs are known to promote biodegradation. The water flow affects the redox conditions which in turn affects removal mechanisms, resulting e.g. in a better removal of metformin under oxic conditions in a sub-surface flow CW. Other factors, such as plants presence, plants species and temperature (seasonal) can also determine compounds removal. For instance, the removal of E1, E2 and EE2 increased in summer compared to winter. On the other hand, erythromycin and clarithromycin removals were favoured in the presence of plants, particularly in the presence of *Iris tectorum*. Triclosan removal was also favoured by a higher temperature and by the presence of the plant *Phragmites australis*. Details on these studies are given in Table SM4.

Despite the high removal rates observed for the above-mentioned compounds, at least three compounds showed limited removal in CWs, due to their more recalcitrant nature. Diclofenac, carbamazepine and sulfamethoxazole were poorly removed in most studies, with only 1 or 2 studies showing higher removal. For example, a reported removal of carbamazepine in sub-surface horizontal flow CWs higher than 88% is remarkable (Garcia-Rodríguez et al., 2014), as this pharmaceutical is known to be poorly biodegradable. The mechanism of carbamazepine removal has not been fully elucidated, but Garcia-Rodríguez et al., (2014) describe a relation between the removal efficiency and residence time in the CW. The few parameters that are known to have a positive effect, e.g. vertical subsurface flow, higher temperature and plant presence, only slightly improved the removal of these three compounds. As a result, these 3 compounds are considered moderately removed by CWs indicating that CWs treatment should be combined with other wastewater treatments for an efficient removal of these compounds for wastewaters.

Other CEC, such as the antibiotics enrofloxacin (veterinary application) and ciprofloxacin, have not been mentioned in studies of urban/domestic wastewater CWs treatment. However, studies with e.g. livestock wastewater show the potential of CWs for secondary treatment (Hsieh et al., 2015; Almeida et al., 2017).So far, removal of the majority of industrial chemicals (see Table 5), neonicotinoids, and selected pesticides in a CW has not been described. Of the neonicotinoids, 100% removal of imidacloprid in a CW has been reported, although spiked water was used instead of real wastewater. These results indicate that more research on CWs applicability to remove these compounds from wastewater is needed.

To conclude, CWs can be used for secondary treatment of wastewater containing selected CEC. There are several factors important when using a CW, such as the available area, CW design and operational conditions and the impact of seasonal conditions. Just like CAS systems, current CWs are not able to entirely eliminate CEC from wastewater. The efficiency of the processes occurring in CWs depends primarily on the operation mode, design, type of substrate and the presence and type of plants. The effectiveness of the processes in the CWs can be increased by the use of hybrid systems, which combine CWs of different design connected in series (Vymazal 2011b; Garcia-Rodríguez et al., 2014; Verlicchi and Zambello 2014; Zhang et al., 2014; Díaz-Cruz and Barceló 2015). Combinations of CWs with other processes are also feasible, e.g. processes induced by sunlight (with/without photocatalysts) as the final stage of purification (Mahabali and Spanoghe 2013; Felis et al., 2016; He et al., 2016).

Table 5. Range of the removal efficiencies of selected CEC in different types of CWs[a]

Category	**Removal efficiency (%)**	**References**
Antibiotics		
Trimethoprim	0-100	(Hijosa-Valsero et al., 2011a; Dan et al., 2013; Du et al., 2014; Chen et al., 2016; Ávila et al., 2017)
Erythromycin	0-92	(Hijosa-Valsero et al., 2011a; Ávila et al., 2014b; Du et al., 2014; Chen et al., 2016)
Clarithromycin	11-98	(Hijosa-Valsero et al., 2011a; Chen et al., 2016; Vymazal et al., 2017)
Azithromycin	N.A.	
Sulfamethoxazole	0-75	(Hijosa-Valsero et al., 2011a; Dan et al., 2013; Du et al., 2014; Chen et al., 2016; Auvinen et al., 2017; Ávila et al., 2017)
Enrofloxacin	N.A.	
Ciprofloxacin	N.A.	
Other pharmaceuticals/antimicrobials		
Diclofenac	0-75	(Matamoros and Bayona 2006; Matamoros et al., 2007; Matamoros et al., 2009; Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011a; Hijosa-Valsero et al., 2011b; Hijosa-Valsero et al., 2012; Reyes-Contreras et al., 2012; Ávila et al., 2013; Ávila et al., 2014a; Ávila et al., 2014b; Carranza-Diaz et al., 2014; Du et al., 2014; Hijosa-Valsero et al., 2016; Auvinen et al., 2017; Vymazal et al., 2017)
Metformin	99±1	(Auvinen et al., 2017)
Carbamazepine	0-50	(Hijosa-Valsero et al., 2010b; Hijosa-Valsero et al., 2011a; Hijosa-Valsero et al., 2011b; Reyes-Contreras et al., 2011; Camacho-Muñoz et al., 2012; Hijosa-Valsero et al., 2012; Reyes-Contreras et al., 2012; Carranza-Diaz et al., 2014; Du et al., 2014; Hijosa-Valsero et al., 2016; Auvinen et al., 2017; Ávila et al., 2017)
Lamotrigine	N.A.	
Triclosan	2-88	(Matamoros et al., 2007; Reyes-Contreras et al., 2011; Ávila et al., 2014b; Carranza-Diaz et al., 2014; Vymazal et al., 2017)
Industrial Chemicals		
2,6-Ditert-butyl-4-methylphenol(BHT)	N.A.	
Tris(2-chloroethyl) phosphate (TCEP)	N.A.	
Tetrabromobisphenol A	N.A.	
Hexabromocyclododecane (HBCD)	N.A.	
Benzotriazole (BTA)	8-100	(Matamoros et al., 2010)
N-Nitrosodimethylamine (dimethyl-nitrosamine) (NDMA)*	N.A.	

Perfluorobutanoic acid (PFBA)	N.A.	
Perfluoropentanoic acid (PFPeA)	N.A.	
Perfluorohexanoic acid (PFHxA)	N.A.	
Estrogens		
Estrone (E1)	0-90	(Peterson and Lanning 2009; Qiang et al., 2013; Vymazal and Březinová 2015; Dai et al., 2016)
17β-Estradiol (E2)	0-100	(Peterson and Lanning 2009; Qiang et al., 2013; Vymazal and Březinová 2015; Dai et al., 2016)
17α-Ethynylestradiol (EE2)	8-100	(Kumar et al., 2011; Qiang et al., 2013; Ávila et al., 2014b; Vymazal and Březinová 2015)
Personal care products		
2-Ethylhexyl ethoxycinnamate (EHMC)	N.A.	
Neonicotinoids		
Imidacloprid	N.A.	
Thiacloprid	N.A.	
Thiamethoxam	N.A.	
Clothianidin	N.A.	
Acetamiprid	N.A.	
Pesticides		
Methiocarb	N.A.	
Oxadiazon	N.A.	
Triallate	N.A.	

4.5 Moving bed biofilm reactor

Moving bed biofilm reactors (MBBRs) seem to be a promising alternative for the elimination of micropollutants. However, only few studies reported the application of the MBBR technology for CEC removal (Escola Casas et al., 2015a; Mazioti et al., 2015), and the studies based on real wastewater and full- to pilot-scale systems are missing. Therefore, lab-scale studies evaluating MBBR process as a secondary treatment for CEC removal from wastewater, which were based either on synthetic wastewater or hospital wastewater, are also considered. The contribution of biofilm communities (Torresi et al., 2017), its add-in value inside a hybrid MBBR system (Falas et al., 2013; Escola Casas et al., 2015b) or its contribution as a polishing treatment (Escola Casas et al., 2015b; Tang et al., 2017; Torresi et al., 2017) for CEC removal were also investigated. Details of these studies can be found in Table 6, Table SM5 and Table SM6.

The performance of an MBBR system for the removal of pharmaceuticals from pre-treated hospital raw wastewater was evaluated by Escola Casas et al., (2015a). The system consisted of three identical reactors in series, with biomass concentrations of 3.1, 1.4, and 0.5 g/L respectively. The results showed that both high organic load (co-metabolism in the first reactor) and low organic load (more effective biofilm in the third reactor) acted for the overall removal of the pharmaceuticals. However, the comparison of the kinetic coefficient k_{biol} between the three reactors showed that four pharmaceuticals had higher k_{biol} in the third reactor (carbamazepine, clarithromycin, ciprofloxacin, and erythromycin) while diclofenac, sulfamethoxazole, and trimethoprim showed higher k_{biol} in the second one. Escola Casas et al., (2015a) paved the way for the development of MBBR reactors with higher concentration of efficient biomass for the removal of recalcitrant pharmaceuticals.

Mazioti et al., (2015) compared degradation of benzotriazole in CAS with a sludge return (HRT 26.4 ± 2.4 h), MBBR at high organic load rate (OLR) (0.25 ± 0.16 kg m^{-3} d^{-1}, HRT 10.8 ± 1.2 h), and MBBR at low OLR (0.6 ± 0.4 kg m^{-3} d^{-1}, HRT 26.4 ± 2.4 h). Results showed similar removal efficiencies for the MBBR and CAS system at low OLR and worse results at high OLR. Specific removal ($\mu g\ g^{-1}\ d^{-1}$) tripled between the first reactor at high OLR and the first reactor at low OLR ($11.9 \pm 1.3\ \mu g\ g^{-1}\ d^{-1}$) or the second bioreactor at high OLR ($11.0 \pm 5.3\ \mu g\ g^{-1}\ d^{-1}$). As co-metabolism (COD and NH_4) showed nearly no differences for benzotriazole removal, this difference should be in relation with biomass specification even no bacterial communities' analysis was performed.

In general, the efficiency of biological process is linked with physicochemical characteristics of the compound (k_{biol}, k_d) and process parameters (temperature, HRT, SRT, pH, redox conditions). As MBBR is a biological process, the main removal mechanism is biodegradation which is quantified by the k_{biol} constant ($L\ h^{-1}g^{-1}$). SRT, OLR, and nitrification rate are higher in MBBR and have a positive impact on CEC removal (Oulton et al., 2010).

These studies showed that both co-metabolism and balanced bacterial diversity could enhance CEC removal to some extent. The application of MBBR is not restricted to secondary biological treatment but may also have a successful future in polishing treatment. A comprehensive bibliographic review has been done on use of bacterial supports for the CEC removal and is summarized in Table 6, Table SM5 and Table SM6.

629 **Table 6.** Range of the removal efficiencies of the selected CEC in MBBRs

Category	Removal efficiency (%)	References
Antibiotics		
Trimethoprim	2-96	(Escola Casas et al., 2015a; Escola Casas et al., 2015b; Tang et al., 2017)
Erythromycin	16-35	(Escola Casas et al., 2015a; Escola Casas et al., 2015b)
Clarithromycin	47-61	(Escola Casas et al., 2015a; Escola Casas et al., 2015b)
Azithromycin	BDL-34	(Escola Casas et al., 2015a; Escola Casas et al., 2015b)
Sulfamethoxazole	(-28)-28	(Escola Casas et al., 2015a; Escola Casas et al., 2015b; Tang et al., 2017)
Enrofloxacin	(-36)-21	(Escola Casas et al., 2015a; Escola Casas et al., 2015b; Tang et al., 2017)
Ciprofloxacin	2-96	(Escola Casas et al., 2015a; Escola Casas et al., 2015b; Tang et al., 2017)
Other pharmaceuticals/antimicrobials		
Diclofenac	25-100	(Falas et al., 2013; Zupanc et al., 2013; Luo et al., 2014; Luo et al., 2015; Tang et al., 2017)
Metformin	N.A.	
Carbamazepine	0-75	(Falas et al., 2013; Zupanc et al., 2013; Luo et al., 2014; Escola Casas et al., 2015a; Escola Casas et al., 2015b; Luo et al., 2015; Tang et al., 2017)
Lamotrigine	N.A.	
Triclosan	80-92	(Luo et al., 2014; Luo et al., 2015)
Industrial Chemicals		
2,6-Ditert-butyl-4-methylphenol(BHT)	N.A.	
Tris(2-chloroethyl) phosphate (TCEP)	N.A.	
Tetrabromobisphenol A	N.A.	
Hexabromocyclododecane (HBCD)	N.A.	
Benzotriazole (BTA)	43-76	(Mazioti et al., 2015)
N-Nitrosodimethylamine (dimethyl-nitrosamine) (NDMA)*	N.A.	
Perfluorobutanoic acid (PFBA)	N.A.	
Perfluoropentanoic acid (PFPeA)	N.A.	
Perfluorohexanoic acid (PFHxA)	N.A.	
Estrogens		

Estrone (E1)	65-95	(Luo et al., 2014; Luo et al., 2015; Amin et al., 2018)
17β-Estradiol (E2)	95-100	(Luo et al., 2014; Luo et al., 2015; Amin et al., 2018)
17α-Ethynylestradiol (EE2)	90-98	(Luo et al., 2014; Luo et al., 2015; Amin et al., 2018)
Personal care products		
2-Ethylhexyl ethoxycinnamate (EHMC)	N.A.	
Neonicotinoids		
Imidacloprid	N.A.	
Thiacloprid	N.A.	
Thiamethoxam	N.A.	
Clothianidin	N.A.	
Acetamiprid	N.A.	
Pesticides		
Methiocarb	N.A.	
Oxadiazon	N.A.	
Triallate	N.A.	

5. Effect of secondary treatments on microbial CEC fate

Although antibiotic resistance and antibiotic residues may occur together in the environment, antibiotic resistance is not a direct consequence of chemical environmental contamination (Michael et al., 2013; Varela et al., 2014). Instead, ARB&ARGs are emitted from human and animal sources, also irrespective of the occurrence of antibiotics, and have the capacity to survive or self-replicate in the environment. These arguments place ARB&ARGs among the broad group of CEC (Pruden et al. 2006; Berendonk et al. 2015). Given the current state of the art and the knowledge gaps concerning the effect of secondary treatment on antibiotic resistance, this section discusses why urban wastewater treatment plants are reservoirs of ARB&ARGs (Berendonk et al., 2015; Manaia et al., 2016) and why control strategies are so difficult to devise and implement. WWTPs collect most of the pharmaceutical compounds, including antibiotic residues which are increasingly used in the modern medicine and poorly metabolized in the human body (Segura et al., 2009; Segura et al., 2011; Michael et al., 2013). Unfortunately, antibiotic residues do not come alone. They are mingled with a wide diversity of human commensal and pathogenic bacteria, many of which harbour ARGs, acquired in a bacterial struggle for survival, while being able to persist and spread in the environment (Manaia et al., 2016). ARGs may be located on chromosomes or on plasmids, making the horizontal transfer of genes among neighbouring cells a possibility. Resistance genes encode different types of defence mechanisms that alone or in combination with other genetic determinants, may increase the capacity of bacteria to survive adverse conditions (Yomoda et. al., 2003; Kim et al., 2014).

Wastewater secondary treatment systems have the potential to offer ideal conditions for bacteria to spread their genes, in particular ARGs, and hence they can be associated with antibiotic resistance dissemination (Rizzo et al., 2013, Bouki et al., 2013). The wealth of nutrients and cell-to-cell interactions, aided by the presence of antibiotic residues and, eventually, other selectors, are believed to enhance the chances of survival or even proliferation of ARB (Berendonk et al., 2015; Bengtsson-Pvaalme and Larsson, 2016).

The need of elucidating the potential impact of WWTPs on the dissemination of ARB&ARGs has been urged by the accumulation of evidences that the use of reclaimed water used for irrigation may contribute to the transmission of ARB and other water-borne bacteria through different environmental compartments. Potential microbiological risks associated with water reuse in irrigation cannot be neglected (Pachepsky et al., 2012; Al-Jassim et al., 2015) and this review aimed at assessing what is known regarding ARB&ARGs removal by full-scale WWTP systems operated with different secondary treatment technologies.

Recent studies on this topic that share common overall experimental approaches are reviewed in this paper (Table 7). Given the relevance of the disinfection effects on the fate of ARB&ARGs and the difficulty in identifying the role of the secondary treatment units from the available literature, some data reported in the Table 7 includes also the disinfection step. A few aspects that can explain the variation in the data presented are worth mentioning (Table 7). First, diverse methodologies are used for the screening of genes in total DNA extracts or cultivation methods, a disparity that is enhanced by a wide array of variables that may influence the results. For culture-based methods, the results will be strongly influenced by the choice of the culture medium or the imposition of some selective pressures. For culture-independent methods, the DNA extraction process, the primers used for PCR-based gene search or the technique and conditions used for metagenome analyses as well as the database and analytical pipeline used, are enough to influence the results. Second, there is a lack of information on the external conditions during the full-scale conventional treatment, not only those referring to operational settings, but also climate conditions and numerous quality parameters. Third, the sampling scheme is different among studies and microbial targets analysed. In spite of such potential confounding variables, we can conclude that full-scale CAS plants have a limited capacity to reduce antibiotic resistance to negligible levels. In the next section, we will discuss the impact of the WWTP processes on: i) culturable total and ARB, ii) multi-drug resistance phenotypes, iii) ARGs and iv) metagenomics insights of antibiotic resistance.

5.1 Fate of culturable antibiotic-resistant bacteria

The reduction in the number of total and ARB has been examined in various studies, in the influent and secondary effluent of WWTP as a method to infer the efficiency of wastewater treatment to remove antibiotic resistance. This is achieved with the use of bacterial cultivation and enumeration methods, in selective media supplemented or not with antibiotics. This approach can be used to assess the effectiveness of the WWTP process as for instance is reported by Zanotto et al., (2016). These authors showed that a CAS process could reduce the ampicillin and chloramphenicol-resistant coliforms and *Escherichia coli* by 2 log units. However, the biological treatment did not reduce the percentage of ARB among total bacteria (maintenance of prevalence values). It has been shown in this study that the disinfection step with peracetic acid was important in the reduction of ampicillin-resistant *E. coli,* to densities below 10 CFU/100 mL. In contrast, in another study by Mao et al., (2015), it was observed that bacteria harbouring ARGs persisted throughout all treatment stages, surviving better after chlorination than total bacteria. Su et al., (2014) observed that even though total culturable bacteria and *E. coli* decreased after the WWTP process (2.3-3.3 log unit reduction), the quinolone- and ampicillin-resistant bacteria prevalence was not significantly reduced (from 55% in the influent to 61% in the effluent). Sidrach-Cardona and Bécares (2013) have shown removal of 90-99% ARB from urban wastewater in CWs. This study showed that CWs design can affect the system performance, with planted sub-surface flow CWs being more efficient for this type of biological pollutants. Processes such as filtration, adsorption, aggregation, and metabolic activity of biofilm microorganisms and macrophytes are responsible for bacterial removal in CWs (García et al., 2008; Wu et al., 2016). It is not clear if plants have a direct effect on bacterial removal, as the presence of plants can indirectly increase removal through conductivity modification, gas transport and enhancement of biofilm development, adsorption, aggregation and filtration (García et al., 2008). The above suggest that the tertiary treatment is important in the removal of total bacteria, but it is not always effective in removing ARB, thus leading to their persistence in the disinfected effluent, with possible contamination of the receiving environment.

5.2 Multi-drug resistance phenotypes

Multidrug-resistant (MDR) bacteria have been defined as those that have acquired non-susceptibility to at least one agent belonging to three or more antimicrobial categories (ECDC/EMEA, 2009). It was shown in several studies that MDR phenotypes occur in final effluent samples, evidencing that, as for many other bacteria, also MDR bacteria can survive treatment. Among the studies included in this review, there were MDR-positive isolates to the following antibiotics, among others: ciprofloxacin, trimethoprim and sulfamethoxazole/trimethoprim (Al-Jassim et al., 2015; Zhang et al., 2015b; Lopes et al., 2016; Osinska et al., 2017). The same pattern of MDR *E. coli* isolates was found by Osinska et al., (2017) and Lopes et al., (2016) in the wastewater effluent analysed, showing prevalence values above 30%. The prevalence of MDR *E. coli* isolates reported by Blaak et al., (2015) was lower, but still represented 20% of the total number of isolates in effluent wastewater. Kotlarska et al., (2015) also reported MDR *E. coli* in wastewater effluent in two WWTPs (2.4 (0.1–6.1) $\times 10^5$ and 2.1 (0.8–3.1) $\times 10^5$ CFUs per 100 mL). Zhang et al., (2015b) selected 200 heterotrophic bacteria from three WWTPs (influent and effluent), seasonally. They reported MDR isolates ranging from 5 to 64%. From these studies it is not possible to draw a general overview or define a trend. Apparently, more studies targeting MDR phenotype prevalence in wastewater effluents may be needed, preferentially targeting other bacteria besides *E. coli*. Another limitation is the use of ambiguous and not always correct definitions of MDR that are reported in the scientific literature, which may launch several misinterpretations of the meaning and impact of MDR in urban wastewater effluents.

5.3 Fate of antibiotic resistance genes

The quantitative PCR (qPCR) of specific ARGs has brought a new breath to the assessment of wastewater treatment efficiency regarding the removal of antibiotic resistance genes. Rafraf et al., (2016) observed the presence of various ARGs including the integrase gene except *bla*$_{\mathrm{CTX-M}}$ in the influent and effluent samples of five WWTPs employing biological processes (CAS, CAS-UV, aerated lagoon). The quantification of the examined ARGs showed that there was no difference in their abundance before and after the treatment which is also in agreement with Xu et al., (2015), once more highlighting the tolerance of ARB and their associated genes to the applied WWTP treatments. This is supported by the study of Al-Jassim et al., (2015), where it was observed that *tetO, tetQ, tetW, tetH, tetZ* were also present in the post-CAS chlorinated treated effluent. Wen et al., (2016) observed that the biological treatment had an important role in the removal of ARGs followed by UV disinfection, although high concentrations of ARGs were found in the treated effluents. Mao et al., (2015) observed a 90% reduction in ARGs from influent to effluent in CAS. However, even after chlorination, the remaining ARGs were still in high levels, and *tetA, tetB, tetE, tetG, tetH, tetS, tetT, tetX, sul1, sul2, qnrB* and *ermC* were discharged through the dewatered sludge and plant effluent at higher rates than influent values. The latter finding is supported by the study of Alexander et al., (2015), where the abundance of various ARGs increased after conventional WWTP process, resulting in the surface water receiving a high abundance of various ARGs. Laht et al., (2014) demonstrated a decrease by several orders of magnitude in raw 16S rRNA and ARGs gene copy numbers (*tetC*, *tetM*, *sul1*, *sul2*, *bla*$_{\mathrm{CTX-M-32}}$, *bla*$_{\mathrm{SHV-34}}$, *bla*$_{\mathrm{OXA-58}}$) in the effluent compared to the influent, in three CAS WWTPs. In the same study, when the ARGs abundance was normalised per 16S rRNA, it was shown that when relative abundances were compared, there was a statistically significant difference ($p<0.01$) between influent and effluent samples, in only four cases, among the three examined WWTPs. This is a finding which is in agreement with a study on CAS by Bengtsson-Palme et al., (2016). CWs have shown the removal potential of both antibiotics and antibiotic resistance genes in a few studies as reviewed by Sharma et al., (2016), which can ultimately affect the amount of antibiotic resistance bacteria in CWs effluents. In these studies, both domestic/urban and livestock wastewaters have been tested. For domestic/urban wastewaters, CWs can remove significant amounts of antibiotic resistance genes (45-99 %) belonging, for instance, to tetracycline, fluoroquinolone and sulfonamides antibiotic classes (Liu et al., 2013; Nolvak et al., 2013; Chen et al., 2015; Huang et al., 2015; Chen et al., 2016; Huang et al., 2017).

However, most of the papers present the removal results after a combined treatment process consisting of biological treatment and disinfection, and do not provide data on the actual biological process removal effectiveness. Therefore, it is not possible to clearly distinguish the effects of the biological treatment on the ARGs.

5.4 Antibiotic resistance through the metagenomics lens

Metagenomics approaches applied to resistome and bacterial community analyses have come into the spotlight in the last few years, due to the rapid technological development and reduction in the potential cost of such equipment. As a result, more studies are arising which perform in-depth analyses of the resistome and wastewater bacterial communities before and after WWTP processes. Christgen et al., (2015) explored five wastewater treatment options, such as: i) a completely mixed aerobic reactor (AER1), ii) an up-flow anaerobic sludge blanket reactor (UASB), iii) an anaerobic hybrid reactor (AHR), and iv-v) two anaerobic−aerobic sequence (AAS) bioreactors following UASB and AHR reactors, respectively. The analysis of the relative abundance of ARGs (abundance of ARG sequences reads the total reads number) showed that the AAS and aerobic treatment were able to remove a higher number of ARGs, among the total number of reads, such as aminoglycosides, tetracycline and β-lactam resistance genes compared to UASB and AHR, indicating the higher capacity of the combined aerobic system for ARGs removal, compared to the anaerobic processes. However, the relative abundance of sulfonamide and chloramphenicol resistance genes was unaffected by AAS. In another study (Yang et al., 2014), identified 271 subtypes of ARGs belonging to 18 classes. The highest abundance of ARGs among the total number of reads was observed in the influent of the WWTP, while 78 ARGs persisted throughout the treatment, among the total number of ARGs reads. Finally, significant statistical correlation between specific bacterial genera which include opportunistic pathogens, and ARGs distribution, was observed, suggesting their contribution as carriers of ARGs.

Table 7. Most recent studies examining the fate of ARB&ARGs in full-scale WWTPs operated with different processes and technologies

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
Poland *(Osinska et al., 2017)*	Conventional Activated Sludge (CAS)	Compare antibiotic resistance and virulence before and after CAS treatment	**Isolates:** *E. coli* resistant to amoxicillin, tetracycline or ciprofloxacin **Approach:** Isolation on mFC**,** genotyping (ERIC-PCR)**,** antibiograms (3 antibiotics)**,** gene detection (PCR)	Reduction of the counts of beta-lactam, tetracycline and fluoroquinolone-resistant *E. coli* after treatment Multi-drug resistance observed in 38% of the 317 isolates analysed Most common antibiotic resistance genes: bla_{TEM} and bla_{OXA} and *tet*A, *tet*B and *tetK* Most common virulence genes: *bfp*A, ST and *eae*
Brazil *(Conte et al., 2017)*	CAS	Survey of beta-lactam and quinolone resistant bacteria after CAS treatment	**Isolates**: *E. coli*, *Klebsiella pneumoniae* and *K. oxytoca* resistant to quinolones **Approach:** Isolation on *MacConkey***,** genotyping (ERIC-PCR), antibiograms (9 antibiotics) and MICs (8 antibiotics), gene detection (PCR) **Antibiotics:** Ciprofloxacin	Cephalosporin and quinolone resistance found in 34.4% of *E. coli* and 27.3% of *K. pneumoniae* Carbapenem resistance found in 5.4% of *K. pneumoniae* and *K. oxytoca* ESBL-producing isolates found in raw and treated water samples Ciprofloxacin residues were absent only in upstream river water
China *(Ben et al., 2017)*	1) Anaerobic/anoxic/oxic (A^2/O)-Membrane Bioreactor (MBR) 2) Oxidation ditch-coagulation/sedimentation 3) Anoxic/oxic (A/O)-MBR 4) A^2/O-ultrafiltration (UF) 5) A/O-biofilter-UF 6) A/O 7) Oxidation ditch-Rotary fibre disk filtration (RFDF) 8) A^2/O- RFDF 9) A^2/O/coagulation/sedimentation-RFDF 10) A^2/O-coagulation/sedimentation-RFDF	Assess possible correlations between antibiotic resistance and sulfonamides (SA) or tetracyclines (TC) in ten WWTPs with different treatment types, all of them including disinfection	**Isolates**: Heterotrophic bacteria, resistant to tetracycline and sulfamethoxazole **Total community DNA** **Approach:** Isolation on LA, gene quantification (qPCR) **Antibiotics:** Sulfonamides, tetracyclines	ARGs detected after treatment in all 10 WWTP, with sulfonamide resistance being the most abundant type of resistance Total SA and TC concentrations were not significantly correlated with the corresponding ARB&ARGs Positive correlation between ARGs and *int*I1 The statistically significant decrease of ARGs abundance evidences the importance of disinfection for antibiotic resistance control

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
Brazil *(Lopes et al., 2016)*	Biological aerated filter system (RALF)	Assess the occurrence of thermotolerant coliforms and *E. coli* resistant to various antimicrobials in an WWTP	**Isolates**: thermotolerant coliforms, antibiotic-resistant *E. coli* **Approach:** Isolation on non-selective medium and antimicrobial susceptibility testing **Antibiotics:** norfloxacin, ciprofloxacin, cephalothin, gentamycin, streptomycin, imipenem, cefaclor, ampicillin, cefoxitin, tetracycline, amoxicillin and chloramphenicol	There were *E. coli* isolates resistant to cephalothin, streptomycin, tetracycline and amoxicillin; A higher prevalence of resistant isolates was observed in the WWTP effluent and downstream of the WWTP.
Tunisia *(Rafraf et al., 2016)*	1) CAS 2) CAS-UV 3) Aerated Lagoons	Assess the efficiency of wastewater treatment on antibiotic resistance removal in five WWTP (four with CAS one of which has CAS-UV, and one with aerated lagoons as the secondary process)	**Total community DNA** **Approach:** gene quantification (qPCR)	The gene *int*I1 and all ARGs, except *bla*$_{CTX-M}$, were detected in influent and effluent samples in all WWTPs tested with relative ARGs abundance being similar before and after treatment The abundance of *bla*$_{CTX-M}$, *bla*$_{TEM}$, and *qnr*S genes was higher in the effluent of the WWTP that receives untreated hospital effluents
China *(Sun et al., 2016)*	A^2/O -MBR	Assess the overall distribution of ARGs by a common wastewater treatment process, the A/A/O-MBR process, in different geographical locations	**Total community DNA** **Approach:** GeoChip 4.0 using 2812 nucleotide probes of ARGs	There was a large diversity of ARGs among the MBRs, with only around 40% of commonly detected ARGs worldwide being detected There were different dominant ARGs groups in each MBR, with the majority of ARGs being derived from *Proteobacteria* and *Actinobacteria* TN, TP and COD of influent and temperature and conductivity of MLSS were significantly correlated to the ARGs distribution in the different MBRs
Finland *(Karkman et al., 2016)*	CAS-Biofilter	Assess seasonal variations of transposase and ARGs abundance in an WWTP utilizing CAS and biofilters as tertiary treatment	**Total community DNA** **Approach:** gene detection (qPCR array)	All transposases and 66% of all ARGs assayed were detected in the effluent and nine ARGs were enriched in the effluent compared to the influent WWTP with tertiary treatment system analyzed substantially decreased the gene abundance and richness (>99% reduction)
Sweden *(Bengtsson-Palme et al., 2016)*	CAS	Assess the occurrence of genes against antibiotics, biocides and metals and their co-selection potential in WWTP utilizing the CAS process	**Total community DNA** **Approach:** Metagenomics-Resistome **Antibiotics:** Macrolides, fluoroquinolones, tetracyclines, sulfonamides **Other:** Metals, biocides	No consistent enrichment of ARGs to any particular antibiotic class, for neither biocide nor metal resistance genes WWTP greatly reduced the number of resistance genes per volume of water, their relative abundance per bacterial 16S rRNA was only moderately decreased A few resistance genes, including the carbapenemase gene *bla*$_{OXA-48}$, were enriched in the treatment process

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
Italy *(Zanotto et al., 2016)*	CAS-Peracetic acid	Assess antibiotic resistance dynamics over different treatment stages (CAS and peracetic acid disinfection)	**Isolates:** Total coliforms, *E. coli* resistant to ampicillin and chloramphenicol **Approach:** Isolation on chromogenic agar, gene detection (PCR)	Biological process effective in the reduction of the ampicillin and chloramphenicol-resistant total coliforms and *E. coli* by about 2-log units No significant decrease of the percentage of ARB through the biological treatment Disinfection significantly reduced the ampicillin-resistant *E. coli*
China *(Wen et al., 2016)*	1) A^2/O 2) A/O 3) Cyclic activated sludge system (CASS) 4) CASS	Assess the distribution and removal efficiency of ARGs in four WWTPs with different treatment processes	**Total community DNA** **Approach:** gene quantification (qPCR)	Of all treatment steps, biological treatment played the most important role in ARGs removal, followed by UV disinfection ARGs were observed in all WWTP effluents after biological treatment process and their abundance was still high in the final effluent
China *(Li et al., 2016)*	1) A^2/O 2) Triple oxidation ditch	Assess antibiotic resistance removal in two WWTP with different treatment types, including UV disinfection	**Isolates**: Heterotrophic bacteria resistant to tetracycline or/and sulfamethoxazole **Total community DNA** **Approach:** Isolation on R2A**,** gene quantification (qPCR) **Antibiotics:** Sulfonamides, tetracyclines, trimethoprim	The ARGs were detected in both WWTP effluents Biological treatment played the most important role on ARGs and antibiotics removal, and physical processes on ARB removal UV disinfection did not significantly enhance the removal efficiency High concentrations of antibiotics and abundance of ARGs and ARB were detected in the excess sludge samples
China *(Mao et al., 2015)*	CAS--Chlorination	Assess the removal efficiency of ARGs, ARB and antimicrobial drugs, in two WWTP utilising CAS and chlorine disinfection	**Isolates:** Heterotrophic bacteria resistant to sulfonamides, tetracyclines, ciprofloxacin and erythromycin **Total community DNA** **Approach**: Isolation on nutrient agar, gene detection (PCR) and quantification (qPCR) **Antibiotics:** Sulfonamides, trimethoprim, tetracyclines, β-lactams, fluoroquinolones, macrolides **Heavy metals:** As, Cd, Cr, Cu, Ni, Pb, Zn	Bacteria harbouring ARGs persisted through all treatment units, surviving better to disinfection by chlorination than total bacteria The abundance of ARGs was reduced from the raw influent to the effluent (~90%), although high levels of ARGs levels were found in WWTP effluent samples The ARGs *tet*A, *tet*B, *tet*E, *tet*G, *tet*H, *tet*S, *tet*T, *tet*X, *sul*1, *sul*2, *qnr*B, *erm*C were discharged through the dewatered sludge and plant effluent at higher rates than influent values
USA *(Naquin et al., 2015)*	CAS-UV	Assess the presence of ARGs in a small town WWTP utilizing CAS followed by UV disinfection	**Isolates**: Total bacteria **Total community DNA** **Approach:** Isolates on TSA**,** antibiograms**,** gene detection (PCR)**,** Genetic transformation assay (*mec*A)	ARGs were present in both raw and treated wastewater during all the sampling periods

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
Saudi Arabia *(Al-Jassim et al., 2015)*	CAS-chlorination	Assess the efficiency of removal of microbial contaminants in a WWTP utilizing CAS and chlorine disinfection	**Isolates:** Total heterotrophic bacteria, total and faecal coliforms **Total community DNA** **Approach**: Isolation on nutrient agar, sulfate and brilliant green bile lactose and EC, antibiograms (8 antibiotics), bacterial community analysis, gene quantification (qPCR) **Antibiotics:** ampicillin, kanamycin, erythromycin, tetracycline, ceftazidime, ciprofloxacin, chloramphenicol, meropenem	16S rRNA gene-based community analysis showed that genera associated with opportunistic pathogens (e.g. *Acinetobacter, Aeromonas, Arcobacter, Legionella, Mycobacterium, Neisseria, Pseudomonas* and *Streptococcus*), were detected in the influent and some were found in chlorinated effluent The *ARGs tetO, tetQ, tetW, tetH, tetZ* were also present in the chlorinated effluent The proportion of bacterial isolates resistant to 6 types of antibiotics increased from 3.8% in the influent to 6.9% in the chlorinated effluent 6.8% of isolates from influent were resistant to meropenem and 24% of the isolates were resistant in the chlorinated effluent 25% of the isolates in the influent and 28% of isolates in the effluent were resistant to at least 5 antibiotics
United Kingdom *(Christgen et al., 2015)*	1. Upflow anaerobic sludge blanket reactor (UASB)2. Anaerobic hybrid reactor (AHR)3. Mixed aerobic reactor (AER1) 4. and 5. Anaerobic aerobic sequence bioreactor (AAS)	Assess ARGs removal in five different domestic wastewater treatment options	**Total community DNA** **Approach**: Metagenomics-Resistome	The AAS and aerobic treatment achieved a higher removal of certain ARGs (aminoglycoside, tetracycline, β-lactam resistance genes) compared to UASB and AHR, indicating the higher capacity of the combined system to remove ARGs compared to each process alone Sulfonamide and chloramphenicol resistance genes were unaffected by the AAS treatment while multi-drug resistance increased from influent to effluent Metagenomic data suggested that aerobic processes may be generally better than anaerobic processes for reducing ARGs
Germany *(Alexander et al., 2015)*	Nitrification-denitrification-phosphorus elimination	Detect and quantify genes and gene carriers of clinical significance; Assess the dissemination of ARGs and opportunistic bacteria in natural populations; Identify and monitor critical water systems and potential microbiological risks for human health	**Total community DNA** **Approach:** Gene quantification (qPCR), quantification of antibiotic residues (LC-MS) **Antibiotics:** (Dehy-)erytromycin, Acetyl-sulfamethoxazole, chloramphenicol, chlortetracycline, clarithromycin, doxicycline, erythromycin, metronidazole, oxytetracycline, roxithromycin, sulfadiazine, sulfadimidine, sulfamerazine, trimethoprim	The removal capacities were up to 99% for some WWTPs tested, but not in all investigated bacteria; The abundance of most ARGs increased in the bacterial population after conventional wastewater treatment. As a consequence, downstream surface water and also some groundwater compartments displayed high abundances of all four ARGs

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
China *(Xu et al., 2015)*	A/O	Assess the abundance and distribution of antibiotics and ARGs in a WWTP utilizing anaerobic/anoxic process and in its effluent-receiving river.	**Total community DNA** **Approach:** gene quantification (qPCR) **Antibiotics:** Tetracyclines, sulfonamides, fluoroquinolones	Concentration of tetracyclines, sulfonamides and quinolones decreased after treatment ARGs abundance did not vary over the different treatment stages Sulfonamide resistance genes were present at relatively high concentrations in all samples
China *(Zhang et al., 2015b)*	CAS	Assess the antibiotic-resistance phenotypes in three WWTP utilizing CAS process.	**Isolates:** Heterotrophic bacteria and total coliforms **Total community DNA** **Approach:** Isolation on R2A and MacConkey**,** antibiograms (12 antibiotics)**,** gene quantification (qPCR)	The proportion of bacterial isolates resistant to more than 9 antibiotics was lower in effluent isolates than in the influent Gram-negative bacteria dominated in influent and Gram-positive in effluent The ARGs examined had higher prevalence in ARB from the influent than in the effluent, except for *sul*A and bla_{CTX} The abundance of ARGs in activated sludge from two of the three plants were higher in aerobic compartments than in anoxic ones
Poland *(Kotlarska et al., 2015)*	1) A^2/O 2) Primary and secondary anoxic treatment	Assess the antibiotic resistance profiles of *E. coli* isolated from two WWTP, their marine outfalls and from a major tributary of the Baltic Sea, in order to evaluate the role of the studied wastewater effluents and tributaries in the dissemination of integrons and ARGs.	**Isolates:** *E. coli* **Total community DNA** **Approach:** Isolation on mFC agar, antimicrobial susceptibility tests, gene detection (PCR), sequencing of gene cassette arrays	Ampicillin-resistant *E. coli* were the most frequently observed bacteria (<32%) 32% and 3.05% of the isolates were positive for class 1 and 2 integrons, respectively The presence of integrons was associated with increased frequency of resistance to fluoroquinolones, trimethoprim/sulfamethoxazole, amoxicillin/clavulanate, piperacillin/tazobactam and MDR-resistance phenotype. The most predominant gene cassette arrays were *dfrA1-aadA1, dfrA17-aadA5 and aadA1*
China *(Du et al., 2015)*	A^2/O-MBR	Assess the variation of ARGs throughout a A^2/O-MBR wastewater treatment process	**Total community DNA** **Approach**: Gene quantification (qPCR)	ARGs concentrations decreased in the anaerobic and anoxic effluent but increased in the aerobic effluent and sharply declined in MBR effluent The reduction in *tetW*, i*ntI1* and *sul1* was positively correlated with the variation of the 16S rRNA gene abundance ARGs concentrations reduced in the effluent samples as: sul1>intI1>tetX>tetG>tetW All ARGs concentrations were higher in spring compared to other seasons
Spain *(Rodriguez-Mozaz et al., 2015)*	CAS	Assess the variation of antibiotics concentration and ARGs abundance in urban and hospital effluent from a WWTP utilizing CAS treatment	**Total community DNA** **Approach:** Gene quantification (qPCR) **Antibiotics:** 62 antibiotics	ARGs copy numbers of bla_{TEM}, qnr_S, erm_B and *sul*1 were highest in hospital effluent and WWTP influent The copy number of ARGs decreased significantly in WWTP effluents but this reduction was not uniform across ARGs Prevalence of *erm*B and *tet*W decreased after WWTP treatment but bla_{TEM}, qnr_S and *sul*1 prevalence increased

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
Estonia and Finland *(Laht et al., 2014)*	CAS-Secondary sedimentation	Assess the role of three WWTP utilizing CAS followed by tertiary disinfection in the distribution of ARGs	**Total community DNA** **Approach:** Gene quantification (qPCR)	*sul1, sul2,* and *tetM* were detected in all samples while statistically significant differences between the influent and effluent were detected in only four cases The purification process caused no significant change in the relative abundance of ARGs, while the raw abundances fell by several orders of magnitude Standard water quality variables (BOD_7, TP and TP, etc.) were weakly related or unrelated to the relative abundance of ARGs
China *(Yang et al., 2014)*	CAS	Study the fate of ARGs in a WWTP utilizing CAS process	**Total community DNA** **Approach:** Metagenomics-resistome	271 ARGs subtypes belonging to 18 ARGs types were identified by the broad scanning of metagenomics analysis Influent had the highest ARGs abundance, followed by effluent, anaerobic digestion sludge and activated sludge 78 ARGs subtypes persisted through the biological wastewater and sludge treatment process Significant correlation between specific bacterial genera, included potential pathogens, and the distribution of ARGs were observed
China *(Su et al., 2014)*	1) CAS - chlorination 2) CAS-oxidation ditch-UV disinfection	Assess the effect of treatment on antibiotic resistance profiles in two WWTP utilizing: a) CAS followed by chlorine disinfection and b) oxidation ditch followed by UV disinfection	**Isolates:** *E. coli* resistant to quinolones and *β* -lactams **Approach:** Isolates on nutrient agar, modified mTEC agar**,** antibiograms (12 antibiotics)**,** gene detection (PCR) **Antibiotics:** ampicillin, piperacillin, cefazolin, ceftazidime, gentamycin, streptomycin, ciprofloxacin, levofloxacin, sulfamethoxazole/trimethoprim, trimethoprim, tetracycline, chloramphenicol	98.4% of the isolates were resistant to the examined antibiotics and 90.6% were resistant to at least 3 antibiotics The number of the total cultivable bacteria and *E. coli* decreased after treatment Disinfection significantly reduced total bacteria but not ARB prevalence
Portugal *(Novo et al., 2013)*	CAS	Assess the influence of abiotic factors on the levels of antibiotic resistance and bacterial structure community of the CAS-treated final effluent	**Isolates:** Heterotrophic bacteria, enterobacteria and enterococci resistant to amoxicillin, tetracycline, ciprofloxacin and sulfamethoxazole **Approach:** Isolates on PCA, m-FC and m-Ent, genotyping (DGGE) **Antibiotics:** Tetracyclines, β-lactams, sulfonamides, fluoroquinolones **Metals:** Cd, Pb, Cr, As and and Hg **Other:** Triclosan	The bacterial community was distinct in raw and in treated wastewater In Autumn, but not in Spring, amoxicillin and ciprofloxacin resistance prevalence increased significantly after wastewater treatment while temperature was positively correlated with the prevalence of sulfonamide resistant heterotrophs and enterobacteria in treated wastewater The concentration of tetracyclines, penicillins, sulfamides and quinolones and the abundance of antibiotic-resistant cultivable bacteria in the raw wastewater were positively correlated with the abundance of *Epsilonproteobacteria* in treated wastewater and negatively with *Gamma-*, *Betaproteobacteria* and *Firmicutes*

Country & Reference	Process/ Technology	Aim(s)	Biological target/experimental approach/chemical analyses	Study findings
China *(Chen and Zhang 2013)*	CAS, constructed wetlands (CWs), MBRs	Assess the occurrence and removal of *tet* and *sul* resistance genes in 12 wastewater treatment systems with different treatment capacities and treatment processes including CAS, constructed wetlands and MBRs	**Total community DNA** **Approach:** gene quantification (qPCR)	Significant correlation between the gene copy numbers and wastewater receiving capacity were observed Statistical analysis revealed a positive correlation between the gene copy numbers of *sul*1 and *int*I1, whereas the gene numbers of *tet*M and sul1 were strongly correlated with 16S rRNA gene
Spain (Sidrach-Cardona and Bécares 2013)	Seven CWs of different types	Evaluate removal of antibiotic resistant bacteria from urban wastewater by CWs with different design	**Isolates:** *E. coli*, Coliforms and Enterococcus **Approach:** Isolates on coliform agar and SB agar **Antibiotics:** amoxicillin, azithromycin, amoxicillin+clavulanic acid, and doxycycline	Removal efficiency 90 and 99%. Better results for Sub-surface flow CW, planted with *Phragmites* spp. Design parameters influencing their performance, those with sub-surface flow proving better than hydroponic, and planted better than unplanted
Estónia (Nolvak et al., 2013)	Pilot system consisted of a septic tank, followed by six parallel vertical subsurface flow mesocosms, a collection well, and 21 parallel HSSF MCs	Evaluate removal of antibiotic resistant genes from municipal wastewater by CWs with different design	**Total community DNA** **antibiotic** resistance genes **Antibiotic**: tetracyclines, macrolides, sulfonamides, penicillins, and fluoroquinolones	In general, the proportions of different ARGs decreased in mesocosm effluent bacterial communities (compared to the influent) during the treatment process – no percentages removal given Antibiotic resistance genes in the wetland media biofilm and in effluent were affected by system operation parameters, especially time and temperature
China (Chen et al., 2015)	four surface and subsurface flow-CWs, and a stabilization unit	Evaluate removal of antibiotic resistant genes from rural domestic wastewater by CWs with different design	**Total community DNA** **antibiotics** leucomycin, ofloxacin, lincomycin, and sulfamethazine	>99% in total CW3 with 43.6%, followed by CW2 (27.5%), CW1 (11.9%), and CW4 (11.9%). The least contributing treatment unit was CW5, with a contributing rate of 2.6 % Sorption onto soil or medium and biodegradation are two main mechanisms for ARGs elimination in the ICW system.
China (Chen et al., 2016)	Six mesocosm-scale CWs	Evaluate removal of antibiotic resistant genes Raw domestic sewage by CWs with different design	**Total community DNA** 12 genes including three sulfonamide resistance genes (sul1, sul2 and sul3), four tetracycline resistance genes (tetG, tetM, tetO and tetX), two macrolide resistance genes (ermB and ermC), two chloramphenicol resistance genes (cmlA and floR)	Removal efficiency between 63.9 and 84.0% HSSF-CWs and VSSF-CWs showed higher removals of pollutants than the SF-CWs Planting in the CWs was beneficial to pollutant removal. Mass removals attributed to biodegradation, substrate adsorption, and plant uptake.

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6. WWTPs design, operation and upgrading for CEC removal: techno-economical evaluations

6.1 Impact of CEC removal implementation on WWTPs design and operation

As pointed out in the previous sections, the effect of wastewater treatment on the fate of CEC occurring in wastewater depends on different factors including: (i) wastewater characteristics, (ii) initial concentration of target CEC, (iii) size of WWTPs, (iv) type of biological process/technology, (v) operating conditions of biological process/technology and (vi) presence of tertiary and/or advanced treatment. Wastewater characteristics also depend on the size of the WWTP because large WWTPs (e.g., > 50,000 – 60,000 PE) often collect hospital and industrial wastewater, while small WWTPs (SWWTPs, < 3,000 – 5,000 PE), particularly those in remote and/or rural area, are not or little affected by this kind of wastewaters. Moreover, treatment methods in medium/large WWTPs are basically different compared to small WWTPs. In medium/large WWTPs, CAS, MBRs or MBBRs are typical options for secondary (biological) treatment, while for small WWTPs (in particular for those in the low range of PE (e.g. < 1,000-2,000) some options may be not sustainable in terms of investment and management costs (e.g., MBRs) and cheaper solutions may be used (e.g., CWs, rotating biological contactors, Imhoff tanks, etc.).

Achieving CEC removal through optimization of existing WWTPs will vary between different treatment processes, but in general it will be based on adjustment of the operational process parameters typically proposed in the literature (Omil et al., 2010; Li et al., 2015; Tiwari et al., 2017) as well as of those, mentioned in early sections, which affect pollutants removal:

- Increased SRT to enhance biodegradation of typically moderately biodegradable compounds through microbial community diversification due to increased growth of slow growing microorganisms such as nitrifying bacteria at longer SRTs (Holbrook et al., 2002; Stephenson and Oppenheimer 2007; Tiwari et al., 2017). Although SRT of above 15 days are typically recommended (Li et al., 2015), different CEC may require different SRTs for achieving optimal removal rate. Nevertheless, operation at very high SRT to promote extra biological transformation will lead to higher operating costs due to higher oxygen requirements of biomass (Krzeminski et al., 2017).

- Increased HRT to improve removal of compounds that are moderately biodegradable (high k_{biol}) and have low sorption potential (low K_d) (Eggen and Vogelsang 2015). Enhanced CEC removal in CAS has been reported at HRT of above 16 hours (Guerra et al., 2014). However, HRT also increases capital costs while CEC removal improvement at higher HRT is still debated (Taheran et al., 2016).
- Increased MLSS to enhance biodegradation provided by high biological activity per unit volume leading to generation of slow-growing bacteria able to degrade certain biologically-recalcitrant pollutants (Bernhard et al., 2006; Sipma et al., 2010; Clouzot et al., 2011; Tran et al., 2013).
- Implementation of nutrient removal stages associated with varying redox conditions (nitrification and de-nitrification) leading to increased microbial diversity, broad enzymatic range and microorganisms' activity. Heterotrophic microbes are of importance for fast biodegradable compounds whereas lithotrophic ammonia oxidizers and nitrifyers are of importance for slowly biodegradable compounds (Tran et al., 2013). In particular, presence of anoxic zones and high ammonia loading rates seems to favour CEC removal in CAS (Li et al., 2015).
- Presence of fat during primary treatment that favours absorption of lipophilic compounds with high K_{ow} such as musks (Li et al., 2015).
- Combination of different processes, such as CAS and CWs, or combination of CWs with different designs, as varying redox conditions should significantly improve pollutants removal.

The possibility of establishing favourable operating conditions for CEC removal is different for large/medium WWTPs and small WWTPs. For example, in CAS process, large WWTPs are operated with high organic loading rate (> 0.5 kg BOD5/(kg MLVSS×d)), which typically results in designing aeration/nitrification tank with relatively low hydraulic retention time (HRT, 6 – 12 h) and sludge retention time (SRT, 3 – 6 d). Differently, CAS process in SWWTPs is typically designed to operate under extended aeration conditions (< 0.05 kg BOD_5/(kg MLVSS×d), which results in larger aeration/nitrification tank (HRT= 36 – 48 h, SRT= 30 – 40 d) (Metcalf and Eddy 2003).

Other factors influencing CEC removal often mentioned in the literature, such as temperature, content of organic matter, ionic strength and conductivity, were considered less realistic for implementation at the full-scale, and thus not discussed further.

6.2 Feasibility of WWTPs upgrading to remove CEC

Possible solutions to successfully minimize the release of CEC into the environment from WWTPs effluents consist of implementation of an effective tertiary treatment, upgrading through re-designing of the existing treatment processes or optimizing operating conditions of the existing biological process according to the flow chart reported in Figure 1.

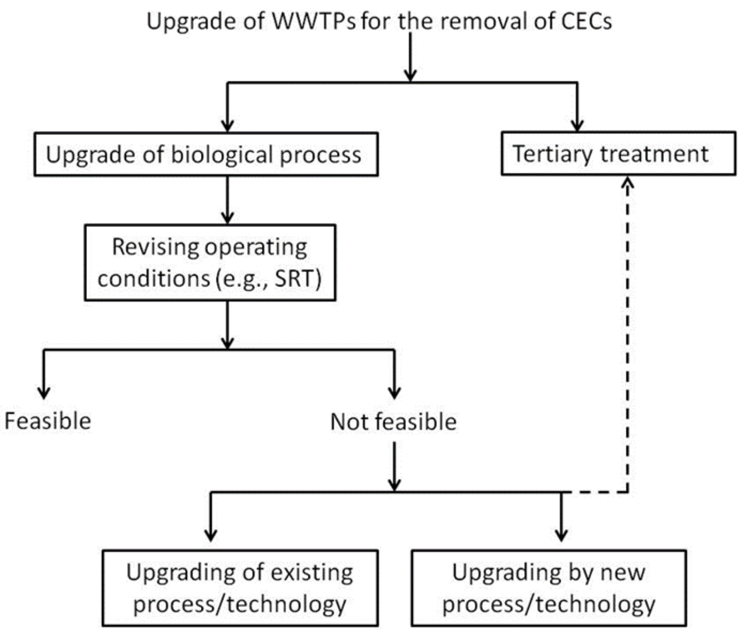

Figure 1: Flow chart for decision making on upgrading conventional WWTPs for CEC removal

The likelihood of implementation of dedicated treatment for CEC removal depends not only on the performance aspects of particular process such as removal efficacy and removal mechanisms, range of treated pollutants and reliability of removal efficiency, but also on significant number of other factors. Among these impact factors, ease of construction and set-up, simplicity of operation and maintenance requirements, flexibility in adapting to the fluctuations in influent flowrate and characteristics, capital and operating costs, cost-effectiveness, environmental friendliness in respect to waste production and disposal needs, overall environmental footprint, associated prospects and constraints, development stage, level of social acceptance, and finally who is supposed to cover the costs of dedicated CEC treatment are mentioned (Eggen and Vogelsang 2015; Bui et al., 2016; Tiedeken et al., 2017).

However, proper economic comparison between different treatment alternatives discussed in this review is very difficult due to scarce information in the literature (Bolzonella et al., 2010; Fatone 2010; Krzeminski et al., 2017) and because each treatment design is unique due to its specific site conditions and operating settings/conditions. The capital and operating costs depend on number of parameters such as scale of treatment, feed water characteristics, targeted pollutants, desired water quality and electricity, chemicals and personnel costs, which vary from country to country (Bui et al., 2016; Taheran et al., 2016).

Furthermore, holistic assessment of different alternatives taking into account environmental impacts is needed to quantify benefits of CEC removal. Approaches, such as Life Cycle Assessment (Corominas et al., 2013), nonmarket valuation (Kotchen et al., 2009; Logar et al., 2014) and distance function approach based on shadow prices, to quantify environmental benefits from reduced discharges of CEC (Molinos-Senante et al., 2013) have been proposed (Schröder et al., 2016; Tiedeken et al., 2017). For example, research findings of the LCA studies review (Corominas et al., 2013) indicate that in general environmental benefits do not outweigh the costs of advanced treatment implementation. However, LCA studies evaluating secondary treatment alternatives for the removal of CEC to the best authors' knowledge have not been published.

Alternatively, in cases when the implementation costs would outweigh the environmental benefits, or if cost would be considered too great, existing WWTPs could be optimized for CEC removal (Jones et al., 2007) by adjusting operating parameters reported in the previous section.

6.3 Techno-economical comparison of the selected technologies

To define the technology to be implemented for achieving a more effective removal of the selected CEC and producing effluents suitable for re-use, a comparison of the proposed technological solutions, summarizing the data reported in the manuscript, is reported in Table 8. In order to achieve an integrated, coherent comparative efficiency assessment of the examined technologies, besides the achievable removal efficiencies, other evaluation parameters such as complexity in lay out and management, scale of application and need of a post-treatment are included. It is worth noting that updated specific quantitative cost data related with CEC removal in discussed secondary treatment processes are not available in scientific literature, thus a qualitative evaluation based on the literature review has been performed, where some important economic factors (i.e. energy and chemical consumptions) are being discussed.

In addition, with the objective to give a first simplified comparative evaluation of the technologies, a score was assigned in a scale from 1 to 4, where 1 is the worst and 4 is the best evaluation of each technology, according to each examined parameter. The score was determined based on the available technical data elaborated for the purposes of this review.

The ARB&ARGs removal figures are not reported in Table 8 because data available is scarce and not following a systematic protocol of analyses, leading to results biased by large variability in the nature of approaches reported in the existing in scientific literature so far. Majority of studies examines prevalence of resistance in selected isolated colonies and does not focus on the removal of ARB&ARGs as such. In addition, many studies report removal efficiencies at the end of the WWTP which may involve a tertiary or disinfection step and do not provide data on the actual biological process removal efficiency.

Table 8. Techno-economical comparative evaluation of the proposed technologies to produce effluents suitable for reuse. Data for the different groups of CEC are with reference to the ones included in this review. A score assigned in a scale from 1 to 4 (where 1 is the worst and 4 is the best evaluation of each technology according to the examined parameter) is reported in parentheses.

Parameter	**Group of compounds**	**Technology**			
		CAS	**MBR**	**MBBR**	**CW**
Range of removal efficiencies (%)	Pharmaceuticals	<0 – 90	<0 – 99	0 – 100	0 – 99
	Antibiotics	<0 – 90	<0 – 99	<0 – 96	0 – 100
	PCPs	30 – 55	N.A.	N.A.	N.A.
	Estrogens	18 – 96	20 – 100	65 – 100	0 – 100
	Neonicotinoids	11 – 18	N.A.	N.A.	N.A.
	Pesticides	N.A.	N.A.	N.A.	N.A.
	Industrial chemicals	<0 – 100	<0 – 94	43 – 76	8 – 100
Need of post-treatment		YES	NO	YES	YES/NO
Complexity in lay out/Ease of construction		▪ Simple lay out (4)	▪ Commercially available, TRL=9 (4)	▪ Commercially available and simpler than CAS (2 -3)	▪ Ease of construction ▪ Commercially available (4)
Complexity in operation		▪ Easy management not requiring complex control systems (4)	▪ High process automation ▪ Skilled staff needed (2-3)	▪ Easy management ▪ Needs maintenance ▪ (retention grids of media) ▪ Simpler than CAS (2-3)	▪ Easy management ▪ Needs maintenance (3)
Flexibility		▪ Low flexibility due to high inertia of the system in changing operating conditions (1)	▪ High, modular system (4)	▪ Good flexibility (media addition / HYBAS system) (3)	▪ Low flexibility, not possible to change design (2)
Reliability		▪ Not resilient to permanent inflow variation ▪ Not resilient to influent shock load (1-2)	▪ Stable effluent ▪ Resilient to inflow fluctuations ▪ Relatively resilient to shocks (3-4)	▪ Stable effluent ▪ Very resilient to flow fluctuation ▪ Very resilient to shock loads (3)	▪ Relatively resilient to flow fluctuation ▪ Relatively resilient to shock loads ▪ Can be dependent on temperature (seasonality effect) (2)
Footprint		▪ Large footprint (1)	▪ Small footprint ▪ Space reduction possible	▪ Larger/similar to MBRs and less than CAS and	▪ Large areas required (2)

Parameter	Group of compounds	Technology			
		CAS	MBR	MBBR	CW
			(4)	CWs (3)	
Environmental aspects (waste production, disposal, chemicals)		▪ Production of sludge containing residual CEC (2)	▪ Treatment of concentrate and sludge containing CEC (3)	▪ Low sludge production but containing residual CEC ▪ Less sludge than CAS. ▪ Carriers have very long lifetime (3)	▪ Need previous filtration step to prevent clogging ▪ Might need post treatment to remove some recalcitrant CEC (3)
Investment cost		▪ Lower than MBRs and MBBRs (4)	▪ Typically, higher than CAS ▪ Membrane cost ca. 40-60% of total capital costs (2)	▪ Higher than CAS and CWs, but less than MBRs (2-3)	▪ Reduced costs compared to CAS (4)
Management cost		▪ Energy 0.2-1.4 kWh/m^3 (4)	▪ Energy 0.4-4.2 kWh/m^3 ▪ Membrane replacement ca. 10-14% of total operation costs ▪ Chemicals for membrane cleaning (2)	▪ Slightly higher aeration than CAS needed. ▪ Less than MBRs, more than CWs and CAS (3)	▪ Reduced costs compared to CAS (4)
Legend: N.A. – not available;					

7. Future perspectives and research needs

Despite significant research and monitoring efforts devoted to presence and fate of CEC, data on occurrence and/or removal of some of the emerging compounds are not available. Nevertheless, this review shows the potential of four secondary biological treatment technologies for the removal of selected CEC and the need to reach effluent quality suitable for reuse of treated water for e.g. irrigation purposes. This in turn, allows defining the research needs for the analysed technologies in respect to the removal of CEC.

CAS process is the most investigated process for the removal of CEC. However, the conventional layout (i.e. aerobic process) is ineffective, while operation at high SRT or with sequential anoxic-aerobic phases can ameliorate their performance for some pharmaceutical compounds. Thus, research should be devoted to the optimization of the process performance by modifying the operating parameters (when possible), and/or investigating the combination with more powerful technologies to be applied as tertiary treatment.

MBR technology has been extensively investigated for the removal of CEC, but the mechanisms have not yet been fully unravelled. Further research is needed to understand removal mechanisms of the CEC and microbiological contaminants such as ARB&ARGs. For example, fouling layer interaction and the role of deposits on the membrane surface as potential additional barrier increasing CEC removal is needed. In addition, identification of CEC removing bacterial species and/or enzymes, unravelling optimal operating conditions, and elucidation of the metabolites produced during MBR treatment is required. These products may possess different structural characteristics compared to the parent compounds, making them toxic once they are filtered and end up in the clarified MBR effluent. Finally, cost-effective integrated MBR systems providing synergistic effects of combined technologies, should be further developed with emphasis on system optimization, scaling up, and full-scale validation.

The removal of chemical and microbial CEC by CWs is a recent area of study, and current CWs are not able to effectively eliminate CEC from wastewater. Therefore, more research is needed to identify the feasibility for full-scale applications. The efficiency of the processes occurring in CWs depends primarily on the operation mode, design, type of substrate and the presence and type of plants. Therefore, studies should be designed to reveal the effect of each process on CEC. Only with that information one can optimize CWs design and operating parameters, consequently getting better treatment efficiency and fully supporting CWs utility. In addition, the effectiveness of the processes in the CWs can be increased by the use of hybrid systems that combine CWs of different designs in series or by combining CWs with other processes e.g. solar driven homogeneous advanced oxidation processes (e.g., sunlight mild photo Fenton, sunlight/H_2O_2). As CWs have some specific prerequisites, such as large areas requirements and the fact that it can be dependent on temperature (seasonality effect), their application is site dependant.

The number of wastewater treatment plants designed using the MBBR technology as the main secondary treatment process around the world is estimated by Veolia to be between 20 and 50, mainly in Scandinavia, China and the United States. Even less studies investigated the fate of CEC throughout the process treatment at full-scale. The added value of biofilm for the elimination of CEC still needs to be investigated in laboratory scale and up-scaled to real applications. The global understanding of CEC removal pathways (including diffusion into the biofilm, hydrodynamics conditions) and regulation of bacterial communities on biofilm (through biofilm thickness) should be in the scope of new research projects. The occurrence of the highly active biomass in the biofilm in the later stages of MBBR treatment trains could be positive for the removal of recalcitrant organic CEC, but the generally achieved thin biofilm contains too little biomass to complete the CEC degradation in a realistic contact time. This experimental evidence suggests that research should aim to increase the available biomass retained in these parts of the MBBR treatment train while retaining the efficient biomass. In this paper, MBBR technology was studied as the secondary treatment.

However, MBBR as a tertiary treatment should also be considered as an interesting advanced treatment technology for recalcitrant CEC removal.

However, regardless of the applied technology, the removal of CEC depends on the treatment conditions and the physicochemical properties of the individual compounds. Furthermore, the current knowledge suggests that the factors that rule the fate of ARB&ARGs are complex and variable among different WWTP, making each plant a unique microbial ecosystem. Therefore, it is still difficult to assess the CEC impact onto the wastewater receiving environments, as well as the potential ways in which CEC removal can be enhanced. This highlights the need for research to maximize CEC removal by biological processes while successfully removing conventional parameters (namely, BOD, COD, nitrogen, phosphorus, etc.) to promote a safer reuse of treated wastewater.

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