Tetracycline antibiotics in the environment: a review

R. Daghrir · P. Drogui

Abstract Tetracycline antibiotics are one of the primarily antibiotics groups used for veterinary purposes, for human therapy and for agricultural purposes. Amongst the different antibiotics used, more attention is paid to tetracycline's as it exhibits serious environmental problems including ecological risks and human health damages. Due to their extensive usage, most of the actual evidence suggests that tetracycline antibiotics are omnipresent compounds found in different ecological compartments. After medication, more than 70 % of tetracycline antibiotics are excreted and released in active form into the environment via urine and feces from humans and animals. Their highly hydrophilic character and low volatility have resulted in significant persistence in the aquatic environment. Very few studies describe the fate and toxicity of tetracycline antibiotics in the environment. Here, we review several important issues with regard to: (1) the toxicity of these compounds on aquatic and terrestrial organisms; (2) their estrogenic effects; (3) their behavior in different ecological systems and; (4) the by-products generated during water treatment. These antibiotics residues promote the development of antibiotic resistant microorganisms, which can induce adverse effect to human health by increasing the risk of certain infections. Based on recent research results, the occurrence of tetracycline antibiotics in the environment inhibits the growth of some terrestrial and aquatic species. Besides, the residual concentrations of such drugs could affect steroidogenic pathway and consequently may cause endocrine disruption of aquatic species. Most of the wastewater treatment plants are not capable of removing effectively the tetracycline antibiotics. Therefore, there is a need to develop alternative processes to remove them from waters. Advanced oxidation processes have been proposed as alternative methods to ensure higher degradation and mineralization of tetracycline antibiotics are present in waters.

Keywords Antibiotics · Tetracyclines · Occurrence · Fate · Toxicity · Treatment · Waters

Introduction

Over the past few years, the use of pharmaceuticals in the medical field for preserving human and animal health has resulted in their undesirable accumulation in the environment. Most of these pharmaceuticals are stable and difficult to oxidize by conventional treatment processes (Gao et al. 2012). A significant number of these compounds have been frequently detected in different type of waters (wastewater, surface water, drinking water, ground water) and solids (sludge, soil, and sediments) (Christian et al. 2003; Gobel et al. 2005; Kim and Carlson 2007; Kummerer 2009a, b). Due to their excessive occurrences and their persistent characters in the environment, there is a considerable interest for pharmaceutical residues. The long-term and the low-dosed exposures to pharmaceutical products in the environment lead to the adverse impacts to the target organisms including endocrine disruption, chronic toxicity and antibiotic resistance (Andreozzi et al. 2004; Fent et al. 2006).

Among the pharmaceutical compounds present in the environment, special interest has been given to antibiotics (Homem and Santos 2011; Gao et al. 2012; Hu et al. 2010a,

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b; Pan et al. 2011; Onal 2011). Antibiotics belong to a class of pharmaceuticals used extensively to treat and to prevent the disease in human and animal medicine, as well as to increase feed efficiency and improve the growth rate in livestock and poultry industries (Gao et al. 2012; Pan et al. 2011; Sarmah et al. 2006; Chen et al. 2011). The use of antibiotics in feed for growth promotion is banned in European Union (EU; Commission of the European Communities 1998a, b). In some countries such as Canada, USA and Korea, their uses are still common (Sarmah et al. 2006). According to Martinez et al. (2011) and Halling-Sorensen et al. (1998), the annual production volume of drugs has been estimated in several hundreds of tons, whereas its annual use has been globally estimated between 100,000 and 200,000 tons (Kummerer 2003). For instance, it was estimated in 2003 that about 9,200 tons of antibiotics were produced for farming in the United States (AHI 2005). By comparison, the annual production capacity of antibiotics in China is around 210,000 tons (85 % is used for animal husbandry and medicine), while the annual production of antibiotics in Japan is around 2,200 tons (30 % are used for humans and 60 % are used for livestock) (Luo et al. 2011; Miyata et al. 2011). During their use, antibiotics cannot be absorbed or metabolized entirely in vivo and a significant fraction (from 30 to 90 %) is excreted in metabolite forms into the environment via urine and feces (Zhou et al. 2012; Hu et al. 2010a, b; Bound and Voulvoulis 2004).

Antibiotics and their metabolites have been detected in surface water, ground water, sewage water and drinking water at a concentration ranging from ng/L to μg/L (Lòpez-Penalver et al. 2010; Kim and Tanaka 2009; Bautitz and Nogueira 2007). According to previous research (Karthikeyan and Meyer 2006; Xu et al. 2007), antibiotic can enter in the aquatic environment through the direct discharge of animal wastewater and the discharge of effluents from wastewater treatment plants. Besides, the application of manure from livestock farm onto agriculture land contributes to introduce antibiotics in the environment (Shelver et al. 2010; Chen et al. 2011). The introduction of these residual compounds into environment through different sources will lead to serious environmental problems including ecological risk and human health damage.

Tetracycline antibiotics are broad spectrum antibiotics, and exhibit antibiotic activity against infections caused by both Gram (+) and Gram (−) microorganisms as well as mycoplasma, chlamydia, rickettsiae and protozoan parasites (Samanidou et al. 2007; Onal 2011; Ding and Mou 2000). Tetracycline antibiotics are one of the primarily antibiotics groups used for veterinary purposes, for human therapy and in agriculture sector as feed additive (Li et al. 2011; Ding and Mou 2000). Owing to their lower cost and their higher antimicrobial activity, Tetracycline antibiotics

are widely used as veterinary drugs for the prevention and treatment of animal farm to cure several infectious diseases (Onal 2011; Chen et al. 2011). Tetracycline antibiotics are also used as feed additives to promote the growth of animal (Sczesny et al. 2003; Koesukwiwat et al. 2007). As reported by Halling-Sorensen et al. (2002), more than 2,500 tons of TCAs are used annually in Europe in veterinary therapy. Clinical studies of TCAs (Han and Lucy Zhou 1999; Li et al. 2000) have showed that this group of antibiotics have an auxiliary treatment of tumor, inhibit the activity of collagen enzyme and promote bone absorption.

Chlortetracycline, oxytetracycline and tetracycline, which are a kind of tetracycline antibiotics, were the most often used throughout the world (Lòpez-Penalver et al. 2010; Jeong et al. 2010; Halling-Sorensen et al. 2002). Their structural formulas and their physico-chemical properties are listed in Table 1. Their relatively low Henry's constant (from 3.45×10^{-24} to 3.91×10^{-26} atm m^3/mol) indicates that these molecules are weakly lost by volatilization. Their high water solubility (0.008–0.062 mol/L) and lower octanol–water partition coefficient (log K_{ow} from −1.25 to −1.12) defines their hydrophilic character. Tetracycline antibiotics are characterized by three pKa values (Table 1). Tetracycline antibiotics are relatively stable in acids, but not in alkaline media (Halling-Sorensen et al. 2002). Tetracycline is one of the most frequently used antibiotics in aquaculture and veterinary medicine (López Peñalver et al. 2012), whereas chlortetracycline and oxytetracycline are two of the ten antimicrobials licensed as growth promoters in the United States (Jeong et al. 2010; Yang and Carlson 2003). Chlortetracycline is the most commonly used in swine production in USA, although oxytetracycline and tetracycline are also frequently used (Wei et al. 2011). Due to their extensive usage and their higher adsorption capability, tetracycline antibiotics have been detected in terrestrial and aquatic environment: surface water (Li et al. 2011), ground water (Hernandez et al. 2007), wastewater (López Peñalver et al. 2012; Jeong et al. 2010), municipal sewage (Liu et al. 2009), soil and sediments (Liu et al. 2009; Andreu et al. 2009; Chen et al. 2011). Hence, conventional wastewater treatment plants appear unable to completely eradicate these micropollutants. In wastewater treatment plants, the removal efficiency of tetracycline varied from 12 % (Spongberg and Witter 2008) to 80 % (Karthikeyan and Meyer 2006). By considering the risks of tetracycline antibiotics in the ecosystem, the search for new alternatives to prevent environment contamination is become necessary. This review highlights various issues concerning the tetracycline antibiotics occurrence, toxicity, distribution, fate and the different technologies applied so far for their removal from waters.

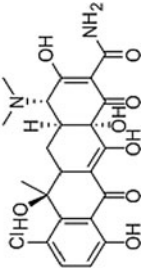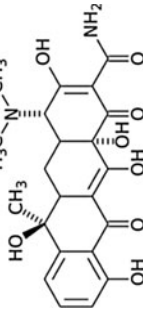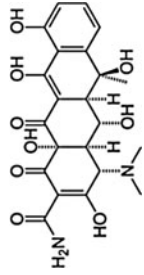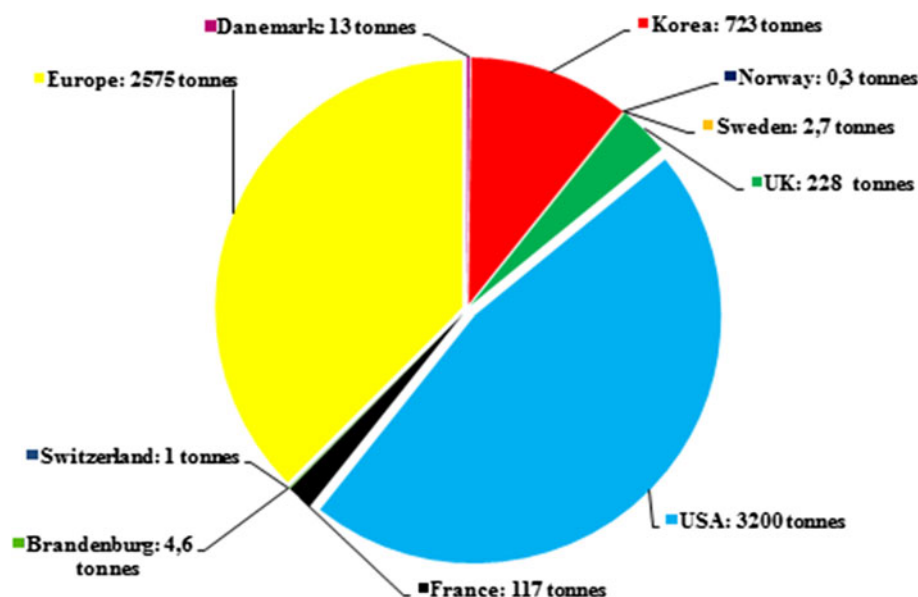**Table 1** Chemical properties of tetracycline antibiotics

Molecule	Molecular formula	Chemical structure	Molecular weight (g/mol)	Solubility (mol/L)	Log K_{OW}	Henry's law constant (atm m³/mol)	Isoelectric point	pK_{a1}	pK_{a2}	pK_{a3}
Chlortetracycline	$C_{22}H_{24}Cl_2N_2O_8$		515.3	0.008	−0.62	3.45E−24	2.27	3.3 ± 0.3	7.55 ± 0.02	9.3 ± 0.3
Tetracycline	$C_{22}H_{25}Cl\ N_2O_8$		480.9	0.041	−1.25	–	–	3.2 ± 0.3	7.78 ± 0.05	9.6 ± 0.3
Oxytetracycline	$C_{22}H_{25}Cl\ N_2O_9$		496.9	0.062	−1.12	3.91E−26	–	3.2 ± 0.3	7.46 ± 0.03	8.9 ± 0.3

Fig. 1 Variation of the total amounts (tons) of tetracycline antibiotics used for veterinary purposes around the world

Worldwide usage of tetracycline antibiotics

The tetracycline antibiotics were discovered in the 1940s and their therapeutic use for preserving human health began in the 1950s (Chopra and Roberts 2001; Roberts 2003). Besides, the use of tetracycline antibiotics has become integral to the livestock production industry as growth promoters and in agriculture sector as feed additive in North America since the 1950s (Roberts et al. 2012; Arikan et al. 2009). Each year, the worldwide production of tetracycline antibiotics is estimated to be in thousands of tons (Michalova et al. 2004).
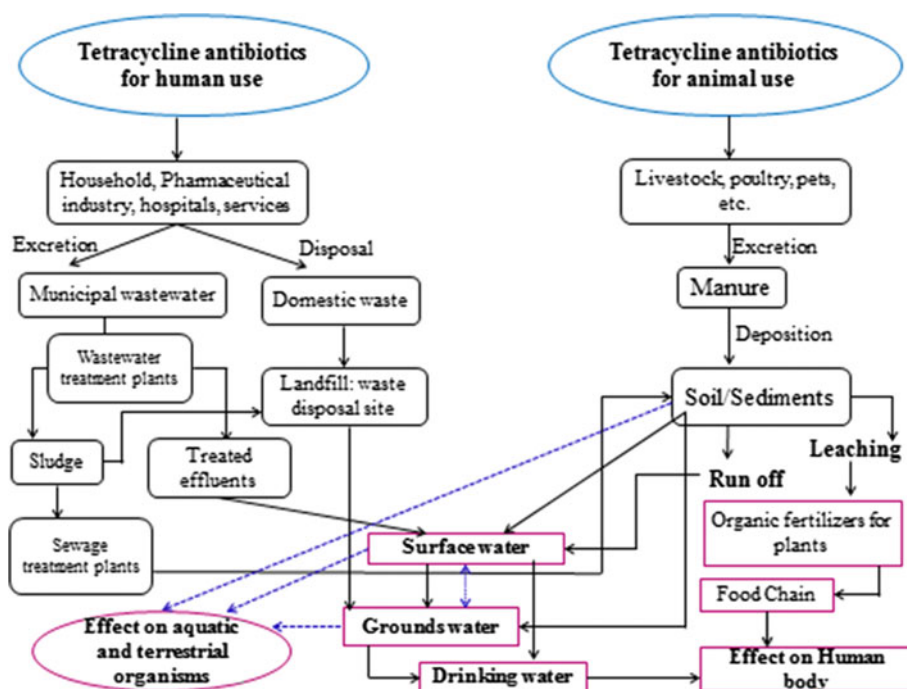
Recent research (Xie et al. 2010; Cheng 2005) show that tetracycline antibiotics are ranked second in the production and usage of antibiotics worldwide and are ranked first in China. Tetracyclines are considered one of the cheapest classes of antibiotics available today. It makes them attractive for use in developing countries with limited health care budgets (Roberts et al. 2012; Michalova et al. 2004). For instance, the amount of tetracycline antibiotics used in European Union in 1997 for therapeutic purpose was around 2,294 tons, whereas during the period 2000–2001 the consumption of tetracycline antibiotics in USA was increase from 3,000 to 3,200 tons, respectively (Michalova et al. 2004).

According to several works (Ding and Mou 2000; Samanidou et al. 2007; Kim et al. 2011; Chen et al. 2012), tetracycline antibiotics still widely used in many countries for the prevention and treatment of diseases and promotion of growth in animal such as cattle, pigs, sheeps, and poultries, among others. Tetracycline antibiotics are widely applied in veterinary medicine for the treatment of gastrointestinal, respiratory and skin bacterial infections, infectious diseases of locomotive organs and of genito-

urinary tract as well as systematic infections and sepsis (Prescott et al. 2000; Michalova et al. 2004). The world wide variation of the total amounts of tetracycline antibiotics used in veterinary medecine is shown in Fig. 1. The USA was the biggest consumer of tetracycline antibiotics (3,200 tons/years) followed by Korea (723 tons/years). The uses of tetracycline antibiotics in veterinary medicine were significantly higher than some European countries (such as Sweeden, Danemark, France, among others) due to the high numbers of livestocks in both Korea and USA and the common agriculture practice of tetracycline antibiotics as feed supplements to promote the growth (Kim et al. 2011).

In human medicine, tetracycline antibiotics have been used for the treatment of different types of infections, especially respiratory infections (pneumonia) due to *Mycoplasma pneumonia*, *Chlamydia pneumonia*, and *Chlamydia psittaci*. In the past decade, they have been also the drug of choice for the treatment of malaria due *Plasmodium falciparum* (Roberts 2003). In addition, it has been suggested by Smith and Rajan (2000) that tetracycline antibiotics could be benefit for the treatment of human infected with flarial nematodes, whereas Chopra and Roberts (2001) show that tetracycline antibiotics are effective to treat infections with Entamoeba histolytica, Giardia lamblia, Leishmania major, Trichomonas vaginalis, and Toxoplasma gondii. This successful use of tetracycline antibiotics around the world is due to the nonantibacterial effects including anti-inflammation, immunosuppression, inhibition of lipase and collagenase activity, wound healing, and enhancement of gingival fibroblast cell attachment, antibacterial effects or the combination between the two properties (Chopra and Roberts 2001; Chaidemenos 2001; Ramamurthy et al. 2002; Roberts 2003).

Fig. 2 Possible sources and pathways for the occurrence of tetracycline antibiotics in the environment

Occurrence of tetracycline antibiotics in the environment

In the last decades, the abusive use of tetracycline antibiotics in veterinary and human medicine was widespread, and consequently, the possibility of environmental contamination with such compounds increased (Chen et al. 2011; Arikan et al. 2009). The occurrence of tetracycline antibiotics in the aquatic environment has received a great attention due to their potential contribution toward increasing bacterial resistance to anti-infective (Sarmah et al. 2006; Baquero et al. 2008). After using such compounds, a fraction of tetracycline antibiotics is metabolized into inactive compounds. Another fraction is excreted as parent compounds or actives metabolites products or both forms by a diversity of input source as shown in Fig. 2 (Kim et al. 2005; Xie et al. 2010). The most of tetracycline antibiotics are released via urine, feces, and manure from humans and animals after medication. As shown by some monitoring data, around 25–75 % or even 70–90 % of tetracycline antibiotics administrated to animals were excreted and released in active form into the environment via urine and feces (Jjemba 2006; Halling-Sorensen 2000). When tetracycline antibiotics are released from animal, manure can contaminated soil and consequently surface and ground waters through leaching or run-off. Similarly, human tetracycline antibiotics are introduced into the environment through excretion, entering in the sewer network and reaching the wastewater treatment plants.

Up to now, wastewater treatment plants are not capable of removing effectively the tetracycline antibiotics. For instance, residual concentrations from 0.15 to 0.97 µg/L of tetracycline have been detected by Miao et al. (2004) in the final effluent from wastewater treatment plants in Canada. Residual concentrations up to 2.37 µg/L have been also detected by Deblonde et al. (2011) in the effluents from wastewater treatment plants. Therefore, they can be transported to surface water and reach ground water after leaching. A residual concentration of 400 ng/L of tetracycline was recorded in ground waters, whereas 32 ng/L of oxytetracycline and less than 690 ng/L of chlortetracycline were measured in overland flow water and surface water, respectively (Krapac et al. 2005). Another important contamination source is the direct release from pharmaceutical production plants.

In their monitoring investigations of various sewages, surface and groundwater in Germany, Hirsch et al. (1999) did not detect tetracycline antibiotics. This result is not surprising because tetracycline antibiotics are easily precipitated with cations such as calcium and accumulate in sewage sludge or sediments (Daughton and Ternes 1999). However, tetracycline antibiotics including tetracycline, chlortetracycline and oxytetracycline have been detected by Kolpin et al. (2002) and Lindsey et al. (2001) in US surface water samples. The average concentrations of tetracycline, oxytetracycline and chlortetracycline detected in US surface water were 0.11, 1.34 and 0.15 µg/L, respectively (Lindsey et al. 2001). By comparison, tetracycline was the most commonly detected (0.11 µg/L) by Kolpin et al. (2002).

Usually, tetracycline antibiotics are accumulated with organic manure in soil. For instance, in Germany the

Table 2 Variation of the residual concentration of tetracycline antibiotics with animal type

Animal type	Manure generated tetracycline antibiotics (tons/years)	Tetracycline antibiotics used (tons/years)	Tetracycline antibiotics concentrations (µg/kg)			References
			Chlortetracycline	Oxytetracycline	Tetracycline	
Cattle	16,676,949	42.4	11–208	–	–	Hamscher (2000), Arikan et al. (2008), Kim et al. (2011)
Pig	14,363,192	366	46–880	29–78	23–81	Aust et al. (2008), Martinez-Carballo et al. (2007), Hamscher (2000), Xiang-Gang et al. (2008), Kim et al. (2011)
Poultry	4,349,489	104.5	57–94.7	62	69	Xiang-Gang et al. (2008), Bao et al. (2009), Kim et al. (2011)

residual concentration of tetracycline and chlortetracycline recorded by Hamscher et al. (2002) in soil were up to 86–199 and 4.6–7.3 µg/kg, respectively, whereas the maximum concentrations of oxytetracycline measured by Boxall et al. (2006) in soil were 305 µg/kg oxytetracycline remained biologically active in soil under field conditions at a concentration greater than 25 µg/L for at least 40 days (Kulshrestha et al. 2004; Polubesova et al. 2006).

Furthermore, the release of tetracycline antibiotics can be taken up by various plants, crops and soil animals on farmland. For instance, chlortetracycline has been shown quite persistent in soil. Research group of Hamscher (2000) have reported an average concentration of 9.5 µg/kg chlortetracycline in the upper 10 cm of the soil. Previous investigations showed that the excretion rate and the total amount used influence the residual concentration of tetracycline antibiotics detected in the environment (Table 2). Due to its persistent character in soil, chlortetracycline is the most antibiotic frequently detected in the environment at higher concentrations up to 880 µg/kg in pig manure (Hamscher 2000). After 10 days of chlortetracycline medication, the concentrations of chlortetracycline and its metabolites (Epi-chlortetracycline and Iso-chlortetracycline) in pig faeces recorded by the research group of Grote were 281,000, 157,000 and 67,000 µg/kg, respectively (Grote et al. 2004). Hamscher (2000) detected higher concentrations of chlortetracycline in pig manure slurry (1,435 µg/kg) compared to 11 µg/kg of chlortetracycline recorded in the cattle manure slurry. Chlortetracycline has been also detected in water samples at the maximum concentrations of 0.03 µg/L (Arikan et al. 2008), 0.16 µg/L (Yang and Carlson 2003) and 0.69 µg/L (Kolpin et al. 2002) and even in sediment at concentrations from 2 to 10 µg/kg dry weight (Arikan et al. 2008). In the investigation of veterinary antibiotics used for livestock, Hu et al. (2010a, b) have detected residual concentrations of tetracycline, chlortetracycline and oxytetracycline in both manure and soil. The amount of oxytetracycline, tetracycline and chlortetracycline recorded in soil (in winter) were up to 2,683, 105 and 1,079 µg/Kg, respectively, whereas

residual concentrations of 183.5, 43.5 and 26.8 mg/kg for oxytetracycline, tetracycline and chlortetracycline, respectively have detected in manure. Thereby, the occurrence and the accumulation of these tetracycline antibiotics in the environment could lead to toxic effects in animals as well as humans.

Toxicity

Up to now, more attention has been paid to ecological risk and potential toxic effects of tetracycline antibiotics residues in the environment (Xie et al. 2010; Halling-Sorensen 2000; Hui-zhu et al. 2008). These tetracycline antibiotics residues promotes the evolution or the development of antibiotic resistant microorganisms, which can induce adverse effect to human health when present in drinking water or irrigation water used for fruit and vegetable (Stackelberg et al. 2007; López Peñalver et al. 2012; Arikan et al. 2008). These antimicrobial agents may disturb the microflora of the human intestinal and increase the risk of certain infections (Heuer et al. 2009). Given this fact, it is not surprising to find many researches trying to determine and estimate the toxicity of tetracycline antibiotics on aquatic and terrestrial species, and even their estrogenic effects.

Effects of tetracycline antibiotics on aquatic species

The chronic and acute toxic effects of tetracycline antibiotics on various aquatic species have been widely conducted. As reported by Halling-Sorensen (2000), tetracycline antibiotics are mainly bacteriostatic, with a broad spectrum of antimicrobial activity. Owing to an active transport process, tetracycline antibiotics are taken up into sensitive bacterial cell. Once within the cell, they bind reversibly to the 30S subunit of the ribosome, they prevent the binding of aminoacyl transfer to DNA and they inhibit protein synthesis and hence cell growth.

Photoautotrophic microalgae, as primary producers, play an important role in the structure and functioning of the whole

aquatic ecosystem (Yang et al. 2008). As reported in the literature data, microalgae are more sensitive than crustaceans and fish to antibacterial agents such as tetracycline antibiotics. Study of Yang et al. (2008) has shown that chlortetracycline could potentially affect the growth of green alga in freshwater systems. On the basis of the growth inhibiting test, Yang and his co-worker calculated the median inhibitory concentration value of chlortetracycline to be 3.49 μM. On the other hand, it has been found by Brain et al. (2004) that chlortetracycline had photo-toxicity to the aquatic plant *Lemna gibba* with effective concentration EC25 values of 114 μg/L. The toxic effect of oxytetracycline (growth inhibition) on various aquatic species (*Microcystis aeruginosa*, *Rhodomonas salina* and *Selenastrum capricornutum*) has been investigated by Holten Lützhøft et al. (1999). Oxytetracycline was found in water and sediment from the outflow of a breeding pond and below fish farms (Migliore et al. 1996). The few tests done by Holten Lutzhoft show that *Microcystis aeruginosa* (the half live effective concentration $(EC_{50}) = 0.207$ mg/L) was more sensitive to oxytetracycline compared to both *Rhodomonas salina* $(EC_{50} = 1.6$ mg/L) and *Selenastrum capricornutum* $(EC_{50} = 4.5$ mg/L).

The same aquatic species (*Microcystis aeruginosa* and *Selenastrum capricornutum*) have been also used by Halling-Sorensen (2000) to evaluate the effects of tetracycline and chlortetracycline. In this investigation, *Microcystis aeruginosa* and *Selenastrum capricornutum* were found to be more sensitive to chlortetracycline and tetracycline than oxytetracycline. It was observed that the growth inhibition rates (EC_{50}) of *Microcystis aeruginosa* and *Selenastrum capricornutum* by tetracycline were 0.09 and 2.2 mg/L, respectively, while the growth inhibition rates of *Microcystis aeruginosa* and *Selenastrum capricornutum* using chlortetracycline were 0.05 and 3.1 mg/L, respectively.

The acute toxicity of tetracycline and chlortetracycline on aquatic organisms such as Daphnia magna, Danio rerio and Carassius auratus has been evaluated by Hui-zhu et al. (2008). According to this research group, it has been found that chlortetracycline toxicity to the three organisms was significantly higher than that of tetracycline. The acute toxicity of Daphnia magna, Danio rerio and Carassius auratus to TC were 617.2 mg/L (48 h-EC50), 406.0 mg/L (96 h-LC50) and 322.8 mg/L (96 h-LC50), respectively. By comparison, the acute toxicity of Daphnia magna, Danio rerio and Carassius auratus to chlortetracycline were 137.59 mg/L (48 h-EC50), 61.15 mg/L (96 h-LC50) and 34.68 mg/L (96 h-LC50), respectively.

Effects of tetracycline antibiotics on terrestrial organisms

Research on toxic effects of tetracycline antibiotics in terrestrial organisms including crops is still scarce. As

mentioned by Xie et al. (2010), knowledge of the dual effect (promotion and inhibition) on the growth and genotoxicity of chlortetracycline in plants as crops is lacking. The first report on the phototoxic effects of tetracycline antibiotics in crops shows that the presence of chlortetracycline influences negatively the growth of pinto beans in soil (Michael et al. 2007). It has been also reported by Xie et al. (2010) that chlortetracycline at higher concentrations significantly inhibited the percentage germination of wheat (25–300 mg/L), the root length (25–300 mg/L), the bud length (50–300 mg/L) and the mitotic index (25–300 mg/L). In addition, the lowest concentration of chlortetracycline slightly increased the frequency of micronucleus (MN), the chromosomal aberration (CA) and the sister chromatid exchange (SCE) in the root tips, thus resulting in acute cell toxicity. Xie et al. (2010) pointed out that sister chromatid exchange was the most sensitive to chlortetracycline followed by chromosomal aberration, and micronucleus was the least sensitive to chlortetracycline genotoxicity in wheat.

Estrogenic effects of tetracycline antibiotics

Among others antibiotics (tylosin, amoxicillin), oxytetracycline can modulate the expression of gene and the production of hormone related to steroidogenesis (Gracia et al. 2007). The effects of tetracycline antibiotics related to the reproduction have been reported for Japanese medaka fish. For example, oxytetracycline and chlortetracycline induce the production of vitellogenin in male Japanese medaka fish as *Oryzias Latipes* (Kang et al. 2005; Kim 2007). The results recorded by Kim (2007) show that CTC induces vitellogenin in male medaka, and consequently may cause endocrine disruption in fishes. From 10 mg/L, chlortetracycline is an inducer of vitellogenin in male fishes, whereas it was a reducer of vitellogenin in female fishes from 0.1 mg/L of chlortetracycline concentration (Kim 2007).

In addition, chlortetracycline and oxytetracycline affected several reproduction related endpoint such as the first day of the reproduction, the number of young per female and the growth rate of populations (Park and Choi 2008). Chlortetracycline and oxytetracycline have been also tested by Ji et al. (2010) to evaluate their effects on steroidogenesis in vivo with male medaka fish. The concentration of 17β-estradiol (E2) in the plasma of male medaka fish increased significantly after 14 days exposure to chlortetracycline (40 mg/L) and oxytetracycline (50 mg/L).

Furthermore, the effects of chlortetracycline and oxytetracycline on steroidogenesis in vitro with human adrenocarcinoma (H295R) cells have been tested by Ji and his co-workers. Both chlortetracycline (from 0 to 20 mg/L) and oxytetracycline (from 0 mg/L to 20 mg/L) affected the production mechanism of 17β-estradiol (E2) by increasing the catalytic activity of aromatase and enhancing the

expression of CYP17, CYP19, and 3βHSD mRNAs of H295R cells. However, further investigations are needed because the residual concentrations of tetracycline antibiotics are relatively low in the environment (from μg/L to ng/L).

Treatment of tetracycline antibiotics in waters

As mentioned above, most conventional wastewater treatment plants are not designed to remove tetracycline antibiotics from waters and wastewaters. To this end, practical and economical processes must be developed and applied in order to reduce the tetracycline antibiotics discharges into the environment. Physicochemical methods such as membrane filtration and adsorption using activated carbon have been applied to remove tetracycline antibiotics. However, the main disadvantage of such methods is that they do not destroy the pollutants but transfer the pollutant from one phase to another. Nowadays, advanced oxidation processes have been proposed as alternative methods for the elimination of tetracycline antibiotics among others biorecalcitrant compounds in wastewater (Daghrir et al. 2012a, b; Palominos et al. 2009; Jeong et al. 2010; Bautitz and Nogueira 2007). The principle of advanced oxidation processes (including O_3/H_2O_2, UV/O_3, UV/H_2O_2, H_2O_2/Fe^{2+}, and $UV-TiO_2$) is to produce hydroxyl radical in water, a very powerful oxidant ($E° = 2.8$ V) capable of oxidizing a wide range of organic compounds with one or many double bonds (Homem and Santos 2011; Esquivel et al. 2009; Yu and Chuang 2008). As reported by Homem and Santos (2011), hydroxyl radicals are produced from oxidizing agents such as ozone, hydrogen peroxide, often combined with UV radiation or semiconductor/metallic catalysts. An overview of the recent research studies using different processes for tetracycline antibiotics removal is summarized in Table 3.

Membrane processes

The reverse osmosis, nanofiltration and ultrafiltration are membrane processes (Li et al. 2004; Radjenovic et al. 2008; Koyuncu et al. 2008). The reverse osmosis constitutes one of the membranes processes that has been widely used in combination with nanofiltration (or ultrafiltration) to remove tetracycline antibiotics (Li et al. 2004; Kosutic et al. 2007). Oxytetracycline was removed using either reverse osmosis/nanofiltration or reverse osmosis/ultrafiltration processes (Li et al. 2004; Kosutic et al. 2007). These studies revealed for example, that reverse osmosis/ultrafiltration technique is considered as an effective method to remove oxytetracycline (≈ 87.5 %) from pharmaceutical wastewater (Li et al. 2004). By comparison, 50–80 % of tetracycline antibiotics

was removed while treating distilled water spiked with calcium chloride, humic acid and NaCl using nanofiltration technique (Koyuncu et al. 2008). Nevertheless, reverse osmosis, nanofiltration and ultrafiltration techniques are very sensible to the amounts of organic material occurring naturally in the water matrices and the concentration of the dissolved salts (Homem and Santos 2011). The presence of higher levels of these compounds in water could cause the fouling of the membrane.

Adsorption processes

In the adsorption process, the pollutant is transferred from liquid phase to solid surface. Granular activated carbon is the most popular adsorbent used but its cost and the difficulties of regeneration represent the major drawbacks (Crisafully et al. 2008). Despite the fact that the adsorption is a well-known process, this technology has not been widely used to remove tetracycline antibiotics. Adsorption using granular activated carbon in combination with coagulation process was applied by Choi et al. (2008) to remove tetracycline antibiotics (10–100 μg/L) from synthetic water and river water. Higher removal rate of tetracycline antibiotics drugs up to 94 % has been recorded from synthetic water, whereas the removal rate of tetracycline antibiotics does not exceed 67 % from river water. Furthermore, Chen and Huang (2010) analyzed the adsorption of three tetracycline antibiotics (chlortetracycline, oxytetracycline and tetracycline) on aluminum oxide. These compounds were adsorbed and they concluded that structural transformations were produced along the adsorption process.

Different sorbents described earlier have been applied to remove tetracycline antibiotics. The physical–chemical properties (pH, salinity, temperature, etc.) and the chemical composition of water or wastewater (including tetracycline antibiotics and other antibiotics) are main criteria in the selection of sorbents. Choosing the best sorbent for tetracycline antibiotics removal should take into account not only the efficiency but also the cost. From this point of view, biosorbent generated from activated sludge could be an interesting alternative for tetracycline antibiotics removal. However, the main disadvantage of such method is that they do not destroy the pollutant. The adsorption is a process to concentrate the contaminants.

Photochemical processes

In the recent years, the use of UV light irradiations for the degradation of tetracycline antibiotics is one of the approaches that have been widely investigated. Tetracycline antibiotics are very sensitive to the light irradiation. Photolysis processes using UV radiation are simple, clean and less expensive. In direct photolysis, UV radiations absorbed by

Table 3 Removal of tetracycline antibiotics using different treatment processes

Tetracycline antibiotics	Matrix	Treatment	Operating conditions	Results and comments	References
Chlortetracycline	Manure slurry	Anaerobic digestion	Treatment time = 33 days, T = 35 °C, pH = 7.5, [chlortetracycline]° = 100 mg/L, COD = 52, 240–249	75 % degradation rate of chlortetracycline	Arikan et al. (2008)
	Distilled water	Photoelectrocatalytic oxidation	[chlortetracycline]° = 32–230 μg/L, treatment time = 120 min, Ti/TiO$_2$ (anatase, rutile, amorphous) = photoanode, cathode (vitreous carbon, graphite, stainless steel, amorphous carbon), current intensity = 0.39 A, UV light (254 nm), pH = 3.12–9.02	98.0 ± 0.2 % of chlortetracycline 67.3 ± 2.15 % of total organic carbon removal 69.3 ± 3.10 % of total nitrogen removal	Daghrir et al. (2013)
	Aqueous solution	Photocatalysis	50 mg/L of chlortetracycline, 0.4 g (Cu/TiO$_2$), high-pressure mercury lamp (500 W, 360 nm), T = 20 °C ± 2 °C, treatment time = 0–90 min	More than 80 % degradation rate of chlortetracycline ≈75 % removal of chemical oxygen demand ≈28.1 % of total organic carbon removal ≈50 % of biological oxygen demand removal	Bu and Zhuang (2013)
	Beef manure	Composting	Treatment time = 30 days, temperature = 25–55 °C, chlortetracycline = 22 mg/kg/day	Concentrations of chlortetracycline/epichlortetracycline decreased 99 % and 98 % (from 113 μg/g dry weight to 0.7 μg/g dry weight and 2.0 μg/g dry weight) at T = 55 °C. Concentrations of chlortetracycline/epichlortetracycline decreased 49 % and 40 % (from 113 μg/g dry weight to 58 μg/g dry weight and 68 μg/g dry weight) at T = 25 °C.	Arikan et al. (2009)
	Distilled water	Manganese dioxide	pH = 3.0–6.0, [MnO$_2$] = 50–200 mg/L, Temperature = 15–35 °C, [chlortetracycline]° = 65 μmol/L,	k_{obs} = 4.1 ± 0.1 × 10^{-3}/μM/h at pH = 5.02, [CTC]° = 65 μM, and [δ-MnO$_2$]° = 50 mg/L	Chen et al. (2011)
	Livestock wastewater	Ozonation	UV light (4.9 W, 253.7 nm), working volume = 1L, O$_3$ (7.0 g/m^3, 4.9 mg/min), [H$_2$O$_2$] = 0–200 mg/L, T = 20 °C, treatment time = 0–60 min, [chlortetracycline]° = 20 μg/mL	30 % of chlortetracycline was degraded by O$_3$ in 40 min 65 % of chlortetracycline was degraded by O$_3$/H$_2$O$_2$ in 40 min Less than 2 log-reduction was achieved in 1 h using O$_3$ 4 log-reduction in 20 min and 5-log reduction in 40 min using UV Inactivation of chlortetracycline-resistant HPCs after 10 min using O$_3$/UV	Lee et al. (2011)
	Distilled water	Direct photolysis	150-W Xenon short Arc lamp, [chlortetracycline]° = 200 μmol/L, pH = 6.0–9.0, irradiation time = 0–90 min	50 % of Chlortetracycline degradation [H$_2$O$_2$] production = 0.027–0.086 μmol/L min	Chen et al. (2012)
Tetracycline	Distilled water	Semiconductor photocatalysis	MP UV (125 W); pH = 6.0; [TC]° = 10–50 mg/L; TiO$_2$ (100 % anatase or anatase/rutile = 4/1; 1 and 0.4 g/L of catalyst	More than 98 % of tetracycline was oxidized within about 2 h; 100 % of total organic carbon removal using TiO$_2$ (anatase/rutile).	Addamo et al. (2005)

Table 3 continued

Tetracycline antibiotics	Matrix	Treatment	Operating conditions	Results and comments	References
	Deionised water	Semiconductor photocatalysis	UV (254 nm, 365 nm); solarium device (300–400 nm); TiO_2 catalyst; 05–1.0 g/L catalyst; [tetracycline]° = 40 mg/L; treatment time = 120 min	100 % degradation and 90 % total organic carbon removal (UV 254 nm; 0.5 g/L TiO_2; after 120 min)	Reyes et al. (2006)
				100 % degradation and 70 % total organic carbon removal (Solarium device; 0.5 g/L TiO_2; after 120 min)	
				50 % degradation and 10 % total organic carbon removal (UV 365 nm; 0.5 g/L TiO_2; after 120 min).	
	Ultra-pure water	Direct photolysis	UV at 365 nm; pH = 6; [tetracycline]° = 10–40 mg/L	73 % tetracycline degradation; 15 % total organic carbon removal	Jiao et al. (2008)
	Distilled water	Electrochemical oxidation	pH = 3.9–10.0, current density = 15.9–63.5 mA/cm^2, treatment time = 60 min, [Na_2SO_4] = 0.05–0.20 mol/L, Ti/RuO_2–IrO_2: anode, stainless steel: cathode, [OH°] = 0–4.20 mmol/L, [tetracycline]° = 50–200 mg/L, volume = 200 mL	More than 90 % of tetracycline degradation at pH = 3.9, current density = 47.6 mA/cm^2, [Na_2SO_4] = 0.1 mol/L and [tetracycline] = 100 mg/L	Zhang et al. (2009)
	Distilled water	Photoelectrocatalytic process	TiO_2 photoanode, UV light (254 nm, 2.5 mW/cm^2), 0.5 V, pH = 5.5, [$NaSO_4$]° = 0.02 moL/L, [tetracycline]° = 10 mg/L, treatment time = 3 h	More than 80 % of tetracycline degradation	Liu et al. (2009)
	Spiked STP effluent, surface and deionised water	Photo-Fenton	Black light (15 W); solar irradiation; 1–10 mM H_2O_2; 0.20 mM ferrioxalate or $Fe(NO_3)_3$; [tetracycline]° = 24 mg/L	100 % tetracycline degradation under solar irradiation	Bautitz and Nogueira (2007)
	Distilled Water	Semiconductor photocatalysis	Xe lamp (300–800 nm); TiO_2 and ZnO as catalyst; 0.5–1.5 g/L TiO_2; 0.2–1.5 g/L ZnO; pH = 3–10 (TiO_2); pH = 6–11 (ZnO); [tetracycline]° = 20 mg/L	100 % tetracycline degradation and 50 % total organic carbon removal (after 15 min, 1.5 g/L TiO2, pH = 8.7)	Palominos et al. (2009)
				100 % tetracycline degradation and mineralization (after 10–60 min, 1.0 g/L ZnO, pH = 11)	
Oxytetracycline	Pharmaceutical wastewater	Reverse osmosis Ultrafiltration	Reverse osmosis: NTR-7450 membrane; NTR-7459 membrane; area = 155 cm^2; T = 21–23 °C; pressure = 1.8 MPa; volume reduction = 3.5 Ultrafiltration: stirred cell; 3, 10, 30, 50 kDa cut-off membranes; operational pressure = 0.30 MPa; volume reduction = 10 [oxytetracycline]° = 1,000 mg/L; [COD] = 10,000 mg/L	Reverse osmosis: The organic content in the permeate was decreased from 10,000 mg COD/L to 200 mg COD/L (98 % removal); oxytetracycline was reduced from 1,000 mg/L to 80 mg/L (87.5 % removal) Ultrafiltration: the oxytetracycline recovery ratio was higher than 60 %, the purity higher than 80 %	Li et al. (2004)
	Ultrapure water	Ozonation	11 mg/L O_3; [oxytetracycline]° = 100–200 mg/L; pH = 3–11	100 % oxytetracycline degradation after 20 min; BOD_5/COD was higher than 0.3 biodegradable effluent; By-products were more toxic than parent compounds	Li et al. (2008)
	Ultrapure water	Direct photolysis	UV at 365 nm, pH = 4–9; [oxytetracycline]° = 10–40 mg/L	90 % oxytetracycline degradation, 14 % total organic carbon removal, 47 % of inhibition rate after 240 min of irradiation	Shajoun et al. (2008)

Table 3 continued

Tetracycline antibiotics	Matrix	Treatment	Operating conditions	Results and comments	References
	Distilled water	Electrochemical oxidation	Current density = 50 mA/cm^2, pH = 2.10–4.45, $T°$ = 21 ± 1.0 °C, electrolysis time = 0–120 min, anode = RuO$_2$, [oxytetracycline] = 4.83 × 10^{-5}–8.85 × 10^{-5} mol/dm^3	Rate constants: 9.9 × 10^{-5}/s (pH 2.10), 1.9 × 10^{-4}/s (pH 5.45) Complete loss of the antimicrobial activity of oxytetracycline after 120 min of electrolysis time and at 50 mA/cm^2	Rossi et al. 2009
	Pharmaceutical wastewater	Reverse osmosis Nanofiltration	[oxytetracycline]° = 10 mg/L, XLE and HR95PP membranes (Reverse osmosis), NF90 and HL Desal membrane (nanofiltration).	Higher degradation using reverse osmosis followed by nanofiltration	Kosutic et al. (2007)
Chlortetracycline Oxytetracycline Tetracycline	Distilled water	Adsorption with aluminium oxide	C° = 20–110 µg/L, 0.8–3.5 g/L Al$_2$O$_3$	Rapid adsorption of tetracycline (43 %), chlortetracycline (57 %) and oxytetracycline (44 %)	Chen and Huang (2010)
Chlortetracycline Oxytetracycline Tetracycline	Aqueous solution	Photoelectrocatalytic process	[tetracycline]° = 10 mg/L; [chlortetracycline]° = 10 mg/L; [oxytetracycline]° = 10 mg/L; medium pressure mercury lamp (15 W, λ ≥ 365 nm, 21.2 µW/cm^2, [Na$_2$SO$_4$] = 0.1 moL/L, potential applied = 0.6–3.0 V, treatment time = 0–180 min, pH = 3–12	About 95 % of tetracycline antibiotics degradation	Liu et al. (2012)
Chlortetracycline Doxycycline Oxytetracycline Tetracycline	Aqueous solution Wastewater animal husbandry	Electrochemical oxidation	Current intensity = 1.5 A, Ti/IrO$_2$ (or Ti/PbO$_2$) : anode, Ti: cathode, electrode gap = 10 mm, [NaCl] (or [Na$_2$SO$_4$]) = 1,000 mg, treatment time = 6 h, [Tetracycline antibiotics]° = 100 mg/L, [oxytetracycline]° = 100 mg/L	[Tetracycline antibiotics] final = 0.6 mg/L, [oxytetracycline]° = 0.7 mg/L after 6 h of treatment time	Miyata et al. (2011)
Chlortetracycline Doxycycline Oxytetracycline Tetracycline	Distilled water spiked with calcium chloride, humic acid and NaCl	Nanofiltration	NF 200 membranes (14.6 cm^2 area), pH = 7, T = 20 °C.	Degradation of tetracycline antibiotics between 50 and 80 % after 90 min	Koyuncu et al. (2008)
Chlortetracycline Doxycycline Oxytetracycline Tetracycline	Distilled water	Oxidation/reduction	pH = 7.0 ± 0.1, 5 mM phosphate buffer, $T°$ = 22.0 ± 1.0 °C, Xe arc lamp (172 nm), [TOC]° = 13 µg/L, electron pulse radiolysis (472 nm, G = 5.2 × 10^{-4} m^2/J	The efficiencies for OH° reaction = 32–60 % The efficiencies for e$^-$ reaction = 15–29 %, for chlortetracycline = 97 %	Jeong et al. (2010)
Chlortetracycline Oxytetracycline Tetracycline	Ultrapure water Surface water Ground water Wastewater	Gamma radiation	Temperature = 25 °C ± 1.0 °C, pH = 2–10, radiation dose = 1.66–3.83 Gy/min, [HCO$_3^-$] = 0.0–7.2 meq/L, [SO$_4^{2-}$] = 0.0–41.0 mg/L, [NO$_3^-$] = 0.0–4.4 mg/L, [Tetracycline antibiotics] = 20–100 mg/L	Toxicity inhibition: surface water (43.2 % of tetracycline, 36.3 % of chlortetracycline, 47.2 % of oxytetracycline); Ground water (32.7 % of tetracycline, 55.6 % of chlortetracycline, 44.4 % of oxytetracycline)	López Peñalver et al. (2012)
Chlortetracycline Doxycyline Oxytetracycline Tetracycline Demeclocycline Minocycline	Spiked synthetic and river water	Coagulation adsorption with activated carbon	Contact time 5 min, 10 µg/L for adsorption process, 100 µg/L for coagulation, coagulation PACI (5–60 mg/L), granular activated carbon filtration: calgon F400 and coconut-based carbon	Synthetic water: 43–94 % removal of the drugs (40 mg/L of coagulant) River water: 44–67 % removal of the drugs	Choi et al. (2008)

H_2O molecule allow the generation of powerful oxidizing species such as the hydroxyl radicals ($OH°$) and the hydrogen peroxide (H_2O_2) (Heit et al. 1998; Kim and Tanaka 2009). The oxidation efficiency of UV radiation (365 nm) promotes the degradation rates of 50, 90 and 75 % of chlortetracycline, oxytetracycline and tetracycline, respectively (Chen et al. 2012; Jiao et al. 2008; Shajoun et al. 2008). Despite this higher degradation of tetracycline antibiotics, a lower mineralization rate (14–15 % of total organic carbon removal) has been reached depending on the types of tetracycline antibiotics tested and the experimental conditions. The low removal of total organic carbon indicates the presence of intermediate compounds, which can be more toxic than the original one (Jiao et al. 2008; Shajoun et al. 2008).

The performance of the photolysis process in wastewater treatment is affected by several factors such as the absorption spectrum of the target compounds, the type of matrix and the intensity of the radiation (Kummerer 2009a, b; Homem and Santos 2011). The maintenance and the electrical energy costs are also some limiting factors for the application of UV system in wastewater treatment. To this end, researches focus on the combinations of UV radiations with oxidant species such as H_2O_2 and O_3 (UV/H_2O_2 and UV/O_3).

Ozonation technique was applied to remove oxytetracycline and chlortetracycline from water and livestock wastewater, respectively (Lee et al. 2011; Li et al. 2008). The ozone is a strong oxidant ($E° = 2.07$ V) capable to act direct or indirectly with pollutants (Homem and Santos 2011). Otherwise, the presence of hydroxide ions could initiate the decomposition of ozone in water to form hydroxyl radicals (Andreozzi et al. 1999). A 100 % removal of oxytetracycline has been reached using 11 mg O_3/L after 20 min of treatment time, whereas 30 % of chlortetracycline has been removed from livestock wastewater after 40 min and at 7.0 g O_3/m^3.

In order to improve the performance of this kind of treatment, it is possible to combine ozone with UV irradiation (O_3/UV) or hydrogen peroxide (O_3/H_2O_2). Lee et al. (2011) verified that H_2O_2 (0–200 mg/L) combined with O_3 (namely perozonation process) increased the removal efficiency of chlortetracycline (up to 65 % removal in 40 min), but the ecotoxicity was not totally removed. Another pathway to enhance the ozonation performance is to combine O_3 with UV irradiation. According to Hernandez-Alonso et al. (2002), the photolysis of ozone produces hydrogen peroxide, which initiates the further decomposition of residual ozone into hydroxyl radical. This technique (O_3/UV) has been investigated by Lee et al. (2011). The inactivation of chlortetracycline-resistant HPCs has been recorded after 10 min, while <2 log-reduction of chlortetracycline was achieved in 1 h using O_3 alone. According to the results reported above, the efficiency of the ozonation process on the removal of tetracycline antibiotics showed a

difference. The operating conditions imposed during the treatment (pH, Type of tetracycline antibiotics, dose of ozone, mixing inside the reactor, etc.) and the mass transfer limitations are a relevant factor to be considered in the oxidation process with ozone.

As reported by Homem and Santos (2011), this system requires the transfer of ozone molecules from gas phase to liquid phase, where the attack on the organic molecules occurs. It is worth noting that the presence of organic matter, suspended solids, carbonate/bicarbonate and chlorine ions could also affect the performance of ozone process (Gunten 2003; Andreozzi et al. 1999). As far as, the high cost of the equipment and maintenance, as well as the energy required to supply the process constitutes one of the disadvantages of the ozonation technique.

Photo-Fenton process ($UV/Fe^{2+}/H_2O_2$) is another attractive oxidation system because it uses low cost reagents, iron is abundant and a non-toxic element and hydrogen peroxide is easy to handle and environmentally safety. The use of UV radiation increases the efficiency of the oxidation process due to the highly generation of hydroxyl radicals by the photolysis of ferric complexes and the regeneration of ferrous ions (Gonzàlez et al. 2007, Bautitz and Nogueira 2007). As shown in Table 3, 100 % degradation rate of tetracycline was obtained at 0.14 J/cm^2 (1.5 min irradiation) using 3.0 mmol/L of H_2O_2 and 0.20 mmol/L of FeOx (Bautitz and Nogueira (2007)). Tetracycline was removed from different water sources (Spiked wastewater treatment plants effluent, surface and deionized water) under solar irradiation.

Under these conditions, the average mineralization rate recorded in wastewater treatment plants, surface water and deionized water were 77, 83 and 91 %, respectively. These results suggest that the radiation may have been attenuated by the organic matter in the wastewater treatment plants matrices. The photolysis of aqueous $Fe(OH)^{2+}$ has been hindered and consequently, the generation of $OH°$ was limited. Photo-Fenton process is generally inapplicable to wastewater with high organic matter such as hospital and antibiotic manufacturing wastewater because the turbity prevents the penetration of UV radiations (Homem and Santos 2011). The high chemical consumption which sometimes produces a secondary pollution and a huge volume of sludge, and the relatively higher treatment cost constitutes another major drawback for large scale application of these processes (Martínez-Huitle and Ferro 2006; Panizza and Cerisola 2004).

Electrochemical process

Nowadays, electrochemical technologies applied for the treatment of tetracycline antibiotics have received considerable attention in the environmental field (Miyata et al.

2011; Rossi et al. 2009). Electrochemical method combining chemistry and electronic science (electron transfer) has widely proved to be a clean, flexible and powerful technique for water and wastewater treatment (Grimm et al. 1998). Electrochemical treatment is characterized by simple equipment, easy operation, safety, selectivity, environmental compatibily and brief retention time (Rajeshwar and Ibanez 1997). Compared to chemical oxidation, no addition of chemicals is necessary in the process of electrochemical degradation. In electrochemical oxidation processes, pollutant can be removed electrochemically by a direct anodic oxidation, where pollutant are firstly adsorbed on the anode surface and then destroyed through the anodic electron exchange. On the other hand, pollutants could be also degraded indirectly in the liquid bulk through reactive oxidant species ($OH°$, O_3, H_2O_2, chlorinated species, etc.), which act as intermediates for electrons transference between the electrode and the refractory organic compounds (Panizza and Cerisola 2009; Homem and Santos 2011). This technology has been widely applied to remove tetracycline antibiotics under different experimental conditions. More than 90 % of tetracycline degradation has been recorded by Zhang et al. (2009) using $Ti/RuO_2–IrO_2$ as anode electrode at 47.6 mA/cm^2 of current density, after 60 min of electrolysis time, at pH value of 3.9 and using of 0.1 mol/L of Na_2SO_4. By comparison, electrochemical oxidation (chlortetracycline, oxytetracycline, tetracycline and doxycycline) promote the reduction of tetracycline antibiotics from 100 mg/L to 0.6 mg/L in aqueous solution (removal of 99 % of tetracycline antibiotics) at 1.5 A of current intensity, after 6 h of electrolysis time and using Ti/IrO_2 as anode (Miyata et al. 2011). The same electrochemical process applied by Miyata et al. (2011) favored the reduction of oxytetracycline in livestock wastewater from 100 to 0.7 mg/L after 6 h of treatment. Microbiological studies with *Staphylococcus aureus* ATCC 29213 have shown that oxytetracycline lost antibacterial activity after 120 min of electrolysis time and at 50 mA/cm^2 (Rossi et al. 2009). According to Homem and Santos (2011), electrochemical processes seem to be suitable to treat manufacturing wastewaters containing high concentrations of antibiotics and COD. Despite this higher degradation of tetracycline antibiotics recorded using electrochemical technology, the applicability of this process for large scale remains limited. The high operating cost due to the high energy consumption is still the main drawback which limits the application of the electrochemical process (Anglada et al. 2009).

Photocatalytic and photoelectrocatalytic processes

Over the past 20 years, there has been a growing interest in system employing heterogeneous photocatalytic process (Zouaghi et al. 2007; McCullagh et al. 2011; Tsai and Cheng 1997; Chen et al. 2010; Leary and Westwood 2011; Braham and Harris 2009). Photocatalytic technology has a great potential due to the low treatment cost, environmental friendly and a sustainable treatment process in the field of wastewater treatment (Chong et al. 2011). In photocatalysis process, the reactions of oxidative degradation require the presence of two basic components: a catalytic photo-sensitive surface (such as TiO_2, ZnO) and a source of photon energy. As reported in several review, the principle of this methodology is mainly based on the generation of oxidant reactive species upon absorption of artificial UV light (or sunlight) by the photo-catalyst (Daghrir et al. 2012a, b). The application of energy greater or equal to the energy of the band gap of the photo-catalyst leads to the transfer of the electron from the valence band to the conduction band and the formation of a positive hole in the valence band. In water and wastewater treatment, the pollutant species such as antibiotic could be degraded directly on the surface of the semi-conductor or indirectly by reacting with hydroxyl radical and through other radical species derived from oxygen (Homem and Santos 2011; Daghrir et al. 2012a, b). Several authors studied the applications of this method to degrade tetracycline antibiotics and they concluded that semiconductor photocatalysis process was very efficient. Addamo et al. (2005) studied the application of this technique to treat aqueous solution contaminated with tetracycline. They concluded that the rate of tetracycline degradation above 98 % occur within 2 h, associated with total mineralization (100 % removal of total organic carbon) using TiO_2 (anatase/rutile) as photo-catalyst irradiated with UV light. By comparison, Reyes et al. (2006) who studied TC degradation using photocatalytic process show 100 % of tetracycline degradation after 120 min and higher mineralization level (≈ 90 %) using 0.5 g/L of TiO_2 and under 254 nm of UV irradiation. These results were consistent with those obtained by Palominos et al. (2009), who studied the degradation of TC using photocatalytic process. The degradation rates of tetracycline were high using either TiO_2 or ZnO (≈ 100 %), as well as mineralization (≈ 50 % using TiO_2 and ≈ 100 % using ZnO). A recent study of Bu and Zhuang (2013) using photo-catalysis process (0.4 g of Cu/TiO_2 as photo-catalyst and under 360 nm of UV irradiation) could be effective to remove more than 80 % of chlortetracycline.

Under these conditions, 75, 28.1 and 50 % of chemical oxygen demand, total organic carbon and biological oxygen demand were recorded, respectively. It has been shown by Homem and Santos (2011) that photocatalytic processes seem to be very promising for the treatment of waters (drinking water, surface and groundwater) containing low concentrations of organic matter. In addition, the practical application of photocatalytic processes at large scale

remain limit due to the fast recombination of photo-generated electrons/holes pairs (e^-/h^+).

Nowadays, recent research focus on improving the photocatalytic process by combining catalytic reaction with electrochemical technology named photo-electrocatalytic process (Daghrir et al. 2012a, b; Liu et al. 2011, 2012). However, the application of this technology to remove tetracycline antibiotics remains limited compared to the conventional photocatalytic process. Photoelectrocatalytic process has been applied by Liu et al. (2012) to remove 30 mg/L of tetracycline antibiotics (chlortetracycline, oxytetracycline and tetracycline). In this study, about 95 % of the three antibiotics were achieved after 180 min of treatment time at 3.0 V of external potential applied, under UV irradiation and at neutral pH. Moreover, the photoelectrocatalytic treatment of tetracycline (10 mg/L) in aqueous solution during 3 h, at 0.5 V and using 254 nm of UV irradiation promotes the removal of 80 %. On the other hand, Daghrir et al. (2013) also studied the use of Photoelectrocatalytic oxidation process for the removal of chlortetracycline (30–230 µg/L). They obtained higher degradation efficiency of chlortetracycline (98.0 ± 0.2 % of chlortetracycline removal) followed by higher mineralization (67.3 ± 2.15 % of total organic carbon removal and 69.3 ± 3.10 % of total nitrogen removal) after 120 min of treatment time, using Ti/TiO$_2$ as photo-anode, vitreous carbon as cathode at 0.39 A of current intensity and under 254 nm of UV light.

Due to the successful results at the laboratory scale for the degradation of tetracycline antibiotics, the photoelectrocatalytic processes merit further research, particularly for the design of pilot units to remove tetracycline antibiotics and others recalcitrant compounds from drinking water and from different effluents (municipal, industrial and domestic wastewaters).

Future trends and perspectives

This paper underlines the worldwide usage of tetracycline antibiotics, their fate and toxicity in the aquatic and terrestrial environment. On one hand, the cheapest cost and the therapeutic effects of tetracycline antibiotics make it more suitable for preserving human and animal health and even as feed additive in agriculture sector; and on the other hand, it also make it potentially significant as environmental contaminants due to its higher stability and persistence. Halling-Sorensen et al. (2005) found that the average degradation half live of CTC varied from 25 to 34 days in two Danish soils, whereas Samuelsen et al. (1994) reported that no degradation was observed for OTC after 6 months of incubation in marine sediment.

Up to now, the environmental consequences of the presence of tetracycline antibiotics and the resistant bacteria in the environment remain indistinct. Generally, the impact of tetracycline antibiotics drugs administrated for example to animals in terrestrial and aquatic environments depends not only on the amount used and the type of the administration, but also on animal husbandry practices, metabolism within the animal, manure handling and storage and degradation rate in it. Thus, the prudent use of tetracycline antibiotics and the claim for "co-ordination" between human, veterinary and the different environmental sectors become mandatory.

Although extensive studies have been conducted on the tetracycline antibiotics (tetracycline, chlortetracycline and oxytetracycline), the fate and effect of its metabolites is still unknown and pose challenges. Major studies focus to develop new remediation techniques for the removal of TCAs from environmental media, for the general protection of human health and ecosystems. The lower mineralization yields recorded at the end of the most treatment processes indicated that only a small fraction of tetracycline antibiotics was completely oxidized into water and carbon dioxide. The majority of the contaminant was transformed into by-products. Thus, more attention has to be paid to these intermediates. Halling-Sorensen et al. (2002) have investigated the fate of important tetracycline antibiotics and their degradation products under environmentally relevant conditions (pH, chelation and photo-degradation). They analyzed whether these degradation products were potent to environmentally relevant sludge and soil bacteria. According to Halling-Sorensen et al. (2002), the tetracycline antibiotics degradation products were formed dependently on the pH, the presence of cations and the light exposure. At pH levels exceeding 6.5, iso-chlortetracycline, iso-tetracycline, keto-chlortetracycline and iso-oxytetracycline are the major by-products formed, whereas epi-tetracycline, epianhydro-tetracycline, epi-chlortetracycline, epi-anhydrochlortetracycline, keto-chlortetracycline, α-Apo-oxytetracycline and β-Apo-chlortetracycline were considered as the major degradation products to be found in the environmental aquatic matrices at pH below 6.5. Majors of these degradation products were found potent to both sludge and soil bacteria, especially anhydro-tetracycline, epi-anhydro-tetracycline, epi-chlortetracycline and anhydro-chlortetracycline which are very toxic to all the resistant isolates. According to Blackwood and English (1970), the corresponding potency of anhydro-tetracycline, iso-tetracycline, epi-tetracycline, epi-oxytetracycline was 270, 0.09, 54 and 29 %, respectively. Belong to the "atypical tetracycline antibiotics", anhydro-tetracycline, anhydro-chlortetracycline and epi-anhydrochlortetracycline have a different mode of action than tetracycline antibiotics by being bactericidal instead of bacteriostatic (Halling-Sorensen et al. 2002). They interfere with membrane permeability and they exhibit activity against organisms that are resistant to

chlortetracycline, oxytetracycline and tetracycline (Chopra 1994; Chopra et al. 1992).

Furthermore, it is clear that there is a gap of reliable studies on the relationship between the occurrence of residual concentrations of tetracycline antibiotics and the antibiotic resistance microorganisms. This resistance is mainly due to the repeated exposition of bacteria to sublethal dosages of antibiotics (Kemper et al. 2008). Generally, tetracycline antibiotics is regularly fertilized in soils with manure (Hamscher et al. 2002). Thus, the long term dispersion of liquid manure on fields may result in serious contamination due to the accumulation character of tetracycline antibiotics in the environment (Kemper et al. 2008). Consequently, a transfer of antimicrobial is possible. According to Richter et al. (1996), the transmission of these antibiotic resistance microorganisms is possible via the direct contact or via the food chain.

Besides, reported concentrations of tetracycline antibiotics in different environmental compartments are still detected in lower trace levels and ultimately depend on spatial and climatic variations. Given this fact, techniques developed for the detection cannot be extrapolated. In this context, analytical method for the detection should have higher sensitivity, selectivity and specificity. According to Shelver and Varel (2012), sensitive analytical methods should be used to demonstrate the presence of chlortetracycline for example in manure, agriculture wastewater and in ground water at lower concentrations (from ng/L to µg/L). Thus, it is critical to find multi-residual method to detect tetracycline antibiotics and its by-products. Liquid chromatography coupled to mass spectrometry which provides new opportunities for analysis of tetracycline antibiotics in water, is highly recommended. Liquid chromatography coupled to mass spectrometry has been developed and effectively implemented by several research groups (Daghrir et al. 2013; Arikan et al. 2009; Arikan et al. 2008) for the determination of tetracycline antibiotics mainly due to the known advantage of mass spectrometry detection over conventional detection method such as UV and fluorescence. According to Onal (2011), mass spectrometry—mass spectrometry proves to be a useful analysis technique able to identify and clarify the structure of the compound in complex matrices.

It should be also mentioned that several questions remain unanswered for the conventional treatment processes (biological or physico-chemical treatments) generally applied to remove tetracycline antibiotics through wastewater treatment plants. The occurrence of tetracycline antibiotics in the aquatic and terrestrial environmental is mainly due to the unsuccessful of conventional treatment processes (coagulation, sedimentation, UV irradiation, and biological) applied in wastewater treatment plants in the removal of these compounds. These tetracycline antibiotics promote the proliferation of antibiotic resistant microorganisms, which can pose a major public health concern. Previous studies (Auerbach et al. 2007) have investigated wastewater treatment plants as possible sources for the development and proliferation of tetracycline antibiotics resistance genes in the activated sludge. According to the results reported with Auerbach et al. 2007), the concentrations of tet(Q) resistance genes were found to be highest in wastewater influent while the concentrations of tet(G) genes were highest in activated sludge. As a matter of fact, investigations of the effects of UV disinfection as a tertiary treatment process in wastewater treatment plants showed no reduction in the number of detectable resistant gene types (tet[R]).

To overcome this drawback, novel approaches that use and integrate the chemical data including advanced oxidation processes have been developed and applied to remove tetracycline antibiotics from water, wastewater, soil and sludge. Until date, applications of advanced oxidation processes for tetracycline antibiotics removal were carried out at the laboratory scale. Future research should be focused on the development of advanced oxidation processes for large scale applications. Advanced oxidation processes are one of the most powerful processes for the removal of antibiotics from the environment (Homem and Santos 2011). In addition, these processes can be effectively used to remove by-products toxicity and enhance the mineralization rate of tetracycline antibiotics. The microorganisms used in biological process are sensible to the toxic pollutants. Thus, advanced oxidation processes could be applied as pre-treatment step in which the pollutant are oxidized to by-products that are easily biodegradable and less toxic. This combined process avoids the death of microorganisms that are present in biological treatment (Tekin et al. 2006). Likewise, coupling a biodegradation process with physicochemical process would improve tetracycline antibiotics removal and reduce the operating cost.

Conclusion

This review emphasizes the widespread usage of tetracycline antibiotics, their occurrence and their toxicity in different aquatic and terrestrial compartments. Due to their extensive applications in the medical field and in the agriculture sector, residual concentrations of such drugs have been detected in the environment. The introduction of these residual compounds into environment through different sources will lead to serious environmental problems including ecological risk and human health damage. Despite the extensive knowledge about tetracycline antibiotics, advanced studies need to be carried out to evaluate the toxicity of tetracycline antibiotics. Most of the

conventional wastewater treatment plants are not able to remove tetracycline antibiotics from waters. Advanced oxidation processes have been proposed as alternative methods to ensure the higher degradation and mineralization of tetracycline compounds.

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