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REVIEW ARTICLE

Advanced Oxidation Processes for Antibiotics Removal: A Review

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Abstract: Year-by-year, the amount of antibiotics for human and veterinary use increases. Their presence in both treated and untreated wastewater was highlighted in several studies, suggesting that traditional activated sludge processes are unsuitable for their efficient removal. In this review paper, we summarized the role of advanced oxidation processes (AOPs) in antibiotics removal evidencing their pros, cons and limitations. In most cases, they are still applied at laboratory or pilot scale, with just few examples of full-scale applications. Main constraints are related to energy cost, catalyst management and potential residual toxicity in treated effluents. The main advantages are related to the full mineralization of target compounds or the ability to increase their relative biodegradability. Future challenges include nano-based green synthetized catalysts maximizing the use of solar radiation for energy saving. Generally, AOPs application is part of a more structured wastewater treatment process including operating units at various technological contents.

Keywords: Antibiotics, advanced oxidation processes, toxicity, by-products.

1. INTRODUCTION

During the last decades, the production and consumption of antibiotics within the European Union (EU) have increased rapidly with large inter-country difference. According to the European Centre for Disease Prevention and Control [1] the defined daily doses (DDD) per 1000 inhabitants per day can vary from 10.6 (Netherlands) up to 34.1 in (Greece). According to Wang and Tang [2], the total amount of antibiotics used per year, including medical and veterinary uses, overcame 100,000-200,000 tons worldwide. To face the concerns about development of antimicrobial resistance and transfer of antibiotic resistance genes from animal to human microbiota, the EU prohibited the use of antibiotics as growth promoters since January 1, 2006 [3]. By 2030, it has been estimated an alarming global rise in livestock antibiotics consumption up to 67% that is from 63,151 ± 1560 tons up to 105,596 ± 3605 tons [4]. Moreover, the current assessment of pharmaceuticals' consumption (*i.e.* also in case of antibiotics) merely based on sales data is seriously underestimated due to online trading and the increasing availability of drugs as over-the-counter products [5-7]. Thus, large amounts of antibiotics are discharged into the environment through medical waste, industrial wastewater, cattle waste and sewage effluent mostly in their original form [8]. Frequently, they are detected in groundwater [9-11], drinking water [12], surface water [13-15] (sediment [16] and agricultural lands [17, 18]. Current wastewater treatment plants (WWTPs) technological facilities mainly based on activated sludge were not originally designed to deal with micropollutants like pharmaceuticals, and most pharmaceuticals, and antibiotics in particular, pass through WWTPs partially or completely untreated. In Shangai (PRC), Wu *et al.* [19] monitored 10 antibiotics in four WWTPs reporting that they were all present in most effluent samples. WWTPs acted as antibiotics' hot spots for the receiving water bodies. Similar results were reported by Dong *et al.* [20], which investigated the fate of 19 antibiotics in one constructed wetland (CW), one stabilization pond (SP), one activated sludge (AS) and one micro-power biofilm (MP) WWTPs. Although the mean effluent concentrations of target antibiotics were lower than the influent ones, their removal was usually inadequate. The AS and CW outperformed the MP and SP processes: the AS performed better than the CW process. Both the AS and CW processes exhibited higher removal efficiencies in summer than in winter, indicating that biological degradation could play an important role in antibiotics degradation even if their complete removal was not achieved.

An efficient process for biodegradation of antibiotics requires that the microorganisms become adapted to them allowing the development of drug resistant characteristics (*i.e.* modified membrane permeability, enzymatic destruction, alteration of binding sites and extrusion of active principles by means of efflux pumps) [21]. Anyhow, antibiotic-resistant genes can be transferred horizontally among bacteria, passing from the environment to humans, thus integrating the previous knowledge supporting mainly the clinical etiology (*i.e.* use, misuse and/or overuse) [22, 23].

Many active principles derive from microorganisms, especially from bacteria that evolved in parallel to antibiotics developing targeted defensive strategies. This hypothesis has been confirmed by the occurrence in pristine environments (*e.g.* glaciers and permafrost samples) of the same resistance genes, which have been detected in human bacteria [24, 25]. Besides natural ecosystems, solid wastes facilities, WWTPs, as well as agriculture and aquaculture

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practices have been recognized as hotspots of antibiotic resistant bacteria [26-28]. Some classes exhibited an antibiotic-specific resistance to biological degradation. For example, macrolides are more persistent to biological treatment than quinolones and sulphonamides [29]. The limitations of conventional AS WWTPs in removing bio-recalcitrant molecules point toward the urgent need for improved wastewater treatments such as advanced oxidation processes (AOPs). This is a special class of oxidation techniques characterized by the production of $^{\cdot}OH$ radicals, which are very powerful oxidants reacting quickly and unselectively with a broad range of organic compounds [30-33]. AOPs are based on the combination of oxidizing agents (*i.e.* O_3, H_2O_2) and/or catalysts (*e.g.* Fe, Mn, and TiO_2) and/or ultrasound whose action may also be improved by high-energy radiation like UV light and/or electricity [34]. Although AOPs can achieve the complete mineralization of targeted pollutants, most times the main goal is to degrade them to more innocuous compounds paying attention to the whole cost-effectiveness of the treatment as well. But the elimination of mother compounds does not necessarily result in effluent toxicity removal, since advanced degradation can produce intermediate by-products, which can still exert adverse biological effects. Therefore, to evaluate the overall behaviour and efficiency of treatment processes, it is necessary to assess not only the reduction/removal of targeted compounds, but also the whole effluent ecotoxicological characteristics.

The aim of this review paper is to propose a general updated review of AOPs in antibiotics removal considering physico-chemical and toxicity implications.

2. ANTIBIOTICS INTO THE ENVIRONMENT

Within pharmaceuticals, the environmental presence of antibiotics has been widely studied. It was highlighted that due to their specific antimicrobial action they can have possible impacts on the biosphere, namely, on the biomass responsible of biological processes of water treatment. This paragraph will synthesize the main recent findings about the concentration of antibiotics in various environmental matrices and the antibiotic resistance phenomenon.

2.1. The Occurrence of Antibiotics in Wastewater, WWTPs Effluents and Surface Water

Antibiotics have been detected in the environment with a general growing concern about their partitioning into various compartments due to their physico–chemical properties and potentially further (a)biotic transformed products [35] Four main topics have been explored: i) the analytical issues (these substances belong to the category of "trace pollutants", hence they may result in criticalities in detection and quantification); ii) the fate and behaviour of these pollutants in the environment; iii) their removal; and iv) the risk for the living organisms. Nevertheless, beside dozens of published papers about specific drug clusters (*i.e.* defined categories of pharmaceuticals, like anti-inflammatory, psychotropic and antibiotic drugs), there is an increasing number of critical reviews depicting the environmental state-of-the-art. Apart for some overviews focusing on European Countries [36, 37] several studies are now including new geographical areas [38-41]. In Table **1**, we listed the most commonly analysed active principles.

Municipal wastewater loaded of pharmaceuticals, whose concentrations can become significant and antibiotics may provide a significant role in their contamination. Based on the summarized data, the more recurring substances on a class rank basis are: ciprofloxacin (fluoroquinolones): 3,800 ng/L [42]; cephalexin (β-lactams): 4,600 ng/L [42]; doxycycline (tetracyclines): 6,750 ng/L [43]; clarithromycin (macrolides): 319 ng/L [44]; vancomycin (glycopeptides): 10 ng/L [44]; sulfadiazine (sulphonamides): 544.29 ng/L [19]; trimethoprim (diaminopyrimidines): 340 ng/L [42]. Fluoroquinonoles are the most concentrated active principles in effluents, except for Fick *et al*. [45] that measured up to 14,000,000 ng/L of ciprofloxacin in a pharmaceutical industry wastewater and Vergeynst *et al*. [46] that detected up to 1,253 ng/L of moxifloxacin in both influent and effluent. The most frequently investigated and discovered substances are: cephalexin (β-lactams): 69.66 ng/L [19]; tetracycline (tetracyclines): 1,658 ng/L [46]; azithromycin (macrolides): 1031.67 ng/L [47]; vancomycin (glycopeptides): 40 ng/L [44]; sulfamethazine (sulphonamides): 373.84 [47]; trimethoprim (diaminopyrimidines): 4,400 ng/L [45] and 65.92 ng/L [47].

Surface water bodies have been characterised less frequently than sanitation works with antibiotics' concentrations up to ng/L. Considering the most recent papers, the following values were detected in surface water bodies: ciprofloxacin (fluoroquinolones): < 100 ng/L (*i.e*. 6,500,000 ng/L considering pharmaceutical WWTP effluents) [45]; β-lactams are seldom investigated and rarely detected; tetracycline is the only substance belonging to the same category and detected up to 29 ng/L [47]; erythromycin (macrolides): 174.73 ng/L [47]; vancomycin (glycopeptides): 4.8 ng/L [44]; sulfamethoxazole (sulphonamides): 78.38 [47]; trimethoprim (diaminopyrimidines): 4,000 ng/L [45] and 35.53 ng/L [47].

These findings state a milestone to the overall management of pharmaceuticals and more specifically of antibiotics due to their crucial role, as well as their metabolism by-products after their release and/or disposal. Their presence in environmental matrices is significant and persistent. Based on current data, the fate and behaviour of these substances is very difficult to model and understand mainly due to the complexity of the involved metabolic pathways (*e.g.* aerobic, anoxic, anaerobic) and the combined action of various organisms, beside the potential differential toxicity of by-products compared to their parent compounds.

Acid and basic dissociation constants, as well as water/soil or n-octanol or sludge partition coefficients are considered as key parameters describing the behaviour of a substance into the environment. As underlined by Zrnčić *et al*. [48] although the acid-base property is crucial for explaining the toxicokinetics and toxicodynamics of a substance, there is still a huge amount of data either inaccurate or lacking. All the investigated macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin) are basic, while sulfonamides (sulfadiazine, sulfamethazine, sulfamethoxazole), β-lactams (amoxicillin, ampicillin, penicillin G) and tetracyclines (chlortetracycline, oxytetracycline, tetracycline) are quite acid. Ionized forms exhibit greater water solubility, while neutral forms are usually lipophilic, thus more able to pass through cell membranes [48].

As far as persistence is concerned, [49] underlined that biodegradability and toxicity consist in two separate concepts, because harmless molecules can be recalcitrant to by microbial consortia degradation, hence, their environmental half-life cannot be neglected.

Another pivotal issue is represented by the real efficiency of self-purification of the receiving water bodies. Al Aukidy *et al*. [50] showed two examples of rivers flowing through the Po valley, where antibiotics' persistence is dependant not only on its initial concentration, but it is also strictly related to the water body (bio-) activity.

Table 1. Occurrence of the most commonly analysed antibiotics in wastewater, WWTP effluents and in surface water. Only average values are reported; n.d.: not detected; n.q.: not quantifiable. Adachi *et al.* [51] carried out two seasonal monitoring campaigns: the highest values are reported, for safety purposes. Watkinson *et al*. [42] considered the median value. Wu *et al.* [19] reported the median value in the case of surface water samples.

Antibiotics	Wastewater (ng/L)	WWTP Effluent (ng/L)	Surface Water (ng/L)
Fluoroquinolones			
Ciprofloxacin	3,800 [42];513 [44] 2,200 [52]; 3,000-5,250 [43] ; 392 [53] 278; 978 [46]	14,000,000 [45] 640 [42] 25; 284 [50] 120; 104 [46] 151.25 [47] 147 [44] 630 [52] 176 [53]	8.5 [51] 8.32; 28.02; 4.83 [47] 8.8; 19 [44] 25 [52] n.d.-6,500,000 [45] n.d.-36 [53]
Danofloxacin		255.67 [47]	n.d. [47]
Enfloxacin			1.9 [51]
Enoxacin		8.27 [47] n.d. [45]	6.6 [51] n.d.-160,000 [45] 4.83; 4.65; 15.83 [47]
Enrofloxacin	10 [42] n.d. [46] 29.93; 5.04; 4.03; 3.67 [19]	10 [42] n.d. [46] 255.67 [47] 2.47; 3.84; 3.69; 2.35 [19] 210,000 [45]	n.d-30,000 [45] 5.82; 40.12; 75.017 [47] n.d. [19]
Flumequine		n.d. [47]	n.d. [47]
Levofloxacin	n.d.-335 [46] n.d.-6,200 [43]	n.q.;70 [46]	
Lomefloxacin		8,800 [45]	0.5 [51] n.d.-1,100 [45]
Moxifloxacin	149; 688 [46]	62; 1,253 [46]	
Norfloxacin	170 [42] 210 [52]	25,000 [45] 25 [42]63.72 [47] 150 [52]	11 [51] n.d.-520,000 [45] 15.83; 15.17 [47] n.d. [52]
Ofloxacin	463 [44] 980 [52] 2,450-4,120 [43] 2936.94; 2285.50; 1904.83; 165.67 [19] 128 [53]	55,000 [45] 276.67 [47] n.d. [47] 235 [44] 400 [52] 195.88; 1976.08; 1308.01; 899.19 [19] 118 [53]	76 [51] n.d.-11,000 [45] 23.28; 75.017 [47] 5; 10.9 [44] n.d. [52] n.q. [19] n.d.- 33 [53]
β-lactams			
Penicillins (penams)			
Amoxicillin	190 [42] n.d. [46] 18 [44] 16.23; 6.38; 3.09; 3.05 [19]	n.d. [42] n.d. [46] n.d. [44] 3.18; 3.48; 3.38; 2.05 [19]	n.d.; 5.7 [44] n.q. [19]

Table 1. contd…

Antibiotics	Wastewater (ng/L)	WWTP Effluent (ng/L)	Surface Water (ng/L)
Cloxacillin	n.d. [42]	n.d. [42]	
Penicillin G	n.d. [42]	n.d. [42]	
Penicillin V	50 [42]	30 [42]	
Cephalosporins (cephems)			
Cefaclor	500 [42]	n.d. [42]	
Cefalexin	4,600 [42] 109.87; 90.55; 91.09; 175.04 [19]	n.d. [42] n.d. ; 69.66; 14.90; 64.36 [19]	n.q. [19]
Tetracyclines			
Chlortetracycline	n.d. [42] 96 [54]	n.d. [42] n.d. [47] n.d. [54]	n.d. [47]
Doxycycline	n.d. [42] n.d. [52] 1,580-6,750 [43]	n.d. [42] n.d. [47] n.d. [52]	n.d. [47] n.d. [52]
Oxytetracycline	n.d. [42] n.d. [46] n.d. [44] 0-9-400 [43] 125.75; 11.71; n.d.; 26.09 [19] 202 [54]	n.d. [42] n.d. [46] n.d. [44] n.d.; 0.61; n.d.; n.d. [19] 42.12 [47] 92 [54]	n.d.; 1.1 [44] n.d. [19] n.d. [47]
Tetracycline	n.d. [42] n.d. [46] n.d. [52] n.d. [19] 336 [54]	n.d. [42] n.d.-1,658 [46] 171.47 [47] n.d. [52] n.d. [19] 131 [54]	n.d.; 29 [47] n.d. [52] n.d. [19]
Macrolides			
Azithromycin	120 [52] 129 [53]	44; 175 [50] 1,031.67 [47] 130 [52] 143 [53]	14.73; 71.67 [47] 7 [52]
Clarithromycin	319 [44] 200 ([52] 100 [53]	102;283 [50] 237.83 [47] 117 [44] 280 [52] 99 [53]	42.60; 88.83 [47] 1.7; 25.4 [44] 6 [52] n.d.- 19 [53]
Erythromycin	n.q. [42] 12 [44] 46 [52] 28.57; 22.37; 24.12; 27.84 [19] 15 [53]	n.q. [42] 677.00 [47] 52 [44] 15 [52] 11.73; 20.77; 13.57; 15.41 [19] 18 [53]	50.38; 174.73 [47] 2.9; 5.4 [44] n.d. [52] n.d. [53]
Oleandomycin	n.d. [42] 2.2 [44]	n.d. [42] 2.4 [44]	n.d. [44]

Table 1. contd…

Antibiotics	Wastewater (ng/L)	WWTP Effluent (ng/L)	Surface Water (ng/L)
Roxithromycin	25-117 [55] 65 [52] 55.40; 51.99; 27.96; 77.38; [19] n.d. [42]	12; n.d. [50] n.d.; 69 [55] 3.90 [47] 290 [52] 33.37; 25.32; 11.71; 22.68 [19] n.d. [42]	n.d. [47] n.d. [52] 0.58 [19]
Spiramycin	603 [44] n.d. [19]	454 [44] n.d. [19] 141.58 [47]	1.1; 7.9 [44] n.d. [19] 39.90; 68.32 [47]
Glycopeptides			
Vancomycin	41 [44]	40 [44]	2.6; 4.8 [44]
Sulfonamides			
Sulfamethoxazole	245; 429 [46] 246 [44] 55.64 ; 76.79 ; 138.52; 85.48 [19] 348 [56] 70 [53] n.d.-145 [55] 360 [42]	97; 91 [50] 133; 250 [46] 140.48 [47] 46 [44] 39.53; 50.41; 70.60; 65.17 [19] 10 [53] 208 [56] 10.13 ; 14.14 ; 11.43 ; n.d. [19]	39.70; 78.38 [47] 2.1; 5.3 [44] 15.64 [19] n.d.-16 [53]
Sulfadiazine	544.29; 19.17 ; n.d.; 9.46 [19]	n.d.-91 [55] 20.38 [47] 270 [42]	22.42 [19] n.d.; 13.40 [47]
Sulfamethazine	7.26 ; 10.44; 10.07; 8.58 [19]	7.27; 5.57; 14.20; 6.99 [19] 373.84 [47]	5.50 [19] 1.68;112.27 [47]
Diaminopyrimidines			
Trimethoprim	111 [55] 158 [46] 59 [52] 54 [53] 340 [42]	4,400 [45] n.d.; 27 [50] 34 [55] n.d. [46] 65.92 [47] 40 [52] 7 [53] 50 [42]	n.d.-4,000 [45] 16.4-33.53 [47] 2 [52] n.d.-9 [53]

Health, food, water and soil policies are trying to cope with worrying scenarios introducing new guidelines, regulations and threshold limit values. As an example, the Joint Research Center Technical Report of the European Union [1] included the following antibiotics in the watch list accordingly with the environmental quality standards directive: azithromycin, erythromycin, ciprofloxacin and clarithromycin. Scientific literature proceeds with the parallel definition of priority lists, based on the consumption of antibiotics (both for human and veterinary use) and their chemical, physical and (eco-)toxicological characteristics [36, 40].

2.2. Antibiotic Resistance: From the Environment to Humans and Backwards

The environmental matrices contaminated by sewage sludge can be enriched in antibiotic resistant bacteria (ARBs) and antibiotic resistance genes (ARGs) due to the direct inlet of bacteria deriving from humans or animals under antibiotic therapy. Thus, wastewater, biological sludge and WWTPs effluents, as well as water bodies and soils (and, consequently, crops) can act as resistome reservoirs [57]. Many authors postulated that this is a serious risk in terms of development of new strains able to keep their

viability also in presence of significant concentrations of antibiotics [58, 59].

The mechanism for acquiring the antibiotic resistance is still a matter of discussion. According to the microbial scout hypothesis [60, 61], bacterial cells can survive adverse conditions by entering a state of dormancy, from which they can exit stochastically, notwithstanding the environmental conditions. By this way, it is possible to explain the resistance towards antibiotics (non-genetically mediated) and the phenomenon of recurrent infections. Beside dormancy, the most studied phenomenon yielding the survival is definitely the occurrence of genetic mutations. The transmission of resistance genes takes place via both conjugation and transduction, being the vectors of the horizontal gene transfer (HGF) plasmids, transposons and integrons [62].

Primarily, the HGF happens within the gut, where the microorganisms come into contact with the mobilized genetic materials like in environmental hotspots, when favoured by selection pressures. However, metagenomic studies did not succeed yet in demonstrating the efficacy of pressure induced by significant concentrations of antibiotics in WWTPs biological reactors and the co-pressure of factors such as the dissolved oxygen concentration is postulated as well [63,64]

As far as the removal efficiency of resistance genes by means of AS treatments is concerned, the overall reduction obtained by comparing influents and effluents is in effect apparent, since it is caused by the reduction of bacteria concentration. On the contrary, the number of resistance genes as to the DNA content showed to be exiguous [64]. Research has been focusing on detecting the known sequences, *e.g.*, referring to Quinolone Resistance Determining Region - QRDR, plasmids producing qnr-proteins [51], the β-lactam antibiotic resistance gene ampC [64], the vancomycin-resistant genes, which often causes special resistance in enterococci and *S. aureus*, the carbapenem resistance genes, as well as the macrolide resistance genes, which pose serious risks in cases of infection by *Salmonella pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [65-68]. Papers report the details of the primers employed, together with the frequency of gene detection in different environmental matrices and after specific treatments (*e.g.* wastewater and drinking water). Nevertheless this invaluable amount of data, scientists are still discussing about the assessment of actual risks for human health deriving from environmental hotspots [59]. Bengtsson-Palme and Larsson [63] underlined that the transfer of known sequences encoding for resistance, occurring in the environment, is unlikely to pose a risk of spreading and magnify the resistance itself. New genes found in environmental matrices might cause a serious threat towards the efficacy of active principles still under consideration or playing a crucial therapeutic role, when the most employed antibiotics are ineffective.

3. ADVANCED OXIDATION PROCESSES FOR ANTIBIOTIC REMOVAL

An overview about recent literature studies was provided in Table **2** in order to describe which commonly used antibiotics have been treated so far by AOPs.

3.1. Photolysis

Photolysis involves the interaction of artificial or natural light with the target molecule and the induction of photochemical reactions, which can lead to its direct degradation to intermediate products whose further decomposition eventually yields mineral end products [69]. The majority of UV-based AOPs are dependent on the external chemical addition, which could be considered as a limiting factor for their full-scale application. The vacuum ultraviolet (VUV) irradiation is a new class of the chemical-less AOP in which the radical species are generated from the photolysis of the water molecules. In addition, the photolysis of molecular oxygen dissolved in water by VUV photons produces ozone (O_3) that further contributes in removal of contaminants [70]. Accordingly, the reactive oxidizing species can be produced in the VUV process without need to any external chemicals making the process simple to construct and operate.

3.2. UV/H_2O_2

The efficiency of direct photolysis is usually enhanced when irradiation is combined with H_2O_2, a strong oxidant whose photolytic dissociation yields hydroxyl radicals, thus facilitating degradation process. Photolysis of H_2O_2 with radiation UV generates two hydroxyl radicals, degrading the organic matter and forming simpler compounds [71].

3.1. Fenton Based Processes

Among different AOPs, Fenton and photo-Fenton reactions appear as a good option because of their low cost in reagents and small energy demand [72]. It is well known that the Fenton reaction produces $^{\bullet}OH$ efficiently as a result of the reaction between Fe^{2+} and H_2O_2. In addition, Fe^{3+} can interact with the excess of hydrogen peroxide or with $HOO^{\bullet}$, restoring Fe(II) in a reaction sequence referred to Fenton-like process. When the Fenton reaction is conducted under visible light irradiation, the photo-reduction of ferric to ferrous ions is promoted concomitantly with the generation of additional $^{\bullet}OH$, therefore enhancing the extent of pollutant oxidation. Fe (III) absorbs light in the range up to 400 nm, allowing the use of solar light, while promoting the photo-reduction as shown in the equation (1)

$$FeOH^{2+} + h\nu \rightarrow Fe^{2+} + {}^{\bullet}OH \qquad \text{(Eq. 1)}$$

The use of ferrous or ferric salts usually suffers a major drawbacks related to the narrow pH range of operation to avoid the formation and subsequent precipitation of iron oxyhydroxide [72]. Furthermore, the degradation rates of solar photo-Fenton for treating micro-pollutants in MWTP are slow due to the originally low concentrations of contaminants and pseudo-first-order kinetics ($r = k_{ap} C$). Therefore, one of the solutions for increasing the process efficiency would be to increase C_0. The possibility of achieving these conditions by combining AOPs with membrane processes has attracted the attention during the last few years, as the concentration of contaminants in retentates would be much higher than in raw MWTP effluents.

3.3. Ozone Based Processes

O_3 is a strong oxidant that either decomposes in water to form hydroxyl radicals that are stronger oxidizing agents than O_3 itself inducing the so-called indirect oxidation or attacks selectively certain functional groups of organic molecules through an electrophilic mechanism. O_3 oxidation is usually favoured at increased pH values due to the increased production of hydroxyl radicals. Moreover, treatment performance is enhanced if O_3 is combined with light irradiation and H_2O_2 (Irmak *et al*., 2005). The broad spectra of target compounds of ozone may induce an overall positive effect on the reduction of biological activity due to synergistic actions of trace pollutants [73].

Table 2. Antibiotics removal by AOPs.

Antibiotics	AOPs	C_0	Experimental Conditions	Highlights of the Work	References
SMX	UV-A/TiO_2	100 mg/L	Volume 1 L, T = 25 °C; TiO_2 : 0.1-2 g/L; Time: 0-60-120-180-240-360 min	82% of SMX degradation and 23% of TOC reduction was achieved when working with 0.5 g TiO_2/L	[74]
	UV-A/TiO_2	100 mg/L	Volume: 250 mL; T = 25 °C; TiO_2: 0.1 g/L; Time: 0, 10, 20, 30, 40, 50, 60 min	UVA-TiO_2 photocatalysis is shown to be an effective and efficient process for degrading SMX and related sulphonamides in aqueous solutions.	[82]
	H_2O_2/Fe^{2+}	50 mg/L	$FeSO_4$ $7H_2O$: 2.6, 5.2 and 10.4 mg/L H_2O_2 30-210 mg/L	The increase of iron concentration showed a slight improvement on the pollutant degradation and mineralization rate. The increase of H_2O_2 concentration up to 120 mg/L in distilled water reduced the sample toxicity during the photo-Fenton process, what demonstrates that this is a feasible technology for treatment of wastewater containing this compound.	[83]
	O_3 O_3/H_2O_2	0.5 μM	O_3: 0.1–2 mg/L pH=8	Degradation followed second-order kinetics. Water matrix affected O_3 stability, radicals formation and scavenging.	[84]
	O_3 O_3/H_2O_2	0.150 mM	Volume: 5 L O3:0.05- 0.25 mM H_2O_2/O_3 molar ratio 0.5, T= 25 °C; pH: 2-8	When doses of O_3 were transferred to the liquid phase 0.2 mM, in no case did sulfamethoxazole remain in solution	[85]
AMP, DOX, TYL, STZ	UV-A/TiO_2	50 mg/L	Volume: 100 mL; Temperature: n.a.; TiO_2: 50 mg (5 g/L); Time: 0, 15, 30, 45, 60, 75, 90, 120 min	The rate of photocatalytic mineralization of antibiotic is lower than the degradation rates. The photodegradation products are biodegradable and are less antimicrobially active than the initial antibiotic solutions.	[86]
CAP	UV-A /TiO_2	25 mg/L	Volume: 200 mL; T = 20 °C; TiO_2: 0.1, 0.2, 0.4, 0.8, 1.6, 3.2 g/L; pH: 5.5; Time: 5, 10, 30, 60, 120 min	The best combination for CAP and its by-products removal could be set at 1.6 g/L of TiO_2 for 120 min with an average residual toxicity of approximately 10%, that is the threshold set for negative controls in most toxicity tests for blank and general toxicity test acceptability.	[33]
	UV-A /TiO_2	50 g/L	Volume: 200 mL; T = 25 °C; TiO_2: 0.25 -4 g/L; pH: 5.1; Time: 5, 10, 15, 20, 40, 60, 90 min	At 1 g/L, ZnO followed by TiO_2 P-25 appears to be the best catalysts leading after 90 min of illumination to almost complete (90%) degradation of the antibiotic.	[78]
	UV-A /ZnO	50 mg/L	Volume: 200 mL; T = 25 °C; ZnO :1 g/L; pH: 5.1; Time: 5, 10, 15, 20, 40, 60, 90 min		
	UV-C/H_2O_2	20 mg/L	Volume: 300 mL Time: 30,60,90 min H_2O_2: 1.0, 2.0, and 3.0 mmol/L	98 and 5% of degradation were obtained after one and a half hours of exhibition to UVC and solar radiation with 3 mmol/L of hydrogen peroxide.	[71]

Table 2. contd…

Antibiotics	AOPs	C_0	Experimental Conditions	Highlights of the Work	References
VAN	UV-A /TiO_2	50 mg/L	Volume: 200 mL; T = 20 °C TiO_2: 0.1, 0.2 g/L; pH: 5.5; Time: 5, 10, 30, 60, 120 min	Almost total removal was achieved within 2 h of irradiation with the two catalysts loading investigated The removal of 50 mg/L VAN-B solution yields maximum concentrations of 2.45 and 2.53 mg N-NH_3 L^{-1} after 120 min of photocatalytic oxidation using 0.1 and 0.2 g TiO_2/L, respectively. When 0.2 g TiO_2/L were applied up to 87% of the stoichiometric amount of chloride was reached within 120 min of irradiation, corresponding to 0.087 mmol/L.	[34]
CIP	UV-A /TiO_2	33.134 mg/L	Volume solution: 150 mL; T = 25 °C TiO_2: 1.5 g/L; pH: 3, 5, 7, 9, 11; Time: 0, 10, 20, 30, 40, 50, 60 min	The short half-lives suggest that CIP can be degraded or decomposed quickly in the presence of a photocatalyst and illumination.	[87]
AMX, AMP, CLX	UV-A/TiO_2/H_2O_2	104, 105, 103 mg/L	Volume solution: 500 mL; T = 22 °C TiO_2: 0.5, 1.0, 1.5, 2.0 g/L; pH: 3, 5, 8, 11; Time: 0, 60, 120, 180, 240, 300 min	The best operating conditions of antibiotic aqueous solution were TiO_2 1.0 g/L at pH 11 with a degradation of 71, 91 and 100% respectively, a COD removal of 11% and a DOC removal of 5%.	[79]
	UV-A/TiO_2		Volume solution: 500 mL; T = 22 °C TiO_2: 1.0 g/L; H_2O_2: 50, 100, 150, 200, 300 mg/L; pH: 5; Time: 0, 60, 120, 180, 240, 300 min	The best operating conditions of antibiotic aqueous solution were TiO_2 1.0 g/L and H_2O_2 100 mg L^{-1} at pH 5 with a degradation of 100% for all the substances, a COD removal of 26% and a DOC removal of 14.0%.	
	UV-A/ZnO		Volume solution: 500 mL; T = 22 °C; ZnO: 0.2, 0.4, 0.5, 1.0, 1.5, 2.0 g/L; pH: 5, 8, 11; Time: 0, 60, 120, 180, 240, 300 min	The best operating conditions of antibiotic aqueous solution were ZnO 0.5 g/L at pH 11 with a degradation of 100% for all the substances, a COD removal of 28% and a DOC removal of 16.3%.	
OXA	Ultrasound	203.0 µmol/ L	Volume solution: 250 mL Ultrasonic waves of 275 kHz (at 60 W) T = 22 °C Time: 30, 60, 90, 120 min	During the sono chemical process, the AA was eliminated after 120 min.	[81]
LFX	H_2O_2/Fe^{2+}	27.1 mg/L	Volume solution: 400 mL; T = 21 °C; H_2O_2/Fe^{2+}: 5/0.5, 10/0.5, 10/1, 15/1.5, 20/2; pH: 3; Time: 0, 1, 5, 10, 15, 30, 60, 90 min	The highest performance was achieved at a LFX/H_2O_2/Fe^{2+} m/m/m of 1/20/2 with a k value of 116.11 ± 2.2 x 10^{-2} min and complete target compound elimination within 6 min. The mineralization was less than target compound removal. The non-purgeable organic carbon (NPOC) was 26% and 36.5% after 3h oxidation at a LFX/H_2O_2/Fe^{2+} m/m/m of 1/10/1 and 1/15/1.5, respectively.	[88]
	$S_2O_8^{2-}$/Fe^{2+}		Volume solution: 400 mL; T = 21 °C; $S_2O_8^{2-}$/Fe^{2+}: 2.5/1, 5/1, 10/1, 20/1, 40/1; 20/0.5, 20/2, 20/4, 20/8; pH: 3, 5, 7, 9; Time: 0, 1, 5, 10, 15, 30, 60, 90, 120, 180 min	A fast decomposition of LFX was observed during the first minutes and then the target compound was gradually degraded within the remaining reaction time (180 min). The efficiency of LFX degradation was found to decrease gradually with the increase in the initial pH value. The NPOC concentration remained nearly unchanged after 3 h of oxidation at LFX/$S_2O_8^{2-}$/Fe^{2+} m/m/m of 1/20/2 (more than 97% residual concentration). The highest obtained NPOC removal was 11% at LFX/$S_2O_8^{2-}$/Fe^{2+} m/m/m of 1/30/3	
	H_2O_2/$S_2O_8^{2-}$/Fe^{2+}		Volume solution: 400 mL; T = 21 °C; H_2O_2/$S_2O_8^{2-}$/Fe^{2+}: 5/10/1, 10/10/1, 10/5/1, 5/10/2, 10/10/2; 10/5/2; pH: 3; Time: 0, 1, 5, 10, 15, 30, 60, 90, 120, 180 min	A rapid decrease in residual LFX concentration was observed during the first minutes compared with the process described before. Also, the NPOC removal for this process is improved.	

3.4. Photocatalysis

Heterogeneous photocatalysis is based on the use of a semiconductor as a catalyst and UV radiation [74] Titanium dioxide (TiO_2) is the most frequently used semiconductor since it is biologically and chemically inert, cheap and non-toxic [33, 75-77]. The oxidizing species generated during photocatalysis and responsible for degradation of compounds of interest are $^{\bullet}OH$, holes (h_{ve}^{+}) and superoxide radicals ($^{\bullet}O_2^{-}$). Although available at various crystalline forms, a commercially available product containing 80:20 anatase: Rutile (Evonik P25) showed exceptional activity compared to other grades of TiO_2 due to the morphology of its crystallites [78] (supporting an easy electron transfer from rutile to anatase, thus stabilizing charge separation and, lowering the recombination of photogenerated carriers [69]. The main advantage of this process is the lack of mass transfer limitations and operation at ambient conditions [79]. Recently, ZnO was considered a suitable alternative to TiO_2 since its photodegradation mechanism is similar to that of TiO_2. ZnO can absorb a larger fraction of the solar spectrum than TiO_2, being ZnO promoted photocatalysis more suitable for photocatalytic degradation under sunlight.

3.5. Electrochemical Oxidation

Electrochemical oxidation over anodes made of graphite, Pt, TiO_2, IrO_2, PbO_2, several Ti-based alloys and, more recently, BDD electrodes in the presence of a suitable electrolyte (typically NaCl) has been employed for the decontamination of various pharmaceuticals. To date BDD electrodes are preferred for water remediation since they can generate high amounts of weakly physisorbed hydroxyl, which enhance the removal of organic chemicals (Eq. (2)) [80].

$$BDD + H_2O \rightarrow BDD(^{\bullet}OH^{\bullet})_{ads} + H^{+} + e^{-} \quad \text{(Eq. 2)}$$

The electrochemical degradation is achieved by: i) direct anodic oxidation where the pollutants are adsorbed on the anode surface and destroyed by the anodic electron transfer reaction and ii) indirect oxidation in the liquid bulk which is mediated by the oxidants that are formed electrochemically; such oxidants include chlorine, hypochlorite, hydroxyl radicals, O_3 and H_2O_2. The working electrode, the type of supporting electrolyte, the applied current, the effluent pH and the initial organic concentration are the key parameters of the EAOP.

3.6. Ultrasound Based Technologies

Ultrasound irradiation (*i.e.* sonolysis) is a relatively new process for water treatment. It unsurprisingly received lower attention than other AOPs as reported by the small amount of papers concerning antibiotics treatment. Sonochemistry is based on a cyclical sequence where micro-bubbles form and grow until reaching a critical size; then, they collapse violently in a process called acoustic cavitation, which is induced by the interaction between ultrasonic waves and dissolved gases in aqueous solutions. The collapse of the micro-bubbles generates small hot spots with singular conditions of pressure (~1000 atm) and temperature (~5000 K). Under such conditions, hydroxyl radicals are generated by the dissociation of water molecules and oxygen (Eq. (3), Eq. (4), Eq. (5) and Eq. (6)). By means of the recombination of these radicals, hydrogen peroxide can also be formed [81]

$$H_2O+))) \rightarrow {}^{\bullet}H + {}^{\bullet}OH \quad \text{(Eq. 3)}$$

$$O_2+))) \rightarrow 2\,{}^{\bullet}O \quad \text{(Eq. 4)}$$

$$H_2O + {}^{\bullet}O \rightarrow 2\ {}^{\bullet}OH \quad \text{(Eq. 5)}$$

$$O_2 + {}^{\bullet}H \rightarrow {}^{\bullet}O + OH \quad \text{(Eq. 6)}$$

$$2\,{}^{\bullet}OH \rightarrow H_2O_2 \quad \text{(Eq. 7)}$$

4. DISCUSSION

Rates of AOPs degradation are dependent upon several variables including the initial antibiotics' concentration, pH of the effluents, catalyst phase identity and concentration, light source, electron acceptor identity and concentration, and the presence of non-target water constituents, as discussed below.

4.1. Influence of Different Light Sources

As for most of the organic compounds, the photolysis of antibiotics result is strongly influenced by both the wavelength and intensity of UV source. Chatzitakis *et al.* [78] irradiated a CAP solution of 50 mg/L using a lamp emitting between 300 and 400 nm with a maximum at 365 nm and a light intensity of 1.12 x 10^{-7} Einstein/s observing no CAP removal. da Rocha *et al.* [71] reported a CAP removal of 83 % and 21% starting from an initial concentration of 20 mg/L after 12 h of photolysis using UV-C radiation and solar radiation, respectively.

4.2. Catalyst dose

An optimum catalysts concentration must be determined time-by-time to avoid the use of excess reactive agents as well as to ensure that the absorption of radiation photons is maximized for an efficient degradation. The dosage of TiO_2 in slurry photocatalytic processes generally represents a key factor that can strongly influence the degradation of organic compounds [34, 71, 78].

Chatzitakis *et al*. [78] observed that during the photo-catalytic degradation of 50 mg/L CAP rising the TiO_2 concentration from 0.25 to 4 g/L the initial reaction rate increased by a factor of 2 showing a plateau after 1 g/L meaning that the photo-oxidation reached the saturation. Similarly, the degradation rate of 25 mg/L CAP increased when the concentration of TiO_2 increased up to1.6 g TiO_2/L. Beyond this value, the removal efficiency decreased. Approximately the total removal of CAP was already achieved at 0.8 g TiO_2/L after 60 min of irradiation [33]. The best solution should be to balance the hydroxyl radical produced from irradiation keeping TiO_2 as low as possible to avoid aggregation or shading phenomena and thus limiting the photo-reaction efficiency.

An excess amount of Fe^{2+} plays as scavenging factor in Fenton based processes. An increase in iron concentration from 2.6 to 10.4 mg L^{-1} showed only a slight improvement in 10 g/L SMX degradation and mineralization by photo-Fenton process [83]. Because Fe^{2+}, organic substances and Fe^{3+} compete for hydroxyl radicals, the stoichiometric relationship between them has to be established to maximize the efficiency of degradation process [72].

4.3. Influence of H_2O_2 Concentration

In H_2O_2 based reactions, increasing H_2O_2 above the optimum concentration may cause negative effect to the process due to scavenging of $^{\bullet}OH$ by H_2O_2 [72, 89]. The optimal H_2O_2 concentration depends on the nature and concentration of pollutants. Theoretically, the amount of H_2O_2 concentration necessary for the complete mineralization of organic pollutants can be calculated stoichiometrically considering the chemical oxygen demand (COD): 1 g/L COD = 2.125 g/L H_2O_2) [79]. In photocatalysis process the addition

of hydrogen peroxide leads to an acceleration of the degradation [90, 91]. However, a possible reaction between the H_2O_2 with the photogenerated intermediates cannot be excluded. In the presence of excess H_2O_2, it may act as a hole or $^{\cdot}OH$ scavenger or react with TiO_2 to form peroxy-compounds, which are detrimental to the photocatalytic action. In addition, it can also compete with the organic compound for the adsorption sites on the semiconductor's surface, resulting in a ''chromatographic peaking effect'' of the pollutant concentration in the solution during the initial stages of the photocatalytic process [92]. This explains the need for an optimal concentration of H_2O_2 for the maximum effect. Chatzakis *et al.* [78] reported that photocatalytic efficiency of 50 mg L^{-1} of CAP increased as the concentration of H_2O_2 increased from 50-400 mg/L reaching the optimum in the area of 300-400 mg/L. Consequently, it decreased as the concentration of H_2O_2 increased beyond the optimum.

4.4. By Products Identification

The identification of unknown transformation products is not an easy task and very often requires the combined use of several analytical techniques and strategies. The use of LC-MS, combined with a new generation of MS systems, has great advantages for the analysis of polar compounds. They allow sensitive analysis and provide abundant structural information for elucidating unknown structures. Triple quadrupole (QqQ) or linear ion trap (QqLIT or QTRAP) analysers involve transformation product elucidation on the basis of structural information gained in tandem MS/MS experiments, whereas the measurement of accurate mass and subsequent determination of the empirical formula provided by time-of-flight (TOF) or quadrupole time-of-flight (QqTOF) instruments area very valuable information source when assigning structures. All these techniques have been widely applied to the identification of metabolites and transformation products generated by different water treatments [85].

4.5. How to Manage Catalysts Recovery?

One of the main limits related to the application of photocatalysis is related to the potentially complex procedures for separating (nano-) catalysts from the effluent. In order to overcome this drawback, two parallel research lines have been proposed: i) coating photocatalytic film on tube or flatbed of glass, metal, and other materials; ii) loading nano-TiO_2 on granulated material for easier separation, reactivation, and higher efficiency [93] Although films of nano-TiO_2 proved to be effective in degrading contaminants, the efficiency of photocatalytic films was usually lower than particles due to the reduced contact reactive surface area. Besides, photocatalytic films are difficult to be moved out from reactors for reactivation after long time use. A series of zeolites, such as HZSM-5 [94], mordenite [95], Y-zeolite [96], Al-MCM-41, NaX zeolite [97], clinoptilolite [98], and 5A zeolite [93] proved to be ideal supports for loading nano-TiO_2.

Also in Fenton processes the need to recover dissolved ions from the treated solution requires an additional treatment stage. The immobilization of Fenton catalyst on a heterogeneous matrix would enable its use under non-controlled pH conditions as well as its easier recovery from treated effluent. Indeed, this is perhaps a step towards future investigations [69].

4.6. How Matrix Constituents can Affect Processes Behaviour?

Current research on AOPs for antibiotic removal is mostly performed in demineralized water focusing mainly on reactor optimization, reaction kinetics and degradation product identification. Nevertheless to evaluate the applicability of a treatment technique, research in real effluent matrices is necessary. A transition from synthetic matrices to wastewater is on-going, but little knowledge still exists regarding how and to what extent different types of effluent matrix components could affect heterogeneous photocatalytic processes. Van Doorslaer *et al.* [99] proved that suspended particulate matter and selected inorganic and organic matrix could exert up to 70% of inhibition on the degradation rate of target compounds. Optimization of the catalyst and oxidant concentrations relative to the effluent's polluting load could render the process suitable to treat strongly polluted hospital effluents or effluents from pharmaceuticals manufacturing.

4.7. Wastewater Toxicity and Effluent Final Quality

Several papers elucidated the importance of producing higher quality treated wastewater within the perspective of zero emissions or even the zero discharge based on end-of-pipe technologies [100,101]. The main aim is to enhance water recycling and reuse treating pollution immediately after it has been generated. The selection of the best-advanced treatment technology, including AOPs, to be uploaded at a specific WWTP site, like as their optimization, must include not only technical and economic issues, but also the expected environmental objectives to be met [102,103]. Besides physical and chemical parameters, ecotoxicological goals are a current challenge to really boost safe water reuse [104,105] potentially closing the water cycle at various WWTPs scale [106].

Several debates are still open about how safe treated wastewater should be according to their final reuse purpose as well as about both the tools to be used for their monitoring (*i.e.* number of species and their sensitivity in bioassays) and for their toxicity ranking and classification [101, 105]. Frequently, authors investigating AOPs performance do not include toxicity amongst the investigated parameters or take into consideration no more than one or two biological models. Thus effluent data from batteries of toxicity tests including at least three species belonging to different phylogenetic levels are scarcely available [33, 107], limiting the full comprehension of AOPs potential performance in the perspective of water recovery and reuse. An overview of ecotoxicological implications of various AOPs on antibiotics was reported in Table **3**. Most studies focused on bacteria and microalgae. Amongst crustaceans, *Daphnia magna* mortality test was the most widespread method, while only few data are available for macrophytes and respirometric endpoints (AS OUR). Ecotoxicological investigations are becoming really compulsory to fully understand the real performance and potentiality for reuse of AOPs treated effluents.

4.8. Best Operation Scheme: Any?

Depending on the properties of the waste stream to be treated and the treatment goal, AOPs can be employed either alone or coupled with other physico-chemical and/or biological processes. Several authors observed the complete mineralization of contaminants within the AOPs [108]. However, this is quite expensive due to the amount of energy and chemical reagents needed during the oxidation process. Costs could be reduced using AOPs to convert the initially persistent organic compounds into more easily biodegradable ones before the application of AS treatment. Process coupling is conceptually beneficial usually leading to improved treatment efficiencies. On the other hand and for effluents containing biodegradable fractions, biological pre-treatment followed by chemical post-treatment may be favourable as biodegradable compounds can

Table 3. Toxicity data per organism class on AOPs applied for antibiotics removal.

Antibiotics	AOPs	AS OUR	Bacteria	Microalgae	Macrophytes	Crustaceans	References
AMX	UV-A/TiO_2						[109]
	solar photo-Fenton						[83]
CAP	UV-A/TiO_2						[78]
							[33]
	UVC/H_2O_2						[71]
CEF	UV						[110]
CIP	UV-A/Vis/TiO_2						[111]
	UVC; UVC/H_2O_2						[112]
	EAOP						[80]
DTC	UVC; UVC/H_2O_2						[112]
FLU	O_3						[107]
LIN	Solar photo degr. + O_3						[113]
MOX	UV-A/TiO_2						[99]
NIT	UV						[114]
NOR	EAOP						[80]
OFL	EAOP						[80]
OTC	solar light + TiO_2						[115]
	UV; UV/H_2O_2						[112]
SMX	UV-C/TiO_2						[116]
	O_3						[85]
	UV-A; O_3; O_3/TiO_2; O_3/UV-A; O_2/TiO_2/UV-A; O_3/UV-A/TiO_2						[117]
TC	UV-A/TiO_2 + AS						[118]
	UV-A/TiO_2						[119]
	photolysis						[120]
TRM	solar photo-Fenton						[121]
TYL	UV-A/TiO_2 + AS						[118]
VAN	UV-A/TiO_2						[34]

be easily removed first, and so subsequently do not compete for the chemical oxidant.

4.9. Challenges

The development of catalysts represents the challenge for the near future. They should have with broader range of light absorption for better utilization of sunlight and its integration through nanostructured films on different support in integrated photocatalytic reactor system (*e.g.* membrane-photocalytic reactor which could combine two treatments, photocatalysis and filtration, in one unit). Modification of TiO_2, the most popular photocatalyst, and several other commercially available nano-crystalline semiconductors (*e.g.* ZnO or CuO) by various metal ions or non-metallic species (N, C, S, B, P, F, or I) have already been carried out [122]. However, metal-doped photocatalysts, which better exploit solar light, suffer from the problem of releasing metal pollutant species,

sometimes extremely toxic metals, due to photocorrosion phenomena. The majority of photocatalytic action in non-metal doped photocatalysts illuminated by solar light is still generated by UV-C since the contribution from the visible part of the spectrum is limited. The stability and long-term efficacy of non-metal doped TiO_2 photocatalysts have not been tested yet. Engineering of semiconductor nanostructured materials may significantly enhance the development of green energy saving technologies presenting high efficiency for emerging contaminants removal.

5. CONCLUSION

In the last decades, the scientific research has paid increasing attention to the presence of pharmaceuticals in the environment. Recent data about real and potential environmental concentrations of antibiotics suggested possible risks for human health and aquatic ecosystems. AOPs seem to represent a challenging solution to cope with antibiotics requiring further investigations especially about process optimization and multi-antibiotics treatment. In order to match the sustainability goal, it will be necessary to assess not only technical and economic issues, but also the environmental compatibility of effluents. The implementation of AOPs in a treatment train including membrane could significantly improve the whole process efficiency. Furthermore, a detailed cost analysis should be done considering the additional costs of different processes in the combined systems.

ACRONYMES

AMP	=	Ampicillin
AMX	=	Amoxicillin,
AOPs	=	Advanced Oxidation Processes
AS	=	Activated Sludge
AS OUR	=	Activated sludge oxygen uptake rate
BDD	=	boron-doped diamond
CAP	=	Chloramphenicol,
CEF	=	Cefradine
CIP	=	Ciprofloxacin,
CLX	=	Cloxacillin,
DOX	=	Doxycycline,
EAOP	=	electrochemical advanced oxidation process
EU	=	European Union
FQ	=	fluoroquinolone
FF	=	Florphenicol
LFX	=	Levofloxacin
NIT	=	Nitroimidazole
NOR	=	Norfloxacin
OFL	=	Ofloxacin
OTC	=	Oxytetracycline
OXA	=	Oxacilin
STZ	=	Sulphathiazole,
SMX	=	Sulfamethoxazole
SP	=	Stabilization pond
TAP	=	Tyamphenicol
TC	=	tetracycline
TRM:		
TYL	=	Tylosin,
VAN	=	Vancomicyn
VUV	=	Vacuum UltraViolet
WWTPs	=	wastewater treatment plants
MWWTPs	=	municipal wastewater treatment plants

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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