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A review of the influence of treatment strategies on antibiotic resistant bacteria and antibiotic resistance genes

Virender K. Sharma [a, *], Natalie Johnson [a], Leslie Cizmas [a], Thomas J. McDonald [a], Hyunook Kim [b]

[a] Department of Environmental and Occupational Health, School of Public Health, Texas A&M University, College Station, TX 77843, USA
[b] Department of Energy & Environmental System Engineering, The University of Seoul, 90 Jeonnong-dong Dongdaemun-gu, Seoul 130-743, Republic of Korea

HIGHLIGHTS

- Prevalence of ARB and ARG in rivers, lakes, surface water, wastewater, and sludge.
- Mechanism of resistance include horizontal gene transfer from donor bacteria.
- Chlorine and advanced oxidation processes inactivate ARB and ARG significantly.
- Flow pattern of the constructed wetlands governs removal of ARB and ARG.
- Nanoparticles have a role in investigating mechanism of transfer of ARG from genera.

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ABSTRACT

Antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) in the aquatic environment have become an emerging contaminant issue, which has implications for human and ecological health. This review begins with an introduction to the occurrence of ARB and ARG in different environmental systems such as natural environments and drinking water resources. For example, ARG or ARB with resistance to ciprofloxacin, sulfamethoxazole, trimethoprim, quinolone, vancomycin, or tetracycline (e.g., *tet*(A), *tet*(B), *tet*(C), *tet*(G), *tet*(O), *tet*(M), *tet*(W), *sul* I, and *sul* II) have been detected in the environment. The development of resistance may be intrinsic, may be acquired through spontaneous mutations (*de novo*), or may occur due to horizontal gene transfer from donor bacteria, phages, or free DNA to recipient bacteria. An overview is also provided of the current knowledge regarding inactivation of ARB and ARG, and the mechanism of the effects of different disinfection processes in water and wastewater (chlorination, UV irradiation, Fenton reaction, ozonation, and photocatalytic oxidation). The effects of constructed wetlands and nanotechnology on ARB and ARG are also summarized.

1. Introduction

Access to safe and clean water is a prerequisite for meeting the standards of living in the modern society, but more than one billion people lack access to safe drinking water (Shannon et al., 2008). In the 20th century, safe potable water was achieved through filtration and chlorination; however the water infrastructure of the 21st century is not adequate to meet the challenges of water contamination (Pruden, 2014). For example, many regions of the world such as the Middle East and highly populated urban areas (e.g., Singapore) are struggling to attain water sustainability. Water infrastructure continues to encounter threats from a rising number of contaminants while the treatment systems are not able to effectively treat emerging pollutants. The presence of contaminants in water resources negatively affects public and environmental health (Hong et al., 2015; Richardson and Ternes, 2014).

Generally, unregulated pollutants are referred to as emerging contaminants which include gasoline additives, surfactants, endocrine disruptors, and pharmaceuticals and personal care products (PPCP) (Picó and Barceló, 2015). In recent years, the focus has been on pharmaceuticals as important emerging contaminants, which

* Corresponding author.
E-mail address: vsharma@sph.tamhsc.edu (V.K. Sharma).

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are of concern due to their increasing use worldwide (Khetan and Collins, 2007). A number of pharmaceuticals are not fully removed by wastewater treatment, and effluents are discharged directly into water bodies. Consequently, pharmaceuticals are frequently found in the aquatic environment (Banjac et al., 2015; Evgenidou et al., 2015; Kim et al., 2013; Luo et al., 2014; Verlicchi et al., 2015). Examples of detection of pharmaceuticals in drinking water, ground water, and wastewater include iodinated X-ray contrast media (ICM) in Germany, antidepressants in the United States, and Canada, antibiotics in Australia, and numerous other drugs molecules in the European Union, China, and the United States (Michael et al., 2013; Postigo and Richardson, 2014; Tölgyesi et al., 2010). The persistence of these molecules in different water bodies may pose a risk to aquatic life (Cizmas et al., 2015; de Jesus Gaffney et al., 2015; Li et al., 2015b).

Among the pharmaceuticals, antibiotics have received great attention. Antibiotics are mainly applied to treat bacterial infections, which are a major public health issue. In the United States alone, infections caused at least 2 million serious illnesses and contributed to about 23,000 deaths each year (Friedman, 2015; Rosi-Marshall and Kelly, 2015). Antibiotics are classified into different categories such as sulfonamides, antibiotics, macrolides, β-lactams, pencillins, arsenicals, and aminoglycosides (Bouki et al., 2013; Fatta-Kassinos et al., 2011; Jiang et al., 2013). In the United States, over 250 million antibiotic prescriptions are written annually (Rosi-Marshall and Kelly, 2015). In agriculture, antibiotics are used as veterinary medicine, as biocides in the production of fruit and crops, and as feed additives for livestock and poultry (Table 1) (Silbergeld et al., 2008). The antibiotics shown in Table 1 represent most of the major classes of antimicrobials. Third generation cephalosporin molecules are also included in Table 1. In China, 46% of the 210,000 tons of antibiotics produced annually are being used for animal husbandry (Su et al., 2014). The intensive application of antibiotics in agriculture worldwide has resulted in the release of large amounts of antibiotics to the environment (Silbergeld et al., 2008).

Antibiotics enter into the environment through animal manure and human wastes, which contain significant concentrations of non-metabolized antimicrobials (Berendonk et al., 2015; Martinez, 2008). The fate of antibiotics is determined by their biological and physico-chemical properties (Kim et al., 2014; Kümmerer, 2009a, 2009b; Oncu and Balcioglu, 2013; Sharma et al., 2013). Antibiotics can be persistent in the environment and therefore have been detected in water resources (Gothwal and Shashidhar, 2015; Luo et al., 2014; Verlicchi et al., 2015). There is growing concern that unused antibiotics in the surface water may be causing a risk to human health by promoting antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) (Berendonk et al., 2015). Furthermore, antibiotics in ecosystems can influence the evolution of microbial structure and thus may pose a risk to ecological health (Berendonk et al., 2015; Bouki et al., 2013; Martinez, 2008; Rosi-Marshall and Kelly, 2015).

According to the World Health Organization, antibiotic resistance has become a critical global public health issue of this century. ARB have been found in different aquatic environments (Leonard et al., 2015). Examples of ARB that are usually of concern in healthcare practices are the enterococci, *Klebsiella pneumonia* and *Pseudomonas* spp (Bouki et al., 2013). ARG have also emerged as environmental contaminants (Hsu et al., 2015). ARG have a capacity to spread among bacteria and distribute from human and animal sources to natural environments and drinking water resources (Berendonk et al., 2015; Gillings et al., 2015; Martinez, 2008; Storteboom et al., 2010). ARG have been found in a wide range of environmental matrices, including sediments, lakes, rivers, soils, and wastewater treatment plant effluents. Sediment samples, collected from the Netherlands, showed an increasing trend in ARG during 1940–2008, which conferred resistance to macrolides, penicillins, and tetracyclines (Knapp et al., 2010). ARG were also observed in the sediments and water of Lake Geneva (Czekalski et al., 2015; Thevenon et al., 2012). In the investigation of ARG in the Yangtze River Delta, China, ten tetracycline and sulfonamide resistance genes (*tet*(A), *tet*(B), *tet*(C), *tet*(G), *tet*(O), *tet*(M), *tet*(W), *sul* I, and *sul* II) were detected (Guo et al., 2014). ARG or ARB with resistance to ciprofloxacin, sulfamethoxazole, trimethoprim, quinolone, vancomycin, or tetracycline have been detected in effluents of urban residential areas, hospitals, and a municipal wastewater

Table 1
Antimicrobials that have been registered for use as feed additives in the United States, Canada, European Union, and Australia (adapted from (Silbergeld et al., 2008) with permission from Annual Reviews.).

Group/Class	Antimicrobial	Usage
Arsenicals	3-nitro-arsenic acid	Pigs, Poultry
	Arsenilic acid	Poultry
	Roxarsone, Cabarsone	Poultry
Glycopeptides	Avoparcin	Pigs, Poultry, Cattle
Polypeptides	Bacitracin	Meat poultry, Labs, Pigs, Calves, andTurkeys
Polyethers (Ionophores)	Lasalocid	Cattle
	Narasin	Cattle
	Salinomycin	Pigs, Cattle
	Monensin	Cattle (growth promoters)
Macrolides	Kitasamycin	Pigs
	Oleandomycin	Cattle
	Tylosin	Pigs, Cattle, and Chicken
	Spiramycin	Turkeys, Chickens, Calves, Pigs, and Lambs
	Erythomycin	Chickens
	Tiamulin	Pigs
Quinoxalines	Olaquindox	Pigs
	Carbadox	Pigs
Streptogramins	Virginiamycin	Pigs, Cattle, Poultry, Turkey, Laying hens, Calves, Swine, and Sows
Penicillins	Pencillin G	Chicken
	Pencillin G procaine	Chicken, Turkey, and Sleep
Tetracyclines	Chlorotetracycline	Chicken
	Oxytetracycline	Turkey, Cattle, Sheep, and Swine
Sulfonamides	Tetracycline	Pigs
	Sulfamethazine	Pigs, Cattle
	Sulfathiazole	Pigs

treatment plant system (Amador et al., 2015; Berglund et al., 2015; Li et al., 2015a; Marti et al., 2014; Xu et al., 2015). Interestingly, a study in China showed substantial variability in the total ARG concentrations in sludge from different hospitals, and bacterial cell counts were 3–4 orders of magnitude higher in residential area samples than in hospital samples (Li et al., 2015a).

In this paper, the mechanism of the development of antibiotic resistance is initially presented, followed by an overview of impacts of different treatment strategies on ARB and ARG in water. The treatment approaches discussed include chemical disinfection, constructed wetlands, and nanotechnology.

2. Mechanisms of antibiotic resistance

The occurrence and rise of antibiotic resistance in microbial populations are unavoidable due to the principles of biology and evolution. Resistance may be intrinsic, may be acquired through spontaneous mutations (*de novo*), or may occur due to horizontal gene transfer from donor bacteria, phages, or free DNA (Dodd, 2012). Actions associated with intrinsic or innate resistance include prevention of the antibiotic from initially penetrating the bacterial cell wall or expulsion before the antibiotic reaches its target through specific efflux pumps. In addition, many bacteria intrinsically deactivate or degrade antibiotics. The natural resistance of Enterobacteriaceae to β-lactams is due to the enzymatic destruction of the β-lactam ring and consequent prevention of its antimicrobial mechanism of action (Sykes and Matthew, 1976). Historically, pharmaceutical companies recognized innate resistance of microbes with specific β-lactamases and designed antibiotics to avoid degradation. However, strains eventually developed resistance by producing effective β-lactamases. Since these initial observations, a number of ARG have been identified and ARB are rife. Importantly, resistant phenotypes can effectively shift populations toward antibiotic resistance based on advantageous growth and survival (Tenover, 2006). Horizontal transfer of genes among microbes represents another mechanism of acquired resistance. Thus, even nonpathogenic microbial species that harbor resistant genes serve as an ecological reservoir for pathogenic bacteria (Salyers and Shoemaker, 2006). These mechanisms include the uptake of naked DNA and mobile genetic elements such as plasmids, transposons, integrons, gene cassettes, and bacteriopahges (Nwosu, 2001). Some of these mechanisms can transfer multiple ARG at the same time. Methicillin-resistant *Staphylococcus aureus* (MRSA) represents a clinically relevant example of the acquisition of a gene cassette. The *mec* element carries the *mecA* gene, which encodes a β-lactam-insensitive protein capable of cell wall synthesis even in the presence of an antibiotic (Katayama et al., 2000). Numerous *mec* elements have been identified in different *Staphylococcus* species, indicating horizontal gene transfer (Shore et al., 2011). Advanced genomics has enabled the rapid identification of antibiotic resistance gene mutations in bacterial populations. These technologies are imperative for deciphering the mechanisms of resistance and offer the opportunity to understand clinically relevant mutations. Alternatively, microbial survival following antibiotic treatment can persist even in the absence of genetic mutation. This has been termed collective antibiotic tolerance (CAT) wherein a subset of the population survives a normally lethal concentration (Meredith et al., 2015). Sublethal dosing can also breed resistance either in response to clinical medicine or environmental uses, such as the broad usage of antimicrobials in food animal production (Silbergeld et al., 2010).

The next section summarizes three different treatment approaches that may influence ARB and ARG in different environments. Initially, conventional disinfectants (chlorine and ozone) and advanced oxidation processes (UV, Fenton-reaction, solar-driven Fenton oxidation, and photocatalytical oxidation) are presented. There have been published reports on the impact of wetlands on the ARB and ARG, and the next section summarizes the published literature on this topic. Finally, the use of nanoparticles to produce antibacterial activity in treatment processes is being developed. Nanoparticles have also been shown to play a role in the treatment of antibiotic-resistant biofilms (Taylor et al., 2012). Furthermore, nanoparticles may have effects on the ARG in anaerobic digestion (Miller et al., 2014). The last section therefore reviews a few studies that have been published regarding the use of nanoparticles, which has been particularly prominent in medical treatment.

3. Treatment strategies

3.1. Disinfectants

Chlorine is generally applied to disinfect water because it is readily available and effective (Deborde and von Gunten, 2008). Advanced oxidation processes employing ozone, Fenton reagent ($Fe(II) + H_2O_2 \rightarrow Fe(III) + {}^{\bullet}OH + OH^-$), and photocatalytic systems have also been used in disinfecting water and wastewater (Sharma and Graham, 2010; Sharma et al., 2014b; von Gunten, 2003; Zhang et al., 2011a,b). The ${}^{\bullet}OH$ is the main oxidant/disinfectant in Fenton reactions and photocatalytic oxidations (Pignatello et al., 2006; Sacco et al., 2015; Su et al., 2012). Redox potentials of different oxidants under acidic and basic conditions are given in Table 2 (Sharma, 2011). Redox potentials are pH dependent and the redox potentials of ${}^{\bullet}OH$ are the highest among the oxidants reported in Table 2. The order of redox potentials is ${}^{\bullet}OH > O_3 > H_2O_2 >$ chlorine. The ${}^{\bullet}OH$ radical usually reacts rapidly and non-selectively with most of the compounds (Lee and von Gunten, 2012). The reactions of ${}^{\bullet}OH$ radical involve addition and hydrogen abstraction reactions (Sharma, 2013; Xu and Chance, 2007). The reactions of ${}^{\bullet}OH$ radical with proteins result in damage to both the side chains and backbone; fragmenting the proteins (Sharma, 2013). Similarly, the high reactivity of ${}^{\bullet}OH$ radical with constituents of DNA and RNA are responsible for their damage (Cadet and Wagner, 2014; Pisoschi and Pop, 2015).

In aqueous systems, free available chlorine is primarily present as HOCl and its conjugate base, OCl^- ($pK_a = 7.5$ at 25 °C) (Morris, 1966). As such, the ratio of [HOCl] to [OCl^-] is governed by pH. HOCl is typically a far better oxidizing agent and disinfectant than OCl^- (Deborde and von Gunten, 2008; Sharma, 2008). The reaction kinetics of Cl_2 and aqueous compounds is first-order in $[compound]_{total}$ and first order in $[HOCl]_{total}$, giving an overall second-order reaction (Deborde and von Gunten, 2008). As such, the second-order rate constants (k) for chlorination reactions depend on the pH (Deborde and von Gunten, 2008). The pathways for reactions with organic chemicals include oxidation, addition, and electrophilic substitution, and the second-order rate constant for chlorination of organic compounds varies dramatically, ranging from < 0.1 to 10^9 M^{-1} s^{-1} (Deborde and von Gunten, 2008). Chlorination of inorganic chemicals typically occurs via an electrophilic attack of HOCl (Sharma, 2008).

When a solution containing biological molecules is chlorinated,

Table 2
Redox potentials of different oxidants in water (adapted from Sharma (2011)).

Oxidant	Acidic (pH 14)	E° (V/SHE)	Basic (pH 1)	E° (V/SHE)
Hydroxyl Radical	${}^{\bullet}OH/H_2O$	2.80	${}^{\bullet}OH/OH^-$	1.89
Ozone	O_3/O_2	2.08	O_3/O_2	1.24
Hydrogen peroxide	H_2O_2/H_2O	1.78	H_2O_2/OH^-	0.88
Hypochlorite	$HClO^-/Cl^-$	1.48	ClO^-/Cl^-	0.84

the HOCl reacts quickly with selected functional groups including purine and pyrimidine groups of nucleobases, amine, organosulfur or aromatic moieties of amino acids, and the sulfhydryl moiety of glutathione (Deborde and von Gunten, 2008; Dodd, 2012). HOCl exhibits negligible reactivity with the amide groups of amino acids that are bound to peptides, so only the N-terminal amino acids in peptidoglycan or proteins, or the free organosulfur, aromatic or amine side chains of tyrosine, tryptophan, histidine, cysteine, methionine, or lysine groups in proteins are likely to react with HOCl (Dodd, 2012; Sharma, 2013). In addition, HOCl is minimally to somewhat reactive with unsaturated fatty acids, and minimally reactive with aliphatic hydrocarbons, so that it does not react to a significant extent with saturated fatty acids or saccharides (Dodd, 2012). HOCl is very reactive with free TMP, dGMP and UMP, but less reactive with double-stranded DNA (Dodd, 2012; Prütz, 1998, 1996). Overall, HOCl is analogous to oxidant B (Fig. 1b); it reacts with cell wall constituents but also passes into the cytoplasm and reacts with DNA (Dodd, 2012). The deactivation of ARG inside cells is likely to need chlorine contact times (CTs) at the upper limit of the CTs usually used for water treatment (Dodd, 2012).

In water, ozone is unstable and undergoes decomposition to produce •OH, which is also a very strong oxidant that reacts quickly with a variety of molecules (von Gunten, 2003). Ozone is primarily responsible for disinfection, while both O_3 and •OH participate in oxidation reactions (Sharma, 2008; von Gunten, 2003). Ozone reacts with the inorganic compounds Fe(II), H_2S, nitrite, Mn(II) and cyanide through a mechanism involving oxygen transfer, while reaction of ozone with organic compounds involves attack of double bonds, neutral amines and activated aromatic systems (Sharma, 2008). Ozone is also highly reactive with the unsaturated carbon–carbon bonds and amino acids in the peptidoglycan, lipids and proteins in the cell wall and cell membrane, so it is not initially expected to penetrate deeply into the cells (similar to oxidant A in Fig. 1b) (Dodd, 2012). This is consistent with the findings of a study that assessed *Escherichia coli* inactivation by multiple disinfectants, and found ozone produced a greater change in cell wall permeability than chlorine dioxide, free chlorine and UV irradiation (Cho et al., 2010). It should be noted that at higher ozone exposure levels, once O_3 has penetrated into the cytoplasm, it may be effective in deactivating DNA (Dodd, 2012). In one study of *E. coli* inactivation with ozone, under conditions where essentially all of the bacteria were inactivated, precipitation of DNA also occurred (Hunt and Mariñas, 1999). The reactivity of ozone with nucleobases is similar to the reactivity seen with HOCl, in that O_3 reacts far more rapidly with TMP and dGMP than with dAMP and dCMP (Dodd, 2012; Somensi et al., 2015). Again, as with HOCl, the reactivity of O_3 with double-stranded DNA is lower than expected, probably due to hydrogen bonding between DNA strands (Dodd, 2012; Oncu and Balcioglu, 2013). It should be noted that most studies of O_3 degradation of cellular components have not differentiated between reactions with O_3 and those with •OH, and •OH is highly reactive towards most biological molecules including free double-stranded DNA (Dodd, 2012; Sharma and Graham, 2010).

Significantly, the inactivation of bacteria during disinfection may not guarantee the deactivation of the intracellular ARG (Dodd, 2012). Several studies have found that even after bacteria have undergone 4-log or greater inactivation, at least a portion of the transforming activity of the DNA remained (Dodd, 2012; Roller et al., 1980; Shih and Lederberg, 1976). To deactivate ARG inside cells, the disinfectant must move through the cell envelope to the DNA without undergoing extensive binding to other cellular constituents, so it is present in sufficient quantity inside the cell to react with the ARG-containing DNA (Fig. 1a) (Dodd, 2012). In Fig. 1b, oxidant "A" is one that is quickly bound in the cell envelope and enters only minimally into the cytoplasm, while oxidants "B" and "C" enter the cytoplasm in sufficient quantity to degrade DNA containing ARG (Dodd, 2012). Below is the summary of different studies carried out to learn the variation on inactivation of ARB and ARG using different disinfection processes.

3.1.1. UV disinfection and chlorination

Most of the studies on the inactivation of ARB and ARG by chlorination have been conducted in the last one year (Al-Jassim et al., 2015; Childress et al., 2014; Fiorentino et al., 2015; Guo et al., 2015; Jia et al., 2015; Pang et al., 2015; Yuan et al., 2015; Zhang et al., 2015; Zhuang et al., 2015). Some studies were also extended to ultraviolet (UV) irradiation, allowing a comparison of the two processes (chlorination versus UV irradiation) in terms of their efficacy and mechanism (Guo et al., 2015; Pang et al., 2015; Zhang et al., 2015). In a study of wastewater treatment using chlorination alone, resistance to nine antibiotics (cephalexin, ciprofloxacin, chloramphenicol, erythromycin, gentamicin, rifampicin, sulfadiazine, tetracycline and vancomycin) was examined (Yuan et al., 2015). Doses of chlorine varying from 15 to 300 mg Cl_2 min L^{-1} were investigated. All the bacteria, except sulfadiazine- and erythromycin-resistant bacteria, were inactivated fully by 15 mg Cl_2 min L^{-1}. A chlorine dose of > 60 mg Cl_2 min L^{-1} was needed to inactivate sulfadiazine- and erythromycin-resistant bacteria. A detailed quantitative real time PCR examination of erythromycin (*ere*(A), *ere*(B), *erm*(A), *erm*(B)) and tetracycline resistance genes (*tet*(A), *tet*(B), *tet*(M), and *tet*(O)) in wastewater showed 40% and 80% of these genes, respectively, persisted after chlorination, indicating that chlorination was not able to eliminate ARG effectively (Yuan et al., 2015). A previous UV irradiation study also showed no significant decrease in levels of *tert*(Q) and *tert*(W) (Auerbach et al., 2007).

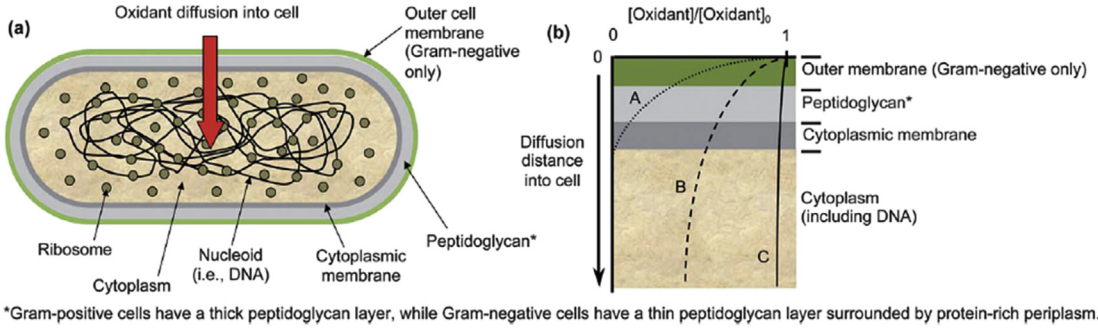

Fig. 1. Overview of (a) a generic vegetative bacterial cell, and (b) variations in concentrations of several hypothetical oxidants with increasing diffusion distance into the cell (where "A" represents an oxidant with high reactivity toward cell envelope constituents, "B" represents an oxidant with moderate reactivity toward cell envelope constituents and DNA, and "C" represents an oxidant with low reactivity toward all cell constituents). (Adapted from Dodd (2012) with the permission of The Royal Society of Chemistry).

The results of inactivation of ARG (*sul*1, *tetX*, *tetG*, *intI1*, and 16S rRNA) by UV alone, chlorination and sequential UV/chlorination are presented in Fig. 2 (Zhang et al., 2015). The results clearly demonstrated a positive relationship between the inactivation of ARG and the dosage of chlorine and contact time (Zhang et al., 2015). An increase in chlorine dosage resulted in increased inactivation of ARG (Fig. 2). The maximum inactivation was in the range from 1.30 to 1.49 log unit at 30 mg L^{-1} chlorine dose. Similarly, an increase in

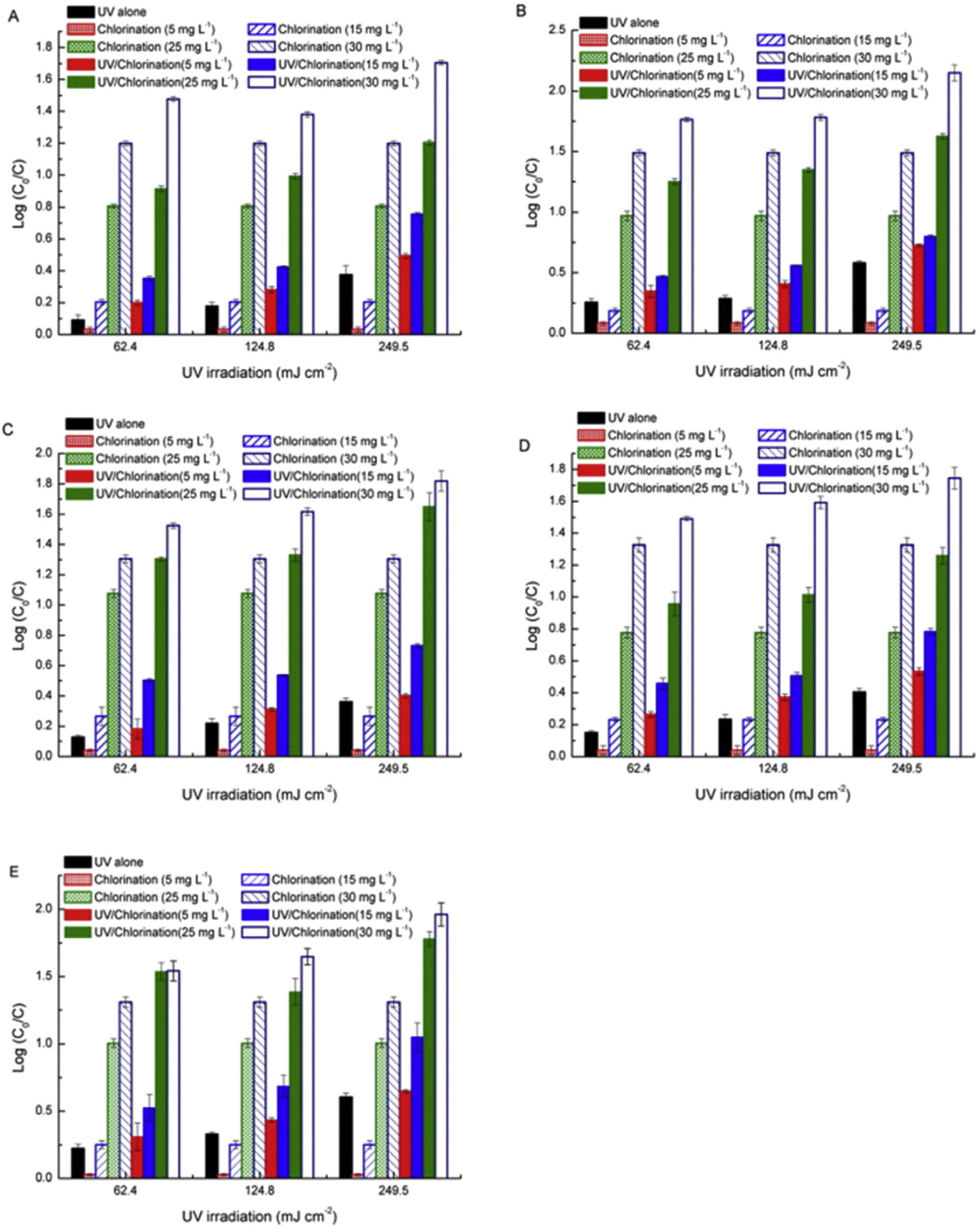

Fig. 2. Influences of UV alone, chlorination and sequential UV/chlorination treatment on the removal of ARGs. (A) *sul1* (B) *tetX* (C) *tetG* (D) *intI1*, and (E) 16S rRNA genes. The horizontal axis indicates three different UV dosages of 62.4, 124.8, and 249.5 mJ cm^{-2}, respectively. (Adapted from Zhang et al. (2015) with permission from Elsevier Inc.).

the intensity of the UV irradiation produced increase in inactivation of ARG (Fig. 2). This is expected because high energy irradiation could penetrate the UV-transparent structures in the cell in order to be absorbed by RNA and DNA (Dodd, 2012). Significantly, the sequential UV/chlorination enhanced the inactivation of ARG (Fig. 2). The maximum synergistic effect may need optimizing dosages of chlorine and UV irradiation. At a fluence of 249.5 mJ cm^{-2}, the inactivation values of *tetX* and 16S rRNA genes were 0.58 and 0.60 log units, respectively. Other ARG had 0.36–0.40 log units inactivation (Fig. 2). An increasing ammonia nitrogen (NH_3–N) concentration reduced the inactivation of ARG by chlorination (Zhang et al., 2015). At doses of 2.56 mg L^{-1} of NH_3–N and 30 mg L^{-1} chlorine, the inactivation of the studied ARG was in the range of from 1.20 to 1.49 log units. When dosages of NH_3–N were increased to 5 mg L^{-1} and 15 mg L^{-1} while keeping the same chlorine dose (30 mg L^{-1}), the inactivation was 0.63–0.79 and 0.03–0.10 log units, respectively (Zhang et al., 2015).

The mechanism of effect of UV irradiation and chlorination on ARG in wastewater was explored with the conjugative transfer model between Gram-negative strains of *E. coli* (Guo et al., 2015). When low UV dosages (up to 8 mJ/cm^2) were used, the frequency of conjugative transfer showed minimal variation and bacterial number was decreased, but no change in the cell permeability was observed; however, with high doses of UV irradiation (>10 mJ cm^{-2}), the frequency of ARG transfer was largely suppressed (Guo et al., 2015). In contrast, chlorine doses up to 40 mg Cl min L^{-1} promoted the frequency of conjugative transfers by 2–5 fold. However, with a chlorine dose higher than 80 mg Cl min L^{-1}, the frequency of ARG transfers was greatly suppressed (Guo et al., 2015). Importantly, chlorination of wastewater generated chloramine, which promoted cell permeability of the *E. coli.* The difference in mechanism between UV irradiation and chlorination was thus presented by Fig. 3. The results suggest that chlorination may augment the risk of ARG transfer in wastewater that contains NH_3-N. With UV irradiation, no effect to the cell membrane occurred, but direct damage to the plasmid with the ARG resulted in death of donor (or recipient). Therefore, UV irradiation may be advantageous over chlorination in controlling the transfer of ARG (Guo et al., 2015).

3.1.2. Fenton and ozone oxidation

A few studies have attempted to determine the effect of solar-driven Fenton oxidation and ozonation on ARB and ARG (Cengiz et al., 2010; Oh et al., 2014; Oh et al., 2016). In Fenton reactions, the oxidative species, •OH, is produced through the reaction of Fe^{2+} with H_2O_2 ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\bullet}OH$) (Pliego et al., 2015). In solar-driven Fenton reactions, the Fe^{3+}, produced in the Fenton reaction, is photo-reduced to regenerate Fe^{2+} (e.g., $[Fe(H_2O)]^{3+} + h\nu \rightarrow Fe^{2+} + H^+ + {}^{\bullet}OH$). This additional step distinguishes solar-driven Fenton oxidation from the conventional Fenton process (Pliego et al., 2015). In one study of Fenton oxidation, the degradation of a mixture of antibiotics (sulfamethoxazole and clarithromycin), the disinfection of *enterococci*, and the inactivation of ARB resistant to sulfamethoxazole and clarithromycin separately and in a mixture were investigated (Karaolia et al., 2014). Experiments were performed using distilled water, and simulated and real wastewater effluents. In distilled water, complete removal of the studied antibiotics was observed during the solar Fenton system. Removal was also seen with only the solar system, but the results were slower than with the solar Fenton method. A 5-log reduction in the resistance of *enterococci* towards both antibiotics was seen when the solar-Fenton system was applied (Karaolia et al., 2014). A study of the effects of ozonation has shown that tetracycline at levels of a few mg L^{-1} or 100 μg L^{-1} can enhance the transfer of ARG (*E. coli* DH5α containing the 64,508 bp nucleotide sequence of the Inc-P-1beta antibiotic resistance plasmid pB10) with and without ozonation (Oh et al., 2014; Oh et al., 2016). A recent study used Fenton-like reaction to successfully eliminate the ARB in the effluent water of WWTP (Macku'ak et al., 2015).

A comparison of the effect of different disinfection processes, chlorination, ozonation, and electron beam is shown in Fig. 4 (Oh et al., 2016). A high dose of chlorine (30 mg L^{-1}) was required to decrease both ARB and ARG. This dose of chlorine seems impractical in treatment processes. Comparatively, a 3 mg L^{-1} ozone dose decreased the levels of ARB and ARG by more than 90%. In the case of the electron beam process, the required energy in the electron beam was 0.5 kGy for a 90% reduction in the ARB and the ARG (Fig. 4). Because of the high energy use and safety issues in electron beam technology, ozonation is the preferable method to control ARG. Furthermore, the effectiveness of ozonation can be increased by adding hydrogen peroxide and persulfate (Oh et al., 2014; Oh et al., 2016).

The influence of the operating conditions for different oxidation processes on the removal of selected ARG, including *sul1*, *intI1, 16S rDNA*, and *tetG*, is presented in Table 3 (Zhuang et al., 2015). The

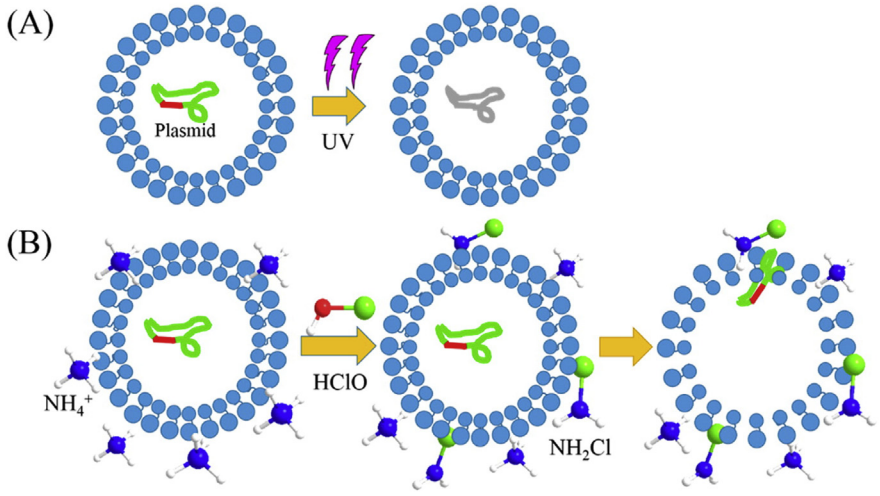

Fig. 3. Comparison of the mechanisms of UV disinfection (A) and chlorination (B) affecting the ARGs conjugation transfer (Adapted from Guo et al. (2015) with the permission of the American Chemical Society).

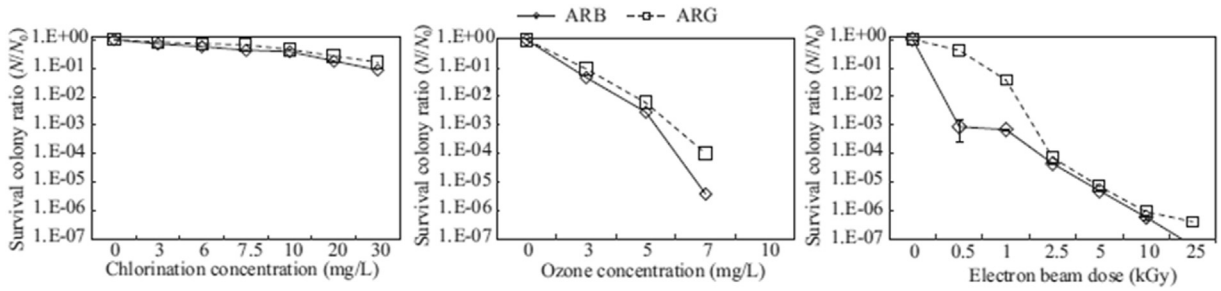

Fig. 4. Survival rate of antibiotic resistant bacteria (*E. coli* DH5α) containing multi-resistance gene (pB10) during chlorination, ozonation, and electron beam process. (Conditions: buffer = phosphate, chlorine contact time = 15 min) (Adapted from Oh et al. (2014) with the permission of Elsevier Inc.).

Table 3
Inactivation of ARG by different treatment methods (Adapted from Zhuang et al. (2015) with permission from Springer).

Technologies	Relative suitable operation condition	Removal of selected genes
Chlorination	Chlorine dose, 40 mg L^{-1}; time, 60 min	1.654~2.28 log
UV irradiation	500 mJ cm^{-2}	0.80~1.21 log
UV/chlorination	UV dose, 62 mJ cm^{-2}; chlorine dose,	
5 mg L^{-1}; time, 60 min	1.12~1.91 log	
Fenton oxidation	pH, 3; H_2O_2 dose, 0.005 M; Fe^{2+}/H_2O_2 (mol), 1/10; time, 2 h	2.42~3.48 log
Ozonation	27 mg L^{-1}	0.60 log

results in Table 3 conducted by the same research group suggest that chlorination was an efficient method for inactivating ARG (Zhuang et al., 2015). Comparatively, ozonation was not very effective for inactivating ARG. Fenton oxidation was able to inactivate ARG by more than 3 log units (Table 3) (Zhuang et al., 2015). Irradiation by UV light was moderately successful at inactivating ARG, but showed an increase in efficiency when it was combined with chlorination (Table 3) (Zhuang et al., 2015). Overall, the economic cost of different technologies may be considered for any realistic, practical application of oxidation technology to inactivate ARG.

3.1.3. Photocatalytical processes

A few reports on the inactivation of ARB by photocatalytic processes have been published (Dunlop et al., 2015; Rizzo et al., 2014; Tsai et al., 2010; Xiong and Hu, 2013).

In the photo-irradiation disinfection stated in section 3.1.1, the direct light induced inactivation of ARB species may take place whereas the photocatalytic processes is indirect regarding which reactive oxygen species ($O_2^{\bullet -}$, •OH, $^1O_2$) are generated (e.g., $TiO_2 + h\nu + H_2O \rightarrow\rightarrow\rightarrow O_2^{\bullet -}$, •OH, $^1O_2$) (Etacheri et al., 2015). A study on photocatalytic activation used ultraviolet A (UV-A)/Titanium dioxide (TiO_2) to oxidize methicillin-resistant *S. aureus* (MRSA), multidrug-resistant *Acinetabacter baumannii* (MDRAB), and vancomycin-resistant *Enterococcus faecalis* (VRE). These ARB can cause nosocomial or community acquired infections (Tsai et al., 2010). To compare the results, controls using antibiotic-sensitive strains of bacteria, *S. aureus* (MSSA), *A. baumannii* (MDSAB), *E. faecalis* (VSE), *E. coli* and bacteriophage were also investigated (Tsai et al., 2010). The survival of bacteria following the use of different amounts of TiO_2 are shown in Fig. 5 (Tsai et al., 2010). An increase in the dose of TiO_2 decreased the survival fractions of bacteria. The photocatalytic process reduced the numbers of bacteria by 1–3 log units. Generally, bacteria were susceptible to photocatalytic oxidation in the following order: bacteriophage MS2 > MDSAB > VRE > *E. coli* > MRSA ≈ MSSA > MDRAB > VSE. There was no significant difference between MSSA and MRSA. However, the effect of photocatalytic oxidation on MDRAB was approximately 2 times higher than the effect on MDSAB. In contrast, the susceptibility of VSE was also about 2 times higher than that of VRE (Tsai et al., 2010). Similar results were also observed in a previous study (Kangwansupamonkon et al., 2009). A later study used an LED lamp in the UV-A/TiO_2 system, which also showed inactivation of ARB, *E. coli* ATCC 700891 (Xiong and Hu, 2013).

Recently, solar simulated nitrogen-doped TiO_2 photocatalysis was studied to evaluate the inactivation of multi drug resistant *E. coli* strain in biologically treated urban wastewater (Rizzo et al., 2014). Total inactivation of ARB was achieved in 60 min of irradiation time. The surviving ARB showed a decreasing trend with increasing irradiation time in resistance to ciprofloxacin and sensitivity to cefuroxime (Rizzo et al., 2014). However, the photocatalytic process did not significantly alter the resistance of *E. coli* to vancomycin and tetracycline (Rizzo et al., 2014). More recently, the influence of photocatalysis on the transfer of ARG in urban wastewater was examined (Dunlop et al., 2015). Two antibiotic-resistant strains of *E. coli*, rifampcin resistant (J-53R) and chloramphenicol resistant (HT-99), and an antibiotic-sensitive strain of *E. coli*, K-12, were treated by photocatalysis using a TiO_2-UVA lamp system. The treatment resulted in inactivation of ARB up to 3-log unit within 180 min. However, a full recovery of ARB was observed during post treatment incubation for 24 h at 37 °C. Comparatively, recovery of *E. coli* K12 was not seen during the same incubation period. Another significant finding of this study was the approximately four-fold increase in the percent of gene pair conjugates in 180 min in the mixtures of J-53R and HT-99 cells (9:1 ratio) treated with photocatalysis, compared to an untreated sample mixture. Experiments showed a lower decreased numbers of ARB and gene pair conjugates in wastewater than that in distilled water (Dunlop et al., 2015). This indicates the influence of inorganic and organic constituents of wastewater in inactivating ARB and gene pair conjugates (Dunlop et al., 2015). Furthermore, the photocatalytic treatment must be sufficiently lengthy before the wastewater effluent is released in order to control release and transfer of ARG and thus the further development of ARB in the natural environment (Dunlop et al., 2015).

A recent study applied solar disinfection, solar-driven advanced oxidation processes (sunlight/H_2O_2, sunlight/TiO_2, sunlight/H_2O_2/

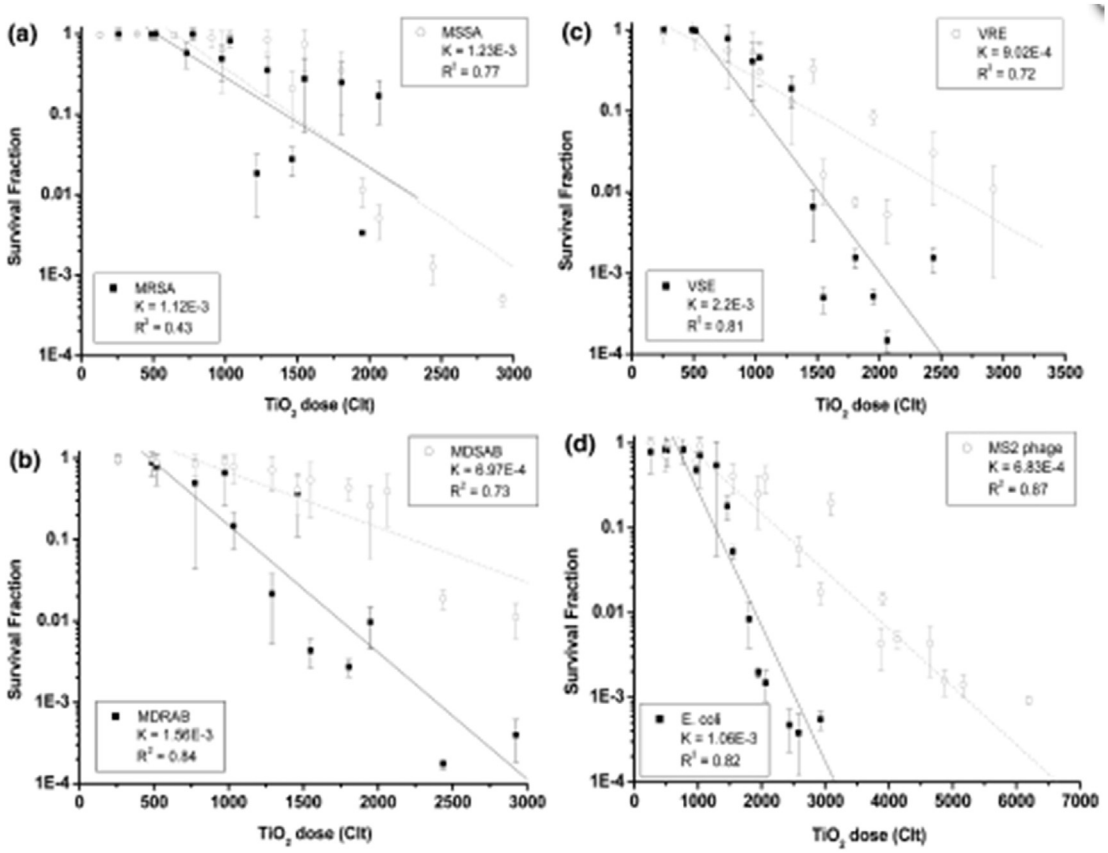

Fig. 5. Survival curves of (a) MSSA/MRSA, (b) MDSAB/MDRAB, (c) VSE/VRE and (d) MS2/*E. coli* exposed to different TiO_2 doses. The cell concentrations of these samples ranged from 10^3 to 10^5 CFU mL^{-1} or PFU mL^{-1}, light irradiation (UV-A) = 400 μW cm^{-2} (Adapted from (Tsai et al., 2010) with permission of Wiley Inc.).

TiO_2, solar photo-Fenton), and chlorination in urban wastewater to assess the inactivation of multidrug (ampicillin, ciprofloxacin, and tetracycline) resistant *E. coli* (Fiorentino et al., 2015). This study allowed the comparison of the disinfection efficiencies of different methods. An evaluation of post-treatment bacterial growth was also carried out (Fiorentino et al., 2015). In using sunlight/H_2O_2/TiO_2, the best disinfection performance (i.e., total inactivation) was obtained at Q_{UV} (cumulative energy per unit volume) of 3–5 *k*J L^{-1}; depending on the ratio of H_2O_2 and TiO_2. In comparison, the sunlight/H_2O_2 process required a Q_{UV} of 8 *k*J L^{-1} ($[H_2O_2] = 50$ mg L^{-1}). When a ratio of 5:10 ($[Fe(II)]:[H_2O_2]$) in the photo-Fenton process was applied, the disinfection efficiency was best at Q_{UV} of 8 *k*J L^{-1}. The value of Q_{UV} was 37 *k*J L^{-1} under solar light conditions. Significantly, all these processes did not change the antibiotic resistance of the surviving colonies. The photocatalytic processes involve the cost of separation of TiO_2 treatment, or the use of TiO_2 supported/film reactors, and the Fenton process generates sludge. Therefore, inactivation using the sunlight/H_2O_2 process is preferable.

Chlorine at a dose of 1.0 mg Cl_2 L^{-1} was able to achieve inactivation in 15 min (Fiorentino et al., 2015). Comparatively, similar inactivation needed 90 min at a H_2O_2 dose of 50 mg L^{-1} in the sunlight/H_2O_2 process (Fiorentino et al., 2015). However, a study on the regrowth after disinfection of total and multidrug resistance (MDR) *E. coli* at different retention times of 6, 12, 24, and 48 h gave an increase in MRD indigenous *E. coli* (Fiorentino et al., 2015). The sunlight/H_2O_2 process produced a decrease in MRD indigenous *E. coli* after disinfection (Fiorentino et al., 2015). Overall, use of the sunlight/H_2O_2 process resulted in a slower inactivation rate than use of chlorine, but it controlled MRD indigenous *E. coli* more effectively than the chlorination process.

3.2. Wetland/biodegradation

Wetland technology is a natural process that has been applied to treat polluted water from various sources since the 1960's due to its low operation and maintenance cost. Initially, natural wetlands with large helophyte dominating vegetation were utilized to treat wastewater from rural villages or animal farms (Cole, 1998). This technology can effectively remove organics from wastewater; a removal efficiency of more than 70% is commonly achieved for both biological oxygen demand (BOD) and suspended solids (United States Environmental Protection Agency, 1994). However, removal efficiency of this wetland technology for N or P is not consistent, and ranges from less than 30% to more than 80% (Nichols, 1983). In particular, P removal efficiency can decrease down to zero, if the soils of a wetland are saturated. Therefore, P removal by a wetland depends heavily on the adsorption capacity of the wetland soils.

Over the past decades, man-made wetlands have been designed and applied to more effectively remove both organics and nutrients from wastewater; they are called constructed wetlands (CWs). Basically, a CW is a small semi-aquatic ecosystem, in which a large population of different microorganism communities proliferates and a variety of physical chemical reactions occur. CWs are mainly divided into three types depending on the pattern of wastewater flowing through the CW: ones with free surface flow, ones with horizontal subsurface flow, and ones with vertical subsurface flow (Cole, 1998; Liu et al., 2013; Liu et al., 2014).

CWs also have been applied to degrade recalcitrant chemicals, for example, pesticides in agricultural runoff. Adsorption to

sediments or soils in a CW and absorption by plants have been identified as major mechanisms for the reduction of pesticides that enter the CW. In particular, adsorption to sediments was reported to account for about 80% of the total concentration decrease of pesticides that enter a CW (Budd et al., 2009).

As in the case with pesticides, pharmaceuticals flowing into a CW can be removed via adsorption to sediments, biodegradation, plant uptake, hydrolysis, or photodecomposition (Fig. 6). Although the first three of these removal processes are considered to be the major removal mechanisms for PPCPs, the rest can to some extent play a role. A chemical with higher hydrophobicity tends to adsorb to sediments (Carvalho et al., 2013). For example, fluoxetine (log K_{ow} = 2.4–3.8) has a relatively high K_{ow} and is susceptible to sorption to sediments or natural organic matter in CWs. Pharmaceuticals with a relatively high solubility or low log K_{ow} (close to or below zero), e.g., tetracyclines (log K_{ow} = −1.3–0.05) and sulfonamides (log K_{ow} = −1.3–0.05), can also be adsorbed to soil particles in a CW if they form a complex with metal ions, e.g., Ca^{2+}, Mg^{2+}, or Fe^{3+} (Avisar et al., 2009; Zhang et al., 2014). However, for these chemicals, biodegradation in the aqueous phase or on the surface of particles, hydrolysis, and photolysis also are important removal pathways.

Within a CW, dissolved or ionized antibiotics (or ones with relatively low log K_{ow}) are absorbed by plants as well as degraded by microorganisms. A CW containing planted *Typha* spp. (a macrophyte) could produce 10–70% better performance than a CW without *Typha* spp. in removing carbamazepine (pK_a = 14, log K_{ow} = 1.5; (Scheytt et al., 2005)), clofibric acid (pK_a = 3.2, log K_{ow} = 2.9; (Scheytt et al., 2005)), and ibuprofen (pK_a = 4.5, log K_{ow} = 1.5; (Scheytt et al., 2005)) (Dordio et al., 2010; Dordio et al., 2011). Since these chemicals exist in the dissociated form or have low lipophilicity, these chemicals could have been absorbed and transpired easily by the plants in the CW. Plants can take up organic compounds with 0.5 < log K_{ow} < 3 as well as dissociated ones (Pilon-Smits, 2005).

Along with pharmaceuticals (especially antibiotics), ARG which are developed before they are discharged from animal farms can flow into a CW. If a CW is designed for further treating effluent discharged from a conventional WWTP, an influx of ARG is likely to occur. In addition, these ARG can be developed within the CW. In general, ARG flowing into a WWTP are seldom removed. Instead, an increase of the ARG is more common in the plant (Rizzo et al., 2013), probably because a large population of microorganisms in activated sludge is continuously exposed to antibiotics.

A few researchers have carried out studies in which the fates of different ARG in CWs were monitored, and reported varying results. A number of these studies are summarized in Table 4. In general, the removal efficiencies for individual antibiotics to some degree varied depending on the flow pattern of the CW under study. It appears that a surface flow CW may be more efficient in removing antibiotics; 60–100% removal efficiency was obtained in various studies (see Table 4). The high removal efficiency is probably due to light penetration and the higher oxidation state created in the surface water; more aerobic biodegradation and photolysis might result under these conditions. In the case of CWs with subsurface flow patterns, relatively lower removal efficiencies were achieved (Table 4).

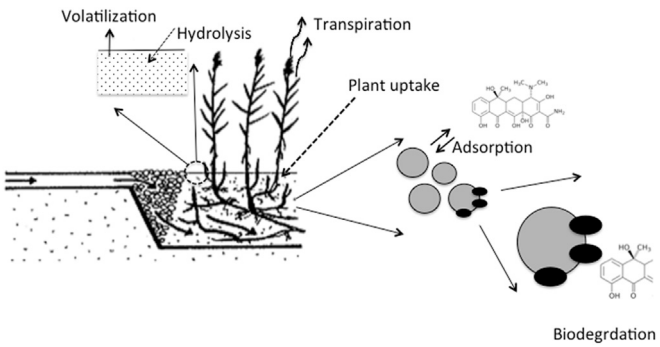

Fig. 6. Major mechanisms of pharmaceutical removal in a CW.

As with the case of antibiotics, CWs with a surface flow pattern showed a good ARG-reduction efficiency. Compared to the levels in the influent water, the ARG levels of the effluents from a CW with a free surface flow were much lower (Liu et al., 2014). The clear reduction of the ARG levels was attributed to the higher oxidation state of the aqueous phase (Liu et al., 2014). In most cases, ARG are not significantly reduced by a CW with a vertical subsurface flow pattern or a horizontal subsurface flow (Liu et al., 2013; Liu et al., 2014). This may be due to the anaerobic conditions that develop in the bed of a CW, especially in a vertical flow CW. Nonetheless, a few studies reported reduction of ARG by a vertical flow CWs. For example, 45–99% of tetracycline resistance genes in swine wastewater were reduced by a vertical upflow CW (Huang et al., 2015) or by a conventional vertical flow one (Huang et al., 2015).

3.3. Nanotechnology

The application of nanoparticles (NPs) to treat ARB and ARG is largely restricted to medical research (Oktar et al., 2015; Singh et al., 2014b). NPs as antimicrobial agents have been shown to be effective against a variety of microorganisms (Hajipour et al., 2012; Huang et al., 2014). The antimicrobial activity of silver nanoparticles (AgNPs) has been demonstrated against Gram-positive and Gram-negative bacteria including multi-drug resistant strains (e.g., methicillin-resistant *S. aureus* (MRSA)) (Dallas et al., 2011; Sharma et al., 2014a). AgNPs coated with natural organic matter have also been shown to possess antimicrobial activity against a number of bacterial strains (Adegboyega et al., 2014). Metal oxide NPs including copper oxide (CuO), zinc oxide (ZnO), and TiO_2 also showed activity against a range of pathogens such as MRSA and *E. coli* (Maniprasad and Santra, 2012; Maniprasad et al., 2013; Ren et al., 2009). Several studies have shown that iron oxide NPs are effective at inactivating *Staphylococcus* and antibiotic-resistant biofilms (Taylor et al., 2012; Tran et al., 2010).

A combination of NPs with antibiotics has been tested to combat multidrug resistant bacteria (Singh et al., 2014a; Singh et al., 2014b). For example, vancomycin was combined with gold NPs to enhance the antibacterial activity of vancomycin against *E. coli*, *S. aureus*, and vancomycin-resistant *S. aureus* (VRSA) (Gu et al., 2003; Mohammed Fayaz et al., 2011a; Mohammed Fayaz et al., 2011b). Another study found the combination of AgNPs with vancomycin, ampicillin, streptomycin, and gentamycin enhanced the effectiveness of antibiotics against *E. coli*, *Pseudomonas aeruginosa*, and *S. aureus* (Birla et al., 2009). ZnO NPs also increased the antibacterial activity of antibiotics (Luo et al., 2013b). Bismuth NPs were able to enhance X-ray radiation killing of multi-drug resistant *P. aeruginosa* (Luo et al., 2013a).

The role of NPs towards ARB and ARG in water and wastewater treatment is mostly elusive (Miller et al., 2013, 2014). A study conducted using nanoalumina showed significant promotion of the horizontal conjugative transfer of multidrug-resistance genes mediated by plasmids across genera (RP4, RK2, and pCF10) (Qiu et al., 2012). There was a 200-fold enhancement in the conjugative transfer of the RP4 plasmid from *E. coli* to *Salmonella* spp. following treatment with nanoalumina (Qiu et al., 2012). The oxidative stress caused by nanoalumina resulted in bacterial cell membrane damage. This enhanced the mating pair formation gene

Table 4
Removal of antibiotics and ARGs by different wetland processes.

Types	Design Parameters	Antibiotics, μg L^{-1}	Removal efficiency, %	ARGs	Removal efficiency, %	Ref
Vertical upflow CW	Q: 5 L d^{-1}	Oxytetracycline (150)	93–99	*intI,*	70–99	Huang et al., 2015
	HRT: 5 d	Tetracycline (5.6)	67–99	*tetA,*	69–99.9	
		Chlorotetracycline (4.3)	88–98	*tetW,*	90–99.9	
				tetO,	58–99	
				tetM,	58–99	
				tetX	90–99	
5 stage integrated CW (horizontal surface flow)	Q: 6.5 m^3 d^{-1}	Leucomycin (120 ± 8.0),	100	*sul1* (7.4 × 10^4 copy g^{-1}),	97	Chen et al., 2015
	HRT: 1.5 d	Ofloxacin (190 ± 76), Lincomycin (61 ± 0.4),	100	*sul2* (5.2 × 10^4 copy g^{-1}),	95	
		Sulfamethazine (54 ± 1)	78	*tetM* (3.0 × 10^4 copy g^{-1}),	99	
			95	*tetO* (1.1 × 10^4 copy g^{-1})	99	
Free surface flow CW	Q: 120 L d^{-1}	Tetracycline (30 ± 3.2)	87–95	*tetW* (1.0 × 10^5 copy g^{-1}),		
	HRT: 15.5 d	Sulfamethoxazole (31 ± 3.1)	50–68	*tetO* (1.0 × 10^6 copy g^{-1}),	90	Liu et al., 2015
				tetM (5.0 × 10^5 copy g^{-1}),	50	
				sul1 (5.0 × 10^6 copy g^{-1}),	0	
				sul2 (5.0 × 10^6 cycle g^{-1})	50	
					30	
Free surface flow CW	Q: 2.9 m^3 d^{-1}	Azithromycin (0.1)	61	*ermB*		Berglund et al., 2014
	HRT: 5.9 d	Ciprofloxacin (0.2)	97	*qnrS*		
		Clarithromycin (0.4)	100	*ermB*		
		Clindamycin (0.2)	100	*ermB*		
		Doxycycline (0.1)	99	*tetA, tetB*		
		Erythromycin (2.0)	100	*ermB*		
		Norfloxacin (1.0)	100	*qnrS*		
		Oxytetracycline (0.4)	100	*tetA, tetB*		
		Sulfamethoxazole (1.0)	77	*sulI*		
		Tetracycline (1.0)	74	*tetA, tetB*		
		Trimethoprim (1.0)	96	*dfrA1*		
		Vancomycin (0.1)	59	*vanB*		
Horizontal subsurface flow CW	Q: 240 L d^{-1}	Tetracycline (30 ± 3.2)	88–97	*tetW* (1.0 × 10^5 copy g^{-1})	Incr	Liu et al., 2014
	HRT: 16.4 d	Sulfamethoxazole (31 ± 3.1)	30–75	*tetO* (5.0 × 10^7 copy g^{-1})	Incr	
				tetM (5.0 × 10^5 copy g^{-1})	Incr	
				sul1 (7.0 × 10^6 copy g^{-1})	90	
				sul2 (1.0 × 10^7 copy g^{-1})	99	
Horizontal surface flow CW	Q: 18 L d^{-1}	NA	NA	*tetA* (1.0 × 10^4–3.2 × 10^5 copy mL^{-1})	90–97	Nõlvak et al., 2013
	HRT: 1.2 d			*tetB* (6.3 × 10^1–1.6 × 10^3 copy mL^{-1})	50–92	
				tetM (1.6 × 10^2–3.2 × 10^2 copy mL^{-1})	87–68	
				sul1 (1.0 × 10^3–6.3 × 10^4 copy mL^{-1})	0–50	
Vertical subsurface flow CW	Q: 30 L d^{-1}	Ciprofloxacin (40–125)	78–84	*tetW* (1.07 × 10^5 copy mL^{-1})	38	Liu et al., 2013
	HRT: 14.2 d	oxytetracycline (25–58)	91–95	*tetM* (4.03 × 10^5 copy mL^{-1})	40	
		sulfamethazine (35–45)	68–73	*tetO* (4.92 × 10^5 copy mL^{-1})	43	
Vertical subsurface flow CW	Q: 120 L d^{-1}	Tetracycline (30 ± 3.2)	97–100	*tetW* (5.0 × 10^6 cycle g^{-1})	Incr	
	HRT: 1.2 h	Sulfamethoxazole (31 ± 3.1)	68–98	*tetO* (1.0 × 10^7 cycle g^{-1})	Incr	Liu et al., 2014
				tetM (5.0 × 10^7 cycle g^{-1})	Incr	
				sul1 (5.0 × 10^7 cycle g^{-1})	Incr	
				sul2 (5.0 × 10^7 cycle g^{-1})	Incr	

Incr.: an increase in ARG during CW treatment.

expression while depressing the global regulatory gene expression that regulates RP4 conjugative transfer. The results of this study demonstrate the important risk involved in the use of nanomaterials in treating water and wastewater.

4. Conclusion

Several studies have shown the prevalence of ARB and ARG in wastewater treatment plant effluents, sludge, biosolids, municipal solid waste leachates, soils, rivers, lakes, and surface water of livestock farms of different regions of world. Detection of ARG include sulfonamide, tetracycline, beta-lactam, and fluoroquinolone resistance genes. There is a lack of information about the abundance and fate of ARB and ARG, mainly in wastewater treatment plants. Also, a more detailed understanding of resistance mechanisms and transfer would assist in properly assessing the risk associated with ARB and ARG to public health and ecosystems.

Studies on the inactivation and deactivation of ARG by disinfection processes in real drinking water and wastewater treatment plants are very limited. Chemical disinfectants include chlorine, ozone, and Fenton reagent, which demonstrated inactivation of ARB and ARG. Several log units of inactivation efficiency were achieved, which varied with the doses of the disinfectants. The inactivation values of selected ARG were 1.65–2.2, 0.60, and 2.42–3.38 log units for chlorination, ozonation, and Fenton oxidation, respectively. However, much more research is needed to improve the understanding of the elimination of ARG from treated

water using chemical disinfection processes, particularly chlorination which is widely used all over the world. Limited work on the use of UV irradiation to inactivate ARB and ARG has demonstrated its effectiveness, but low dose UV was not effective in decreasing the frequency of conjugative transfer. Significantly, high dose UV was only able to reduce the frequency of conjugative transfer. Photocatalytical processes using TiO_2 have shown efficacy in activating ARB and ARG, but the required treatment must be for a long period of time (i.e. hundreds of min). The advancement in photocatalysts under visible light may improve the efficiency of photocatalytical treatment.

Due to the environmentally–friendly nature of a CW, more researchers and engineers are investigating their suitability for removing antibiotics from wastewater. Physico-chemical reactions responsible for the removal of antibiotics flowing in a CW are rather well documented. However, it has not been investigated in depth what microorganisms are responsible for the antibiotic removal in a CW. In addition, the way in which ARG are developed or reduced in a CW has not been sufficiently explored; the operating conditions under which ARGs are developed or reduced needs to be studied further. In particular, the relationship between the flow scheme of a CW and the abundance of ARB or ARG should be explored. Nanoparticles are entering into the wastewater effluent and sludge, but their influence on the ARB and ARG is largely unknown. Future research may include studies of the effect of nanomaterials on the mechanism of transfer of ARG across genera in order to evaluate viability of ARB and residual copy numbers of ARG.

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References

Adegboyega, N.F., Sharma, V.K., Siskova, K.M., Vecerova, R., Kolar, M., Zboril, R., Gardea-Torresdey, J.L., 2014. Enhanced formation of silver nanoparticles in Ag^{+}-NOM-iron(II, III) systems and antibacterial activity studies. Environ. Sci. Technol. 48, 3228–3235.

Al-Jassim, N., Ansari, M.I., Harb, M., Hong, P.-, 2015. Removal of bacterial contaminants and antibiotic resistance genes by conventional wastewater treatment processes in Saudi Arabia: is the treated wastewater safe to reuse for agricultural irrigation? Water Res. 73, 277–290.

Amador, P.P., Fernandes, R.M., Prudêncio, M.C., Barreto, M.P., Duarte, I.M., 2015. Antibiotic resistance in wastewater: occurrence and fate of Enterobacteriaceae producers of Class A and Class C ß-lactamases. J. Environ. Sci. Health A 50, 26–39.

Auerbach, E.A., Seyfried, E.E., McMahon, K.D., 2007. Tetracycline resistance genes in activated sludge wastewater treatment plants. Water Res. 41, 1143–1151.

Avisar, D., Levin, G., Gozlan, I., 2009. The processes affecting oxytetracycline contamination of groundwater in a phreatic aquifer underlying industrial fish ponds in Israel. Environ. Earth Sci. 59, 939–945.

Banjac, Z., Ginebreda, A., Kuzmanovic, M., Marcé, R., Nadal, M., Riera, J.M., Barceló, D., 2015. Emission factor estimation of ca. 160 emerging organic microcontaminants by inverse modeling in a Mediterranean river basin (Llobregat, NE Spain). Sci. Total Environ. 520, 241–252.

Berendonk, T.U., Manaia, C.M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Walsh, F., Burgmann, H., Sorum, H., Norstrom, M., Pons, M., Kreuzinger, N., Huovinen, P., Stefani, S., Schwartz, T., Kisand, V., Baquero, F., Martinez, J.L., 2015. Tackling antibiotic resistance: the environmental framework. Nat. Rev. Microbiol. 13, 310–317.

Berglund, B., Fick, J., Lindgren, P., 2015. Urban wastewater effluent increases antibiotic resistance gene concentrations in a receiving northern European river. Environ. Toxicol. Chem. 34, 192–196.

Birla, S.S., Tiwari, V.V., Gade, A.K., Ingle, A.P., Yadav, A.P., Rai, M.K., 2009. Fabrication of silver nanoparticles by Phoma glomerata and its combined effect against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus. Lett. Appl. Microbiol. 48, 173–179.

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

Budd, R., O'Geen, A., Goh, K.S., Bondarenko, S., Gan, J., 2009. Efficacy of constructed wetlands in pesticide removal from tailwaters in the central valley, California. Environ. Sci. Technol. 43, 2925–2930.

Cadet, J., Wagner, J.R., 2014. Oxidatively generated base damage to cellular DNA by hydroxyl radical and one-electron oxidants: similarities and differences. Arch. Biochem. Biophys. 557, 47–54.

Carvalho, P.N., Pirra, A., Basto, M.C.P., Almeida, C.M.R., 2013. Activated sludge systems removal efficiency of veterinary pharmaceuticals from slaughterhouse wastewater. Environ. Sci. Pollut. Res. 20, 8790–8800.

Cengiz, M., Uslu, M.O., Balcioglu, I., 2010. Treatment of E. coli HB101 and the tetM gene by Fenton's reagent and ozone in cow manure. J. Environ. Manag. 91, 2590–2593.

Chen, J., Liu, Y.S., Su, H.C., Ying, G.G., Liu, F., Liu, S.S., He, L.Y., Chen, Z.F., Yang, Y.Q., Chen, F.R., 2015. Removal of antibiotics and antibiotic resistance henes in rural wastewater by an integrated constructed wetland. Environ. Sci. Pollut. Res. 22, 1794–1803.

Childress, H., Sullivan, B., Kaur, J., Karthikeyan, R., 2014. Effects of ultraviolet light disinfection on tetracycline-resistant bacteria in wastewater effluents. J. Water Health 12, 404–409.

Cho, M., Kim, J.Y., Yoon, J., 2010. Mechanisms of Escherichia coli inactivation by several disinfectants. Water Res. 44, 3410–3418.

Cizmas, L., Sharma, V.K., Gray, C., McDonald, T.J., 2015. Pharmaceuticals and personal care products in waters: occurrence, toxicity, and risk. Environ. Chem. Lett. 13, 381–394.

Cole, S., 1998. The emergence of treatment wetlands. Environ. Sci. Technol. 32, 218A–223A.

Czekalski, N., Sigdel, R., Birtel, J., Matthews, B., Bürgmann, H., 2015. Does human activity impact the natural antibiotic resistance background? Abundance of antibiotic resistance genes in 21 Swiss lakes. Environ. Int. 81, 45–55.

Dallas, P., Sharma, V.K., Zboril, R., 2011. Silver polymeric nanocomposites as advanced antimicrobial agents: classification, synthetic paths, applications, and perspectives. Adv. Colloid Interface Sci. 166, 119–135.

de Jesus Gaffney, V., Almeida, C.M.M., Rodrigues, A., Ferreira, E., Benoliel, M.J., Cardoso, V.V., 2015. Occurrence of pharmaceuticals in a water supply system and related human health risk assessment. Water Res. 72, 199–208.

Deborde, M., von Gunten, U., 2008. Reactions of chlorine with inorganic and organic compounds during water treatment - kinetics and mechanism: a critical review. Water Res. 42, 13–51.

Dodd, M.C., 2012. Potential impacts of disinfection processes on elimination and deactivation of antibiotic resistance genes during water and wastewater treatment. J. Environ. Monit. 14, 1754–1771.

Dordio, A., Carvalho, A.J.P., Teixeira, D.M., Dias, C.B., Pinto, A.P., 2010. Removal of pharmaceuticals in microcosm constructed wetlands using Typha spp. and LECA. Bioresour. Technol. 101, 886–892.

Dordio, A.V., Belo, M., Martins Teixeira, D., Palace Carvalho, A.J., Dias, C.M.B., Picó, Y., Pinto, A.P., 2011. Evaluation of carbamazepine uptake and metabolization by Typha spp., a plant with potential use in phytotreatment. Bioresour. Technol. 102, 7827–7834.

Dunlop, P.S.M., Ciavola, M., Rizzo, L., McDowell, D.A., Byrne, J.A., 2015. Effect of photocatalysis on the transfer of antibiotic resistance genes in urban wastewater. Catal. Today 240, 55–60.

Etacheri, V., Di Valentin, C., Schneider, J., Bahnemann, D., Pillai, S.C., 2015. Visible-light activation of TiO2 photocatalysts: advances in theory and experiments. J. Photochem. Photobiol. C Photochem. Rev. 25, 1–29.

Evgenidou, E.N., Konstantinou, I.K., Lambropoulou, D.A., 2015. Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: a review. Sci. Total Environ. 505, 905–926.

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

Fiorentino, A., Ferro, G., Alferez, M.C., Polo-López, M.I., Fernández-Ibañez, P., Rizzo, L., 2015. Inactivation and regrowth of multidrug resistant bacteria in urban wastewater after disinfection by solar-driven and chlorination processes. J. Photochem. Photobiol. B Biol. 148, 43–50.

Friedman, M., 2015. Antibiotic-resistant bacteria: prevalence in food and inactivation by food-compatible compounds and plant extracts. J. Agric. Food Chem. 63, 3805–3822.

Gillings, M.R., Gaze, W.H., Pruden, A., Smalla, K., Tiedje, J.M., Zhu, Y., 2015. Using the class 1 integron-integrase gene as a proxy for anthropogenic pollution. ISME J. 9, 1269–1279.

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

Gu, H., Ho, P.L., Tong, E., Wang, L., Xu, B., 2003. Presenting vancomycin on nanoparticles to enhance antimicrobial activities. Nano Lett. 3, 1261–1263.

Guo, M.-., Yuan, Q.-., Yang, J., 2015. Distinguishing effects of ultraviolet exposure and chlorination on the horizontal transfer of antibiotic resistance genes in municipal wastewater. Environ. Sci. Technol. 49, 5771–5778.

Guo, X., Li, J., Yang, F., Yang, J., Yin, D., 2014. Prevalence of sulfonamide and tetracycline resistance genes in drinking water treatment plants in the Yangtze River Delta, China. Sci. Total Environ. 493, 626–631.

Hajipour, M.J., Fromm, K.M., Akbar Ashkarran, A., Jimenez de Aberasturi, D., Larramendi, I.R.D., Rojo, T., Serpooshan, V., Parak, W.J., Mahmoudi, M., 2012. Antibacterial properties of nanoparticles. Trends Biotechnol. 30, 499–511.

Hong, Y., Sharma, V.K., Chiang, P.C., Sharma, V.K., 2015. Fast target analysis and hourly variation of sixty pharmaceuticals in wastewater using UPLC-high

resolution mass spectrometry. Arch. Environ. Contam. Toxicol. 69, 525–535.
Hsu, C.-., Hsu, B.-., Ji, W.-., Chen, J.-., Hsu, T.-., Ji, D.-., Tseng, S.-., Chiu, Y.-., Kao, P.-., Huang, Y., 2015. Antibiotic resistance pattern and gene expression of non-typhoid Salmonella in riversheds. Environ. Sci. Pollut. Res. 22, 7843–7850.
Huang, K.-., Shieh, D.-., Yeh, C.-., Wu, P.-., Cheng, F., 2014. Antimicrobial applications of water-dispersible magnetic nanoparticles in biomedicine. Curr. Med. Chem. 21, 3312–3322.
Huang, X., Liu, C., Li, K., Su, J., Zhu, G., Liu, L., 2015. Performance of vertical up-flow constructed wetlands on swine wastewater containing tetracyclines and tert genes. Water Res. 70, 109–117.
Hunt, N.K., Mariñas, B.J., 1999. Inactivation of Escherichia coli with ozone: chemical and inactivation kinetics. Water Res. 33, 2633–2641.
Jia, S., Shi, P., Hu, Q., Li, B., Zhang, T., Zhang, X., 2015. Bacterial community shift drives antibiotic resistance promotion during drinking water chlorination. Environ. Sci. Technol. 49, 12271–12279.
Jiang, J.Q., Zhou, Z., Sharma, V.K., 2013. Occurrence, transportation, monitoring and treatment of emerging micro-pollutants in waste water - a review from global views. Microchem. J. 110, 292–300.
Kangwansupamonkon, W., Lauruengtana, V., Surassmo, S., Ruktanonchai, U., 2009. Antibacterial effect of apatite-coated titanium dioxide for textiles applications. Nanomed. Nanotechnol. Biol. Med. 5, 240–249.
Karaolia, P., Michael, I., García-Fernández, I., Agüera, A., Malato, S., Fernández-Ibáñez, P., Fatta-Kassinos, D., 2014. Reduction of clarithromycin and sulfamethoxazole-resistant Enterococcus by pilot-scale solar-driven Fenton oxidation. Sci. Total Environ. 468–469, 19–27.
Katayama, Y., Ito, T., Hiramatsu, K., 2000. A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in Staphylococcus aureus. Antimicrob. Agents Chemother. 44, 1549–1555.
Khetan, S.K., Collins, T.J., 2007. Human pharmaceuticals in the aquatic environment: a challenge to green chemistry. Chem. Rev. 107, 2319–2364.
Kim, H., Hong, Y., Park, J.-., Sharma, V.K., Cho, S., 2013. Sulfonamides and tetracyclines in livestock wastewater. Chemosphere 91, 888–894.
Kim, H., Hwang, Y.S., Sharma, V.K., 2014. Adsorption of antibiotics and iopromide onto single-walled and multi-walled carbon nanotubes. Chem. Eng. J. 255, 23–27.
Knapp, C.W., Zhang, W., Sturm, B.S., Graham, D.W., 2010. Differential fate of erythromycin and beta-lactam resistance genes from swine lagoon waste under different aquatic conditions. Environ. Pollut. 158, 1506–1512.
Kümmerer, K., 2009a. Antibiotics in the aquatic environment - a review - Part I. Chemosphere 75, 417–434.
Kümmerer, K., 2009b. Antibiotics in the aquatic environment - a review - Part II. Chemosphere 75, 435–441.
Lee, Y., von Gunten, U., 2012. Quantitative structure-activity relationships (QSARs) for the transformation of organic micropollutants during oxidative water treatment. Water Res. 46, 6177–6195.
Leonard, A.F.C., Zhang, L., Balfour, A.J., Garside, R., Gaze, W.H., 2015. Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters. Environ. Int. 82, 92–100.
Li, J., Cheng, W., Xu, L., Strong, P.J., Chen, H., 2015a. Antibiotic-resistant genes and antibiotic-resistant bacteria in the effluent of urban residential areas, hospitals, and a municipal wastewater treatment plant system. Environ. Sci. Pollut. Res. 22, 4587–4596.
Li, Z., Xiang, X., Li, M., Ma, Y., Wang, J., Liu, X., 2015b. Occurrence and risk assessment of pharmaceuticals and personal care products and endocrine disrupting chemicals in reclaimed water and receiving groundwater in China. Ecotoxicol. Environ. Saf. 119, 74–80.
Liu, L., Liu, C., Zheng, J., Huang, X., Wang, Z., Liu, Y., Zhu, G., 2013. Elimination of veterinary antibiotics and antibiotic resistance genes from swine wastewater in the vertical flow constructed wetlands. Chemosphere 91, 1088–1093.
Liu, L., Liu, Y.-., Wang, Z., Liu, C.-., Huang, X., Zhu, G., 2014. Behavior of tetracycline and sulfamethazine with corresponding resistance genes from swine wastewater in pilot-scale constructed wetlands. J. Hazard. Mater. 278, 304–310.
Luo, Y., Guo, W., Ngo, H.H., Nghiem, L.D., Hai, F.I., Zhang, J., Liang, S., Wang, X.C., 2014. A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. Sci. Total Environ. 473–474, 619–641.
Luo, Y., Hossain, M., Wang, C., Qiao, Y., An, J., Ma, L., Su, M., 2013a. Targeted nanoparticles for enhanced X-ray radiation killing of multidrug-resistant bacteria. Nanoscale 5, 687–694.
Luo, Z., Wu, Q., Xue, J., Ding, Y., 2013b. Selectively enhanced antibacterial effects and ultraviolet activation of antibiotics with Zno nanorods against Escherichia coli. J. Biomed. Nanotechnol. 9, 69–76.
Macku'ak, T., Nagyová, K., Faberová, M., Grabic, R., Koba, O., Gál, M., Birošová, L., 2015. Utilization of Fenton-like reaction for antibiotics and resistant bacteria elimination in different parts of WWTP. Environ. Toxicol. Pharmacol. 40, 492–497.
Maniprasad, P., Menezes, R., Suarez, J., Santra, S., 2013. Antimicrobial properties of copper and silver loaded silica nanomaterials. Ceram. Eng. Sci. Proc. 33, 55–67.
Maniprasad, P., Santra, S., 2012. Novel copper (Cu) loaded core-shell silica nanoparticles with improved Cu bioavailability: synthesis, characterization and study of antibacterial properties. J. Biomed. Nanotechnol. 8, 558–566.
Marti, E., Huerta, B., Rodríguez-Mozaz, S., Barceló, D., Jofre, J., Balcázar, J.L., 2014. Characterization of ciprofloxacin-resistant isolates from a wastewater treatment plant and its receiving river. Water Res. 61, 67–76.
Martinez, J.L., 2008. Antibiotics and antibiotic resistance genes in natural environments. Science 321, 365–367.
Meredith, H.R., Srimani, J.K., Lee, A.J., Lopatkin, A.J., You, L., 2015. Collective antibiotic tolerance: mechanisms, dynamics and intervention. Nat. Chem. Biol. 11, 182–188.
Michael, I., Rizzo, L., McArdell, C.S., Manaia, C.M., Merlin, C., Schwartz, T., Dagot, C., Fatta-Kassinos, D., 2013. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: a review. Water Res. 47, 957–995.
Miller, J.H., Novak, J.T., Knocke, W.R., Pruden, A., 2014. Elevation of antibiotic resistance genes at cold temperatures: implications for winter storage of sludge and biosolids. Lett. Appl. Microbiol. 59, 587–593.
Miller, J.H., Novak, J.T., Knocke, W.R., Young, K., Hong, Y., Vikesland, P.J., Hull, M.S., Pruden, A., 2013. Effect of silver nanoparticles and antibiotics on antibiotic resistance genes in anaerobic digestion. Water Environ. Res. 85, 411–416.
Mohammed Fayaz, A., Girilal, M., Mahdy, S.A., Somsundar, S.S., Venkatesan, R., Kalaichelvan, P.T., 2011a. Vancomycin bound biogenic gold nanoparticles: a different perspective for development of anti VRSA agents. Process Biochem. 46, 636–641.
Mohammed Fayaz, A., Girilal, M., Rahman, M., Venkatesan, R., Kalaichelvan, P.T., 2011b. Biosynthesis of silver and gold nanoparticles using thermophilic bacterium Geobacillus stearothermophilus. Process Biochem. 46, 1958–1962.
Morris, J.C., 1966. The acid ionization constant of HOCl from 5 to 35°. J. Phys. Chem. 70, 3798–3805.
Nichols, D.S., 1983. Capacity of natural wetlands to remove nutrients from wastewater. J. Water Pollut. Control. Fed. 55, 495–505.
Nõlvak, H., Truu, M., Tiirik, K., Oopkaup, K., Sildvee, T., Kaasik, A., Mander, U., Truu, J., 2013. Dynamics of antibiotic resistance genes and their relationships with system treatment efficiency in a horizontal subsurface flow constructed wetland. Sci. Total Environ. 461, 636–644.
Nwosu, V.C., 2001. Antibiotic resistance with particular reference to soil microorganisms. Res. Microbiol. 152, 421–430.
Oh, J., Salcedo, D.E., Medriano, C.A., Kim, S., 2014. Comparison of different disinfection processes in the effective removal of antibiotic-resistant bacteria and genes. J. Environ. Sci. (China) 26, 1238–1242.
Oh, J., Medriano, C.A., Kim, S., 2016. The effect of tetracycline in the antibiotic resistance gene transfer before and after ozone disinfection. Desalin. Water Treat. 57, 646–650.
Oktar, F.N., Yetmez, M., Ficai, D., Ficai, A., Dumitru, F., Pica, A., 2015. Molecular mechanism and targets of the antimicrobial activity of metal nanoparticles. Curr. Top. Med. Chem. 15, 1583–1588.
Oncu, N.B., Balcioglu, I.A., 2013. Antimicrobial contamination removal from environmentally relevant matrices: a literature review and a comparison of three processes for drinking water treatment. Ozone Sci. Eng. 35, 73–85.
Pang, Y., Huang, J., Xi, J., Hu, H., Zhu, Y., 2015. Effect of ultraviolet irradiation and chlorination on ampicillin-resistant Escherichia coli and its ampicillin resistance gene. Front. Environ. Sci. Eng. http://dx.doi.org/10.1007/s11783-015-0779-9.
Picó, Y., Barceló, D., 2015. Transformation products of emerging contaminants in the environment and high-resolution mass spectrometry: a new horizon. Anal. Bioanal. Chem. 407, 6257–6273.
Pignatello, J.J., Oliveros, E., MacKay, A., 2006. Advanced oxidation processes for organic contaminant destruction based on the Fenton reaction and related chemistry. Crit. Rev. Environ. Sci. Technol. 36, 1–84.
Pilon-Smits, E., 2005. Phytoremediation. Ann. Rev. Plant Rev. 56, 15–39.
Pisoschi, A.M., Pop, A., 2015. The role of antioxidants in the chemistry of oxidative stress: a review. Eur. J. Med. Chem. 97, 55–74.
Pliego, G., Zazo, J.A., Garcia-Muñoz, P., Munoz, M., Casas, J.A., Rodriguez, J.J., 2015. Trends in the intensification of the fenton process for wastewater treatment: an overview. Crit. Rev. Environ. Sci. Technol. 45, 2611–2692.
Postigo, C., Richardson, S.D., 2014. Transformation of pharmaceuticals during oxidation/disinfection processes in drinking water treatment. J. Hazard. Mater. 279, 461–475.
Pruden, A., 2014. Balancing water sustainability and public health goals in the face of growing concerns about antibiotic resistance. Environ. Sci. Technol. 48, 5–14.
Prütz, W.A., 1998. Interactions of hypochlorous acid with pyrimidine nucleotides, and secondary reactions of chlorinated pyrimidines with GSH, NADH, and other substrates. Arch. Biochem. Biophys. 349, 183–191.
Prütz, W.A., 1996. Hypochlorous acid interactions with thiols, nucleotides, DNA, and other biological substrates. Arch. Biochem. Biophys. 332, 110–120.
Qiu, Z., Yu, Y., Chen, Z., Jin, M., Yang, D., Zhao, Z., Wang, J., Shen, Z., Wang, X., Qian, D., Huang, A., Zhang, B., Li, J., 2012. Nanoalumina promotes the horizontal transfer of multiresistance genes mediated by plasmids across genera. Proc. Natl. Acad. Sci. U. S. A. 109, 4944–4949.
Ren, G., Hu, D., Cheng, E.W.C., Vargas-Reus, M.A., Reip, P., Allaker, R.P., 2009. Characterisation of copper oxide nanoparticles for antimicrobial applications. Int. J. Antimicrob. Agents 33, 587–590.
Richardson, S.D., Ternes, T.A., 2014. Water analysis: emerging contaminants and current issues. Anal. Chem. 86, 2813–2848.
Rizzo, L., Fiorentino, A., Anselmo, A., 2013. Advanced treatment of urban wastewater by UV radiation: effect on antibiotics and antibiotic-resistant E. coli strains. Chemosphere 92, 171–176.
Rizzo, L., Sannino, D., Vaiano, V., Sacco, O., Scarpa, A., Pietrogiacomi, D., 2014. Effect of solar simulated N-doped TiO2 photocatalysis on the inactivation and antibiotic resistance of an E. coli strain in biologically treated urban wastewater. Appl. Catal. B Environ. 144, 369–378.
Roller, S.D., Olivieri, V.P., Kawata, K., 1980. Mode of bacterial inactivation by chlorine dioxide. Water Res. 14, 635–641.

Rosi-Marshall, E.J., Kelly, J.J., 2015. Antibiotic stewardship should consider environmental fate of antibiotics. Environ. Sci. Technol. 49, 5257–5258.
Sacco, O., Vaiano, V., Han, C., Sannino, D., Dionysiou, D.D., 2015. Photocatalytic removal of atrazine using N-doped TiO_2 supported on phosphors. Appl. Catal. B Environ. 164, 462–474.
Salyers, A., Shoemaker, N.B., 2006. Reservoirs of antibiotic resistance genes. Anim. Biotechnol. 17, 137–146.
Scheytt, T., Mersmann, P., Lindstädt, R., Heberer, T., 2005. 1-Octanol/water partition coefficients of 5 pharmaceuticals from human medical care: carbamazepine, clofibric acid, diclofenac, ibuprofen, and propyphenazone. Water Air Soil Pollut. 165, 3–11.
Shannon, M.A., Bohn, P.W., Elimelech, M., Georgiadis, J.G., Mariñas, B.J., Mayes, A.M., 2008. Science and technology for water purification in the coming decades. Nature 452, 301–310.
Sharma, V.K., 2013. Oxidation of Amino Acids, Peptides, and Proteins. Wiley, Inc., New Jersey, USA.
Sharma, V.K., 2011. Oxidation of inorganic contaminants by ferrates(Fe(VI), Fe(V), and Fe(IV))- kinetics and mechanisms - a review. J. Environ. Manag. 92, 1051–1073.
Sharma, V.K., 2008. Oxidative transformations of environmental pharmaceuticals by Cl_2, ClO_2, O_3, and Fe(VI): kinetics assessment. Chemosphere 73, 1379–1386.
Sharma, V.K., Graham, N.D., 2010. Oxidation of amino acids, peptides, and proteins by ozone. Ozone Sci. Eng. 32, 81–90.
Sharma, V.K., Liu, F., Tolan, S., Sohn, M., Kim, H., Oturan, M.A., 2013. Oxidation of β–lactam antibiotics by ferrate(VI). Chem. Eng. J. 221, 446–451.
Sharma, V.K., Siskova, K.M., Zboril, R., Gardea-Torresdey, J.L., 2014a. Organic-coated silver nanoparticles in biological and environmental conditions: fate, stability and toxicity. Adv. Colloid Interface Sci. 204, 15–34.
Sharma, V.K., Zhao, J., Hidaka, H., 2014b. Mechanism of photocatalytic oxidation of amino acids: Hammett correlations. Catal. Today 224, 263–268.
Shih, K., Lederberg, J., 1976. Effects of chloramine on *Bacillus subtilis* deoxyribonucleic acid. J. Bacteriol. 125, 934–945.
Shore, A.C., Deasy, E.C., Slickers, P., Brennan, G., O'Connell, B., Monecke, S., Ehricht, R., Coleman, D.C., 2011. Detection of staphylococcal cassette chromosome mec type XI carrying highly divergent mecA, mecI, mecR1, blaZ, and ccr genes in human clinical isolates of clonal complex 130 methicillin-resistant Staphylococcus aureus. Antimicrob. Agents Chemother. 55, 3765–3773.
Silbergeld, E., Davis, M., Feingold, B., Goldberg, A., Graham, J., Leibler, J., Peterson, A., Price, L.B., 2010. New infectious diseases and industrial food animal production. Emerg. Infect. Dis. 16, 1503.
Silbergeld, E.K., Graham, J., Price, L.B., 2008. Industrial food animal production, antimicrobial resistance, and human health. Ann. Rev. Pub. Health. 29, 151–169.
Singh, R.K., Patel, K.D., Kim, J.J., Kim, T.H., Kim, J.H., Shin, U.S., Lee, E.J., Knowles, J.C., Kim, H.W., 2014a. Multifunctional hybrid nanocarrier: magnetic CNTs ensheathed with mesoporous silica for drug delivery and imaging system. ACS Appl. Mater. Interfaces 6, 2201–2208.
Singh, R., Smitha, M.S., Singh, S.P., 2014b. The role of nanotechnology in combating multi-drug resistant bacteria. J. Nanosci. Nanotechnol. 14, 4745–4756.
Somensi, C.A., Souza, A.L.F., Simionatto, E.L., Gaspareto, P., Millet, M., Radetski, C.M., 2015. Genetic material present in hospital wastewaters: evaluation of the efficiency of DNA denaturation by ozonolysis and ozonolysis/sonolysis treatments. J. Environ. Manag. 162, 74–80.
Storteboom, H., Arabi, M., Davis, J.G., Crimi, B., Pruden, A., 2010. Identification of antibiotic-resistance-gene molecular signatures suitable as tracers of pristine River, urban, and agricultural sources. Environ. Sci. Technol. 44, 1947–1953.
Su, H.-., Ying, G.-., He, L.-., Liu, Y.-., Zhang, R.-., Tao, R., 2014. Antibiotic resistance, plasmid-mediated quinolone resistance (PMQR) genes and ampC gene in two typical municipal wastewater treatment plants. Environ. Sci. Process Impacts 16, 324–332.
Su, M., He, C., Sharma, V.K., Abou Asi, M., Xia, D., Li, X., Deng, H., Xiong, Y., 2012. Mesoporous zinc ferrite: synthesis, characterization, and photocatalytic activity with H_2O_2/visible light. J. Hazard. Mater. 211–212, 95–103.
Sykes, R.B., Matthew, M., 1976. The ß lactamases of Gram negative bacteria and their role in resistance to ß lactam antibiotics. J. Antimicrob. Chemother. 2, 115–157.
Taylor, E.N., Kummer, K.M., Durmus, N.G., Leuba, K., Tarquinio, K.M., Webster, T.J., 2012. Superparamagnetic iron oxide nanoparticles (SPION) for the treatment of antibiotic-resistant biofilms. Small 8, 3016–3027.
Tenover, F.C., 2006. Mechanisms of antimicrobial resistance in bacteria. Am. J. Med. 119, S3–S10.
Thevenon, F., Adatte, T., Wildi, W., Poté, J., 2012. Antibiotic resistant bacteria/genes dissemination in lacustrine sediments highly increased following cultural eutrophication of Lake Geneva (Switzerland). Chemosphere 86, 468–476.
Tölgyesi, A., Verebey, Z., Sharma, V.K., Kovacsics, L., Fekete, J., 2010. Simultaneous determination of corticosteroids, androgens, and progesterone in river water by liquid chromatography-tandem mass spectrometry. Chemosphere 78, 972–979.
Tran, N., Mir, A., Mallik, D., Sinha, A., Nayar, S., Webster, T.J., 2010. Bactericidal effect of iron oxide nanoparticles on Staphylococcus aureus. Int. J. Nanomed. 5, 277–283.
Tsai, T.-., Chang, H.-., Chang, K.-., Liu, Y.-., Tseng, C., 2010. A comparative study of the bactericidal effect of photocatalytic oxidation by TiO2 on antibiotic-resistant and antibiotic-sensitive bacteria. J. Chem. Technol. Biotechnol. 85, 1642–1653.
United States Environmental Protection Agency, 1994. North American Wetlands for Water Quality Treatment Database. U.S. Environmental Protection Agency, Office of Research & Development, National Risk Management Research Laboratory, Cincinnati, Ohio, USA.
Verlicchi, P., Al Aukidy, M., Zambello, E., 2015. What have we learned from worldwide experiences on the management and treatment of hospital effluent? - an overview and a discussion on perspectives. Sci. Total Environ. 514, 467–491.
von Gunten, U., 2003. Ozonation of drinking water: part I. Oxidation kinetics and product formation. Water Res. 37, 1443–1467.
Xiong, P., Hu, J., 2013. Inactivation/reactivation of antibiotic-resistant bacteria by a novel UVA/LED/TiO2 system. Water Res. 47, 4547–4555.
Xu, G., Chance, M.R., 2007. Hydroxyl radical-mediated modification of proteins as probes for structural proteomics. Chem. Rev. 107, 3514–3543.
Xu, J., Xu, Y., Wang, H., Guo, C., Qiu, H., He, Y., Zhang, Y., Li, X., Meng, W., 2015. Occurrence of antibiotics and antibiotic resistance genes in a sewage treatment plant and its effluent-receiving river. Chemosphere 119, 1379–1385.
Yuan, Q.-., Guo, M.-., Yang, J., 2015. Fate of antibiotic resistant bacteria and genes during wastewater chlorination: implication for antibiotic resistance control. PLoS One 10.
Zhang, D., Gersberg, R.M., Ng, W.J., Tan, S.K., 2014. Removal of pharmaceuticals and personal care products in aquatic plant-based systems: a review. Environ. Pollut. 184, 620–639.
Zhang, Y., He, C., Sharma, V.K., Li, X.-., Tian, S., Xiong, Y., 2011a. A coupling process of membrane separation and heterogeneous Fenton-like catalytic oxidation for treatment of acid orange II-containing wastewater. Sep. Purif. Technol. 80, 45–51.
Zhang, Y., Zhuang, Y., Geng, J., Ren, H., Zhang, Y., Ding, L., Xu, K., 2015. Inactivation of antibiotic resistance genes in municipal wastewater effluent by chlorination and sequential UV/chlorination disinfection. Sci. Total Environ. 512–513, 125–132.
Zhang, Y.-., He, C., Sharma, V.-., Li, X.-., Tian, S.-., Xiong, Y., 2011b. A new reactor coupling heterogeneous Fenton-like catalytic oxidation with membrane separation for degradation of organic pollutants. J. Chem. Technol. Biotechnol. 86, 1488–1494.
Zhuang, Y., Ren, H., Geng, J., Zhang, Y., Zhang, Y., Ding, L., Xu, K., 2015. Inactivation of antibiotic resistance genes in municipal wastewater by chlorination, ultraviolet, and ozonation disinfection. Environ. Sci. Pollut. Res. Int. 22, 7037–7044.