J Korean Soc Appl Biol Chem (2012) 55, 701–709
DOI 10.1007/s13765-012-2220-4

REVIEW

Fate, Occurrence, and Toxicity of Veterinary Antibiotics in Environment

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Received: 20 September 2012 / Accepted: 18 October 2012 / Published Online: 31 December 2012

Abstract The increasing worldwide usages of Veterinary Antibiotics (VAs) for therapeutic and nontherapeutic are becoming serious issue due to its adverse effects on all living organisms. Release of VAs into the aquatic and terrestrial environments results in antibiotic resistance in bacteria and toxicity to humans, animals, and plants. This review covers the present scenario on VA usage, occurrence, toxicity, and removal techniques.

Keywords antibiotics · antibiotic-resistance · toxicity · veterinary

Antibiotics are chemical therapeutic agents used to kill or inhibit microorganisms, such as bacteria, virus, fungi, or protozoa. Antibiotics that kill bacteria are called “bactericidal” and antibiotics that inhibit the growth of bacteria are called as “bacteriostatic”. In 1928, the antibiotic penicillin was first isolated from the fungus *Penicillium* by Alexander Fleming. The next discovery was that of streptomycin by Selman Waksman. Streptomycin was isolated from the bacterial genus *Streptomyces*, which is found naturally in soil, and is an antibiotic cure for many intestinal diseases. The antibiotics penicillin and streptomycin are both relatively effective against certain diseases, but there was a lack of broad-spectrum drugs. Thus, a search ensued for a new panacea; an antibiotic to rule them all. By 1949, various laboratories had discovered a series of antibiotics such as aureomycin, chloromycin, and terramycin all of which had broader effective ranges against bacteria than penicillin and streptomycin. Presently, there are about 250 different chemical entities registered and currently being used as human and veterinary antibiotics (VAs) (Kümmerer and Henninger, 2003).

Antibiotics are generally classified based on their structure or by their mechanism of action including subgroups such as beta lactums, quinolones, tetracyclines, macrolides, sulfonamides, and others. Under different pH conditions, antibiotics are neutral, cationic, anionic or zwitter-ionic, as they are complex molecules that may possess different functionalities within the same molecule. Due to these different functionalities, their physical, chemical, and biological properties such as log P_{ow} (Cunningham, 2008), sorption behavior, photoreactivity, activity, and toxicity may change with pH (Kümmerer, 2009).

The production and use of antibiotics increased rapidly worldwide over the last several decades. Numerous pharmacologically active substances are used as human and animal medicines annually for treating and preventing diseases. Approximately 3,000 compounds are used as medicine (Díaz -Cruz et al., 2003; Sarmah et al., 2006; Calisto and Esteves 2009; Kümmerer, 2009) and 100,000–200,000 tons year^{-1} are used globally (Wise, 2002). However, the release of antibiotics into the environment has received attention in recent years.

The use of VAs has become necessary due to the growing animal food industry. VAs are used worldwide to protect animal health, prevent economic loss, and help ensure a safe food supply (Boxall et al., 2002; Halling-Sørensen et al., 2002). However, after use, VAs may enter waterways and possibly pose environmental challenges. The presence of antibiotics in the environment was first detected three decades ago in a UK river (Watts et al., 1982). This initiated monitoring for antibiotics in the environment and studies of their environmental impact in many countries (Sarmah et al., 2006). Among the antibiotic release sources, VAs appear to be the most potent source as they are released into the environment through animal manure and by other means (Baguer et al., 2000). In recent years, the occurrence and fate of antibiotics in the environment, including surface water, groundwater, and soil has drawn the attention of researchers all over the world.

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Use of VAs

VAs are most often used for nontherapeutic purpose such as growth promotion, feed efficiency, and weight gain in animals for increasing food production. Growth promotion effect of VAs was first discovered in the late 1940s in chickens and pigs. VAs can be administered to healthy animals in feed at concentrations <200 mg L^{-1} for >14 days as a growth promoter. This high dose is well characterized from therapeutic and prophylactic antibiotic uses, which are generally delivered at a higher minimum dose of about 20 mg L^{-1} in animals and are generally administered in water (NAAS, 2010). In 1950s the recommended concentration levels in poultry and pig diets were 4 mg L^{-1} for narrow spectrum and 10 mg L^{-1} for broad-spectrum antibiotics. However, these levels have currently increased 10–20 fold (NAAS, 2010). The general classes of VAs are listed in Table 1.

No clear information is available on the total amount of VAs used worldwide. Based on the amount sold in each country, the amount used is estimated, and the use may vary from country to country based upon the number of livestock. Sales reports indicate that the USA ranks first in the use of antibiotics at about 11,148 tons $year^{-1}$ (Benbrook, 2002). These antibiotics are utilized largely to promote growth and prevent disease, thereby reducing production costs. Most of the VAs are sold over the counter and do not require a veterinarian's prescription. The second largest consumer of VAs is China at 6,000 tons $year^{-1}$ (Zhao et al., 2010). VAs use in both countries is higher than that of other countries not only due to the large numbers of livestock but also due to the common agricultural practice using VAs as growth feed additives. The use of VAs in Korea, Japan, and France is 1,533 (Kim et al., 2011), 1,059 (Asai et al., 2007), and 1,064 (EMA, 2011) tons $year^{-1}$, respectively. Of the 20 active ingredients (AIs) in VAs in Korea, five antibiotics such as chlortetracycline, oxytetracycline, sulfamethazine, sulfathiazole, and tylosin are in the top priority group (Seo et al., 2007). Usages of VAs in different countries are listed in Table 2.

Consumers in many developed countries have no qualm about consuming meat or livestock products from animals raised on feed containing antibiotics. Thus the use of large quantities of VAs in the USA has caused their trading partners and competitors such as European countries, New Zealand, and South Korea to implement restrictions and prohibitions on the use of certain antibiotics for subtherapeutic or nontherapeutic purposes in animal production. The European Union (EU) has banned growth promoting antibiotics in production animals (Mark et al., 2003). In June 2001, the EU banned the use of almost all growth promoting antibiotics except monensin sodium, salinomycin sodium, avilamycin, and flavophospholipol and these products have also been banned since January 1, 2006. The Korean Ministry for Food, Agriculture, Forestry, and Fisheries banned the use of eight antibiotics such as enramycin, tyrosine, virginiamycin, bacitracin methylene disalicylate, bambermycin, tiamulin, apramycin, avilamycin, and sulfathiazole as feed additives in July 2010 (Renee, 2011). Furthermore, some Southeast Asian countries including Singapore, Japan, Thailand, Taiwan, and Malaysia are also considering banning the use of growth-promoting antibiotics. South American countries such as Argentina, Brazil, and Uruguay are likely to ban the use of many antibiotics in food-producing animals. The USA, Canada, and Australia continuously review and monitor the use of antibiotics

Table 1 Classes of commonly used veterinary antibiotics

Class	Acronym	Compounds	Formula	M.W
Fluoroqinolones	CIP	Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	331.34
	ERFX	Enrofloxacin	$C_{19}H_{22}FN_3O_3$	359.40
	OFL	Ofloxacin	$C_{18}H_{20}FN_3O_4$	361.36
	PEF	Pefloxacin	$C_{17}H_{20}FN_3O_3$	333.35
Lincosamides	LIN	Lincomycin	$C_{18}H_{34}N_2O_6S$	406.53
Macrolides	TIA	Tiamulin	$C_{28}H_{47}NO_4S$	493.74
Fenicoles	CAP	Chloramphenicol	$C_{11}H_{12}Cl_2N_2O_5$	323.13
Sulfonamides	SCP	Sulfachloropyridazine	$C_{10}H_9ClN_4O_2S$	284.72
	SDZ	Sulfadiazine	$C_{10}H10N_4O_2S$	250.78
	SDM	Sulfadimidine	$C_{12}H_{14}N_4O_4S$	310.33
	SDO	Sulfadimethoxine	$C_{12}H_{14}N_4O_4S$	310.33
	SMT	Sulfamethizole	$C_9H_{10}N_4O_2S_2$	270.33
	SMX	Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.27
	SMZ	Sulfamethazine	$C_{12}H_{14}N_4O_2S$	278.33
	SQX	Sulfaquinoxaline	$C_{14}H_{12}N_4O_2S$	300.36
Trimethoprim	TMP	Trimethoprim	$C_{14}H_{18}N_4O_3$	290.32
Tetracyclines	CTC	Chlortetracycline	$C_{22}H_{23}ClN_2O_8$	478.88
	DOX	Doxycycline	$C_{22}H_{24}N_2O_8$	462.46
	OTC	Oxytetracycline	$C_{22}H_{24}N_2O_9$	460.43
	TC	Tetracycline	$C_{22}H_{24}N_2O_8$	444.43

Table 2 Worldwide total usage of veterinary antibiotics

Country	Amount sold/used (tonnes)	Reference
Africa	14.6	Mitema et al. (2001)
Australia	932	JETACAR (1999)
China	6000	Zhao et al. (2010)
Czech Republic	82	EMA (2011)
Denmark	130	EMA (2011)
Finland	17	EMA (2011)
France	1064	EMA (2011)
Japan	1059	Asai et al. (2007)
Korea	1533	Kim et al. (2011)
New Zealand	93	Sarmah et al.(2006)
Norway	6	EMA (2011)
Sweden	15	EMA (2011)
Switzerland	73.2	EMA (2011)
UK	403	EMA (2011)
USA	11148	Benbrook (2002)

in food animals. Worldwide legislation has been created to control the use of antibiotics for other than therapeutic use. Due to the increase in antibiotic-resistant infections in humans, organizations such as World Health Organization, the American Medical Association, and the American Public Health Association have proposed banning the use of antibiotics as growth-promoting additives. Some cautions/actions against the use of antibiotics in animal feed (Source: NAAS, 2010) are shown in Table 3.

The US Food and Drug Administration (FDA) issued an order on January 4, 2012 prohibiting certain extra-label uses of cephalosporin drugs (not including cepharin). The prohibited uses of cephalosporin include: 1) unapproved dose levels, frequencies, durations, or routes of administration; 2) cattle, swine, chickens, or turkeys, which are not approved for use (e.g., cephalosporin drugs intended for humans or companion animals; 3) disease prevention. This rule was effective beginning on April 5, 2012. The overall outcome of using antimicrobial growth promoters (AGPs) is the availability of more nutrients for growth and production of livestock and poultry. Improved growth rates and feed conversion ratios (feed:gain) have been reported to be 9–16% in piglets, 5.5–9% in growing pigs, 3–10% in broiler chickens, 1–2% in layers, and 7–10% in veal calves. Antibiotics for therapeutic purposes can be purchased only by prescription from a registered medical practitioner; however, they are freely accessible and sold over the counter as growth promoters. The effects of using AGPs are presented in Table 4 (Source: NAAS, 2010).

Occurrence

The occurrence and fate of VAs is a serious environmental threat with the emergence and development of antibiotic-resistant bacteria (Martinez, 2009; Holzel et al., 2010; Tao et al., 2010). VAs are usually released into the terrestrial environment in the form of organic manure, slurries or other types of biosolids. The activity of VAs in soil is not yet fully understood; however, environmental risk assessments of VAs use persistence and adsorption to estimate their fate and activity in the environment. Tetracyclines (TCs) and sulfonamides (SAs) were the most frequently detected compounds among the VAs used. Ok et al. (2011) studied the occurrence of VAs in water, sediment, and soil samples at a composting facility and reported that the concentration of TCs in a water sample was 2.75 μg L^{-1}, whereas they were 7.02 μg kg^{-1} in soil, and were below the detection limit in sediments. In contrast, the detected concentrations of SAs in water samples were 14.85 μg L^{-1}, 120.91 μg kg^{-1} in sediment samples, and 38.82 μg kg^{-1} in soil samples. Sim et al. (2011) reported that influent from livestock wastewater treatment plants (L-WWTPs) in South Korea contained 319–3630 μg L^{-1} of pharmaceuticals, and the antibiotic Lincomycin alone contained about 3005 μg L^{-1} in L-WWTPs. These were of higher concentrations than those in 12 other municipal plants, 4 hospitals, and 4 pharmaceutical wastewater treatment plants when they carried out a nationwide study.

In China, oxytetracycline (OTC) or chlorotetracycline (CTC) are commonly detected VAs in manure with the highest concentrations of 0.2–134 mg kg^{-1} OTC and 0.3–121.8 mg kg^{-1} CTC in the Beijing area (Zhang et al., 2005; Liu et al., 2007; Wei et al., 2008; Zhang et al., 2008). Hu et al. (2008) detected 173.2 mg kg^{-1} of OTC in swine manure and a similar concentration (172.9 mg kg^{-1}) of OTC was detected by Pan et al. (2011). The residual detected concentration of CTC was >2.6 mg kg^{-1} and OTC was >0.4 mg kg^{-1} (Pan et al., 2011).

In EU the detected level concentrations of TCs in swine manure ranged from 0.1–46.0 mg kg^{-1} in Germany (Hamscher et al., 2002), 0.1–24.4 mg kg^{-1} in Denmark (Jacobsen and Halling-Sørensen, 2006), and <0.5 mg kg^{-1} in Turkey (Karcı and Balcıoğlu, 2009). The highest detection concentrations of SAs such as sulfadimidine, sulfadiazine, and sulfathiazole in EU were 20.0, 2.0, and 1.4 mg kg^{-1}, respectively (Haller et al., 2002; Jacobsen and Halling-Sørensen, 2006; Martínez-Carballo et al., 2007).

Decomposition and Elimination in the Environment

Photolysis. Among various removal methods, photolysis or photodegradation contributes the most to antibiotic decomposition on soil surfaces. Photodegradable, water-soluble, and nonvolatile substances are particularly susceptible to photodegradation on soil surfaces (Miller and Donaldson, 1994), and most antibiotics possess these three properties (Thiele-Bruhn, 2003). Organic fertilizers are often spread on soil surfaces; thus the antibiotics therein are exposed to sunlight and may photodegrade. However, photodegradation of antibiotics is difficult when the compounds are mixed in the turbid water of a small stream, river, lake. soil, and sewage pipes, due to poor light penetration. Hence, the effectiveness of photodegradation

Table 3 Cautions/actions against the use of veterinary antibiotics in animal feed (Source: NAAS, 2010)

Year	Warnings/Action
1945	Alexander Flemming warns against misuse of penicillin as 'microbes are educated to resist'
1950	Antibiotic resistance widely recognised-vertical transmission
1950	Tuberculosis bacteria resistant to Streptomycin
1953	Certain strains of dysentery bacillus was found resistant to Chloromphenicol, Tetracycline, Streptomycin, and Sulfanilamides
1958	Tetracycline resistant to poultry
1960	Horizontal transmission recognized
1969	Swann Committee recommends severe restrictions on antimicrobial supplementations in animal feeds.
1970	Swann committee recommendations implemented in the UK and EU
1975	Swann committee recommendations relaxed: tolysin and spiramycin still permitted as growth promoters; vancomycin comes into use
1977	Swedish Agriculture Board considers potential risk of antibiotic resistance, but concludes it is negligible
1984	Swedish farmers ask for government ban on antimicrobials in animal feed due to concerns on health of consumers
1985	Swedish ban on grounds of antibiotic resistance in animals and it's 'uncertain' long-term effects
1995	Avoparcin and Vancomycin resistant Enterococci in pigs and poultry
1995	Norway banned Avoparcin
1996	German government banned Avoparcin
1997	EU banned Avoparcin
1997	Swedish report concludes that risk of antibiotic resistance in humans is 'far from negligible'
1997	WHO scientific meeting concludes that it is 'essential to replace growth-promoting antimicrobials'
1998	Danish government banned Virginiamycin due to Streptococcus resistance
1998	EU bans five antimicrobials in animal feed as 'precautionary' measure, such as Avoparcin, Bacitracin Zn, Spiramycin, Virginiamycin, and Tylosin in animal feedstuffs
1999	EU Scientific Steering Committee recommends phase-out of antimicrobials that may be used in human/animal therapy
1999	Pharmaceutical industry opposes EU bans and takes EU to the European Court; judgment expected end 2001
2000	WHO recommends ban on antimicrobials as growth-promoters if used in human therapy and in absence of risk-based evaluation
2004	U.S. Food and Drug Administration banned the non-therapeutic use of Eenrofloxacin for growth promotion in food animals on the grounds that its use has contributed to fluoroquinolone-resistance in human pathogens
2006	European Commission authorized use of Flavophospholipol, Monensis Na, Salinomycin Na, and Avilamycin in poultry, beef cattle, pigs, rabbits and calves diets, as these are not used in human medicine. The act includes Animal Drug user Fee Act (ADUFA), Strategies to address antimicrobial drug resistance (STAAR), and Preservation of Antibiotics for Medical Treatment Act (PAMTA)
2008	US congress passed a legislation regarding Antimicrobial Growth Promoters

in the environment cannot be achieved as in laboratory experiments (Kümmerer, 2009). The photodegradation process may differ based on the environmental conditions such as pH and water hardness (Werner et al., 2006), type of matrix, location, season, and latitude (Kallenborn et al., 2008). Antibiotics such as tetracyclines, sulfonamides, and fluoroquinolones are photodegradable in liquids (Oka et al., 1989; Lunestad et al., 1995; Burhenne et al., 1997; Halling-Sørensen et al., 2003; Boreen et al., 2004; 2005). The antibiotic TC was 50% photodecomposed when in the solution form with prolonged exposure (Oka et al., 1989). Upon exposure to light for 9 days, 50 mg L^{-1} OTC decreased to 2 mg L^{-1}, and when exposed to underwater light intensity 96% of OTC was removed (Lunestad et al., 1995). Wolters and Steffens (2005) first studied sulfadiazine photodegradation using air-dried soil dust samples (<0.1 mm). Antibiotics such as quinolones, tetracyclines, and sulfanamides are light-sensitive and photodegradable. However, little information is available on the photodegradation of xenobiotics on soil surfaces, particularly on the effects of photodegradation on pharmaceutical antibiotics (Thiele-Brun and Peters, 2007).

Hydrolysis. Hydrolysis is a chemical reaction in which water is split into hydrogen cations (H^+, identical to protons) and hydroxide anions (OH). This reaction is used to break down certain polymers, particularly those made by condensation polymerization. Such polymer degradation is usually catalyzed by either an acid, e.g., concentrated sulfuric acid, or alkali such as sodium hydroxide. Hydrolysis and photolysis may be the major degradation routes for antibiotics in the water environment (Xuan et al. 2010). Acidic conditions favor OTC stability and alkaline conditions favor OTC degradation (Doi and Stoskopf, 2000). OTC is more vulnerable to both hydrolysis and photolysis than oxolinicacid, flumequine, and florfenicol (Pouliquen et al., 2007). Hydrolysis of OTC is mainly affected by temperature and pH (Loftin et al., 2008). Various other factors affecting OTC hydrolytic degradation, particularly multi-covalent cations, have not yet been well-elucidated (Xuan et al., 2010). In general, the hydrolytic degradation kinetics of OTC increases as the pH deviates from pH 7 and as temperature increases. However sulfanomides and quinolones have shown resistance to hydrolytic degradation (Kümmerer, 2009).

Advanced oxidation processes (AOP). Oxidation is a reaction in which atoms in an element lose electrons, and the valence of the element correspondingly increases. Advanced oxidation processes

Table 4 Significance of using antibiotics as growth promoters

Broad Issue	Advantages	Disadvantages
Health	Control of certain diseases (primarily enteric) to some extent	1. Development of antimicrobial resistance 2. Masks sub-clinical disease and infection 3. Limits incentives for hygienic improvements
Welfare	Alleviates and dampens disease signs	Camouflages stress associated with sub clinical disease
Husbandry	Increases production	Stimulates and intensifies animal production
Feed	Enhances shelf life	1. Camouflages bad feed quality 2. Hampers improvements in feed formulation 3. Development of alternatives
Production system	Lowers labor demand due to more intense production methods Betters crop security	1. Hampers the development of animal friendly production systems 2. Development of antibiotic resistance even for pathogens of farm animals
Environment	Better utilization of feed; less manure	Increases the environmental pool of antibiotic resistan genes; antibiotic residues
Human health	None	1. Threat of infection by antibiotic resistant pathogens 2. Increased health care cost due to unmanageable infections 3. Shortens economic life of medical antimicrobials. 4. Occupational hazards through exposure to aerosol and dust contaminated with antimicrobials

are a set of chemical treatment procedures designed to remove organic and inorganic materials in wastewater by oxidation. One such process is called '*in situ* chemical oxidation'. Contaminants are oxidized by ozone, hydrogen peroxide, oxygen, and air in precise, pre-programmed dosages, sequences, and combinations. These procedures may also be combined with UV irradiation and specific catalysts, resulting in hydroxyl radicals. The degradation of TC antibiotics using AOP electron beam irradiation has been investigated in an aqueous solution as a function of irradiation dose. An aqueous TC standard solution was irradiated with an electron beam at 1, 3, 5, and 10 kGy, and efficiency was 83.5, 91.5, 100, and 100%, respectively (Chung et al., 2009). Complete TC degradation was achieved at the irradiation dose of 5 kGy. TC degradation follows an apparent "first-order" reaction rate dependent on irradiation dose. Electron beam technology has been suggested to be a way to degrade antibiotics and may be used as an approach for biological oxidation treatment of domestic and livestock wastewater (Chung et al., 2009). A well known example of AOP is Fenton's reaction. Four different dosing modes of Fenton's reagent were adopted by Ben et al. (2009) to examine the competitive effects of H_2O_2 and Fe^{2+} on antibiotic degradation efficiency. They reported that Sulfamethoxazole (SMX) was degraded rapidly in a batch dosing mode and other antibiotics, Sulfathiazole (STZ), Sulfamethizole (SML), Sulfadimethoxine (SDM), Sulfamethazine (SMN), and Tiamulin fumarate (TIA) degraded slowly in a continuous dosing mode. Ozone has been applied to remove antibiotics from municipal wastewater treatment plant effluents due to its high oxidation potential (Ikehata et al., 2006). Ben et al. (2012) evaluated the potential of ozone degradation method on antibiotics.

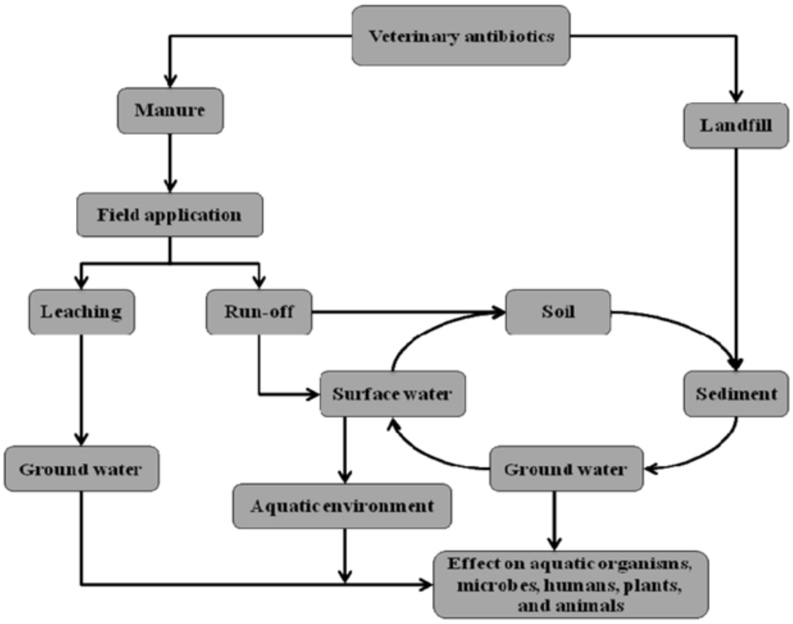
Biodegradation. Biodegradation of VAs can be achieved through various methods such as activated sludge systems, aerobic granules, bacteria, and fungi. Biodegradation of SMX, SMM, and SDM occurs within 36 h by activated sludge of wastewater treatment plant and results in reductions of 76, 81, and 70%, respectively (Yang et al., 2011). Membrane bioreactor-derived activated sludge has higher resistance and degrades 89% of TC (Prado et al., 2009). Compared to the activated sludge process, aerobic granules yield high biomass concentrations and sludge retention times, which are very important in biodegradation (Shi et al., 2011). Biodegradation of SMX is achieved by individual and consortia of bacteria such as *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Rhodococcus equi*, *Rhodococcus erythropolis*, *Rhodococcus rhodocrus*, and *Rhodococcus zopfii* (Larcher and Yargeau, 2011). Use of white rot fungi for antibiotic degradation was reported recently. The white rot fungus *Phanerochaete chrysoporium* is promising for degrading SMX (Rodarte-Morales et al., 2011). Degradation of SMZ by the white rot fungus *Trametes versicolor* has been assessed, and result showed that it eliminated other sulfonamides (Sulfapyridine and Sulfathiazole) antibiotics to near undetectable levels after 20 h in liquid medium when SMZ was added at 9 mg L^{-1}. Further experiments with purified laccase of *Trametes versicolor* and laccase-mediators resulted in almost complete removal of SMZ (García-Galán et al., 2011).

Effects on the ecosystem

Antimicrobial resistance. Prolonged bacterial exposure to inappropriate and low doses of antibiotics increases bacterial resistance and alters the microbial ecosystems of humans, animals, and the environment. Antibiotic resistance occurs when an antibiotic becomes impotent to effectively control or inhibit

Table 5 Timeline of antibiotic resistant bacteria

Year	Name of the antibiotics	Name of the resistant bacteria
1942	Penicillin	*Staphylococcus aureus*
1940-1950s	Chloramphenicol, Tetracycline, Erythromycin	*S. aureus*
Late 1970s	Methicillin	*S. aureus* (MRSA)
1997	Vancomycin	*Enterococcus*
2002	Vancomycin	*S. aureus* (VRSA)



Scheme 1 Possible pathways of veterinary antibiotics in the environment (Modified from Awad et al., 2010).

bacterial growth. When an antibiotic is used, bacteria with antibiotic resistance have a greater chance of survival than those that are susceptible. The current high level of antibiotic resistance is due to the overuse and abuse of antibiotics. Some bacteria are naturally resistant to certain types of antibiotics. However, bacteria may also become resistant by genetic mutation or by acquiring resistance from another bacterium. Antibiotic resistance vertically spreads through bacterial populations when new generations inherit antibiotic resistant genes and horizontally spreads when bacteria share or exchange genetic material with other bacteria. Horizontal gene transfer tcan even occur between different bacterial species. If a bacterium carries several resistant genes, it is called "multi-drug resistant" or informally a "superbug" or "super bacterium". The timeline of antibiotic resistance to bacteria is shown in Table 5. Higher use of VAs in livestock results in an increase in antibiotic resistance in bacteria. Consumption of antibiotic-resistant bacteria-contaminated meat, water, or vegetables grown on VA-contaminated soil may result in human illness that is difficult to treat or death. Hoa et al. (2011) examined SMX antibiotic-resistant bacteria in aquatic environments and identified 25 different genera of antibiotic-resistant bacteria. Among them *Acinetobacter* was the most abundant, followed by *Aeromonas*, *Bacillus*, and *Pseudoalteromonas*.

Phytotoxicity. VAs are generally released onto agricultural land as an organic fertilizer in the form of animal manure and biosolids (Jørgenson and Halling-Sørrenson, 2000; Díaz-Cruz et al., 2003; Golet et al., 2003; Göbel et al., 2005; Díaz-Cruz et al., 2006; Kemper, 2008). The growth and development of plants such as *Phaseolus vulgaris* L., *Glycine max*, *Medicago sativa*, *Zea mays*, and others are affected by some commonly used therapeutic agents. Studies conducted on soil suggest that phytotoxicity may differ from species to species and is greatly dependent on the sorption kinetics of the respective compound, soil organic matter, and soil pH. The presence of antibiotics could impact plant growth and development as well as soil microbial activity (Jjemba, 2002a; 2002b). The effects of chlortetracycline, tetracycline, tylosin, sulfamethoxazole, sulfamethazine, and trimethoprim on plant growth were studied by Liu et al. (2009), who reported that sulfamethoxazole, sulfamethoazine, and trimethoprim are toxic to growth of sweet oat, rice, and cucumber. Phytotoxicty of enrofloxacin to cucumber, lettuce, and radish were evaluated in a simulated laboratory environment. Toxic effects and homesis were observed on these plants at 50–5,000 μg L^{-1} enrofloxacin (Migliore et al., 2003). Other studies of CTC and OTC on *Phaseolus vulgaris* L (Batchelder, 1981; 1982), sulphadimethoxine on *Amaranthus retroflexus*, *Amaranthus retroflexus, Rumex acetosella*, *Panicum miliaceum, Zea mays,* and *Pisum sativum* (Migliore et al., 1995; 1997) as well as sulphamethoxine on *Amarantus retroflexus, Amarantus retroflexus, Zea mays, Rumex acetosella,* and *Rumex acetosella* (Migliore et al., 1998) have been found to exert antibiotic toxicity to plants.

Rhizosphere. The rhizosphere is the narrow zone of soil surrounding plant roots that is directly influenced by root secretions and associated soil microorganisms. This zone is about 1 mm wide and is an area of intense biological and chemical activities influenced by compounds exuded by the root and microorganisms (Hiltner, 1904). Soil chemistry and pH can influence the species mix and functions of microbes such as bacteria, actinomycetes, fungi, and protozoa in the rhizosphere (Yang and Crowley, 2000; Hertenberger et al., 2002). Continuous exposure to antibiotics through animal manure, soil pH, and chemistry may change and inhibit growth of microorganisms, thereby affecting soil enzyme activity. The microbial community structure and soil enzymatic activities of wheat rhizosphere soil exposed to different OTC concentrations are highly affected (Qingxiang et al., 2009; Jian-hua et al., 2010). Exposure to OTC inhibits the growth of *Bacillus* and therefore results in a decline in soil enzyme activity in the wheat rhizosphere (Qingxiang et al., 2009).

Conclusion

Due to insufficient availability of supportive information on VAs, research works should be initiated on VAs monitoring and their effects on environment. Novel eco-friendly removal techniques should be adopted for treating VAs in wastewater and agricultural fields due to the growing use of antibiotics. Many developed countries have banned or controlled the use of VAs for both therapeutic and nontherapeutic purposes, as they are serious environmental threats to all organisms. Strong regulations should also be constituted to control the usage of VAs in other nations. Worldwide attention should be given to controlling the use or banning of VAs for use other than therapeutic purposes.

Acknowledgments This research was supported by "Cooperative Research Program for Agriculture Science & Technology Development" Rural Development Administration, Republic of Korea.

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