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Review

A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment

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Abstract

Veterinary antibiotics (VAs) are widely used in many countries worldwide to treat disease and protect the health of animals. They are also incorporated into animal feed to improve growth rate and feed efficiency. As antibiotics are poorly adsorbed in the gut of the animals, the majority is excreted unchanged in faeces and urine. Given that land application of animal waste as a supplement to fertilizer is often a common practice in many countries, there is a growing international concern about the potential impact of antibiotic residues on the environment. Frequent use of antibiotics has also raised concerns about increased antibiotic resistance of microorganisms. We have attempted in this paper to summarize the latest information available in the literature on the use, sales, exposure pathways, environmental occurrence, fate and effects of veterinary antibiotics in animal agriculture. The review has focused on four important groups of antibiotics (tylosin, tetracycline, sulfonamides and, to a lesser extent, bacitracin) giving a background on their chemical nature, fate processes, occurrence, and effects on plants, soil organisms and bacterial community. Recognising the importance and the growing debate, the issue of antibiotic resistance due to the frequent use of antibiotics in food-producing animals is also briefly covered. The final section highlights some unresolved questions and presents a way forward on issues requiring urgent attention.

Keywords: Tylosin; Tetracycline; Sulfonamides; Partitioning coefficient; Biodegradation; Ecotoxicity

Contents

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1. Introduction

The use of veterinary pharmaceuticals has become integral to the growing animal food industry. For example, in the United States there are approximately 104–110 million cattle, 7.5–8.6 billion chickens, 60–92 million swine, and 275–292 million turkeys (AHI, 2002; NASS, 2002). The number of large animal-feeding operations (AFOs) in swine, poultry, and cattle increased significantly during the 1990s (USEPA, 2001). To maintain economic viability, large agribusinesses began contracting with individual farmers. This arrangement offered a guaranteed price to the farmer and a controlled and stable animal food-producing environment for the agribusiness. The close proximity of the large numbers of animals at these facilities and the potential for the rapid spread of disease has made routine use of pharmaceuticals necessary to maintain the viability of their operations.

A variety of drugs and feed additives are approved for use in food-animal agriculture (Bloom, 2004). Veterinary drugs and food additives fall into several pharmacological categories: anesthetic, antacid, anthelmintic, antihistimine, anti-infective, steroidal and non-steroidal anti-inflammatory, antibacterial, antimicrobial, antiparasitic, antiseptic, astringent, bronchodilator, diuretic, emetic, emulsifier, estrus synchronization, growth promotant, nutritional supplement, sedative, tranquilizer. Drugs are delivered to the animals through feed or water, by injection, implant, drench, paste, orally, topically, pour on, and bolus. The use and length of treatment and whether the drug is delivered to an individual animal, a herd or flock determine, in part, how a specific drug is delivered. Some of the important uses of veterinary pharmaceuticals are to treat and prevent infectious diseases (e.g. tetracycline, β-lactams antibiotics and steroid anti-inflammatories), manage reproductive processes (e.g. steroids, oxytocin, ergonovine, GnRH, HCG and prostaglandins, progesterone, and FSH) and production (e.g. bovine somatotropin; hormonal growth implants; ionophores; sub-therapeutic antibiotics), control parasites (e.g. dewormers, insecticides), and control non-infectious diseases (e.g. nutritional supplements; Rice and Straw, 1996).

Of the drugs approved for agriculture, antibiotics are among the most widely administered for animal health and management. The term 'antibiotic' is normally reserved for a diverse range of compounds, both natural and semi-synthetic, that possess antibacterial activity (Kanfer et al., 1998). Ever since the accidental discovery of penicillin by Alexander Fleming in 1928, hundreds of other antibiotics have appeared on the market and are available for use (1) in human and animals to treat diseases, (2) as growth promoters, and (3) to improve feed efficiency (Addison, 1984). Today, antibiotics play a major role in modern agriculture and livestock industries and their use has been on the rise in many developed nations. One of the major uses of antibiotics in recent years is to enhance growth and feed efficiency in healthy livestock (Levy, 1992). For example, consumption of antibiotics in 1997 in Denmark exceeded more than 150 000 kg, out of which >100 000 kg were used as growth promoters (Jensen, 2001), while there was an increase of nearly 80-fold in antibiotic usage for growth promotion within a span of four decades in the US (USA Today, 1998). A similar increase in antibiotic usage has been observed in several other countries (e.g. Australia, New Zealand, EU countries).

The worldwide increase in antibiotic resistant bacteria (Morris and Masterton, 2002) has led to social and scien-

tific concern that the over prescription and misuse of human prescribed antibiotics and the increased and widespread use of sub-therapeutic doses of antibiotics in agriculture are responsible for this trend (Smith et al., 2002). In the United States a large national program, the national antimicrobial resistance monitoring system (NARMS), exists to monitor the occurrence, and distribution of antibiotic resistant bacteria in food. However, only since the late 1990s has understanding of the environmental dissemination of antibiotic resistant bacteria and antibiotic residues from agricultural and human sources become an important area of research. The knowledge on the occurrence, fate and transport of antibiotic residues and antibiotic resistant bacteria is increasing. However, significant gap still exists in our understanding on the relationship between antibiotic residues, their metabolites and antibiotic resistant bacterial populations after their excretion.

Many antibiotics used in the animal food-producing industry are poorly adsorbed in the gut of the animal, resulting in as much as 30–90% of the parent compound being excreted (Elmund et al., 1971; Feinman and Matheson, 1978; Alcock et al., 1999). In addition, antibiotic metabolites can also be bioactive and can be transformed back to the parent compound after excretion (Langhammer, 1989). Thus, a significant percentage of the administered antibiotics may be excreted into the environment in active forms (Warman and Thomas, 1981; Berger et al., 1986). For example, the excreted sulfamethazine metabolite, glucoronide of *N*-4-acetylated sulfamethazine, is converted back to the parent form in liquid manure (Berger et al., 1986). After the antibiotic is administered, sulfamethazine undergoes conjugation with sugars present in the liver and thus inactivates the compound. After excretion, microbes can rapidly degrade the sugars, thereby allowing the compounds back to their bioactive forms (Renner, 2002). As most of the antibiotics are water-soluble, as much as 90% of one dose can be excreted in urine and up to 75% in animal feces (Halling-Sørensen, 2001). According to a recent study, sheep excrete nearly 21% of an oral dose of oxytetracycline, and young bulls excrete about 17–75% of chlortetracycline as the parent compound (Montforts, 1999). It is therefore likely that when animal wastes are applied as supplement to fertilizer they can find their way into the receiving environment and can be present either as metabolite or as the parent compound.

Antibiotics may be disseminated into the environment from both human and agricultural sources, including excretion, flushing of old and out-of-date prescriptions, medical waste, discharge from wastewater treatment facilities, leakage from septic systems and agricultural waste-storage structures. Other pathways for dissemination are via land application of human and agricultural waste, surface runoff and unsaturated zone transport. Once in the environment, like any other organic chemicals, their efficacy depends on their physio-chemical properties, prevailing climatic conditions, soil types and variety of other environmental factors. If antibiotics in the environment are not efficiently degraded, it is possible that these residues may assist in maintaining or developing antibiotic resistant microbial populations (Witte, 1998). Thus cyclic application of manure on the same location may result in the continuous exposure of soil microbes to antibiotic residues and antibiotic resistant populations of bacteria. This can potentially have deleterious effects in the environment, especially if the residues are transported by surface runoff or leaching through soil and reach nearby rivers or lakes.

While it is possible that antibiotics can find their way into the environment from a variety of sources, whether or not there are adverse effects to human, terrestrial and aquatic ecosystems is not well understood. Only in the last few years has the issue of pharmaceuticals in our environment emerged as an important research topic (Velagaleti, 1997; Halling-Sørensen et al., 1998; Montague, 1998; Ralloff, 1998; Daughton and Ternes, 1999; Hirsch et al., 1999; Jensen, 2001; Dietrich et al., 2002). Most studies since the mid to late 1990s have concentrated on the occurrence and distribution of human and veterinary pharmaceuticals in our environment. Because studies have shown these compounds are transported into surface water and ground water from urban and agricultural sources, researchers have begun to conduct effects based studies (e.g. Patten et al., 1980; Cole et al., 2000; Halling-Sørensen et al., 2002; Sengeløv et al., 2003a; Richards et al., 2004; Loftin et al., 2005). However, there is a paucity of data on the compounds fate and transport behavior in the soil–water environment.

Potential environmental risks posed by these compounds have led many countries (USA, Europe, and Canada) to regulate them in a way that environmental effects are minimized. In the USA, most assessments on environmental risk of veterinary antibiotics can be obtained from the US Food and Drug Administration web site (www.fda.gov/cvm/efoi/ea/ea.htm). Similarly, in the European Union, assessments have been required since 1990s (Boxall and Long, 2005). At the international level, a two-phase approach has been proposed by the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) initiative on environmental risk assessment of these products. VICH is a trilateral programme between EU, Japan and USA, however, countries such as Australia, Canada and New Zealand act only as observers.

This paper presents an overview of current use data on animal antibiotics worldwide, with particular emphasis on the fate and transport of four compounds (tylosin, tetracycline, sulfonamides and to a lesser extent, bacitracin) that are most commonly being used in animal husbandry in several parts of the world. Due to paucity of individual data on ecotoxicological effects of these compounds, we only present a general section covering the environmental effects of veterinary antibiotics. The purpose of this study is not an all-inclusive review, but an attempt to add new information to previously published information. To date, much of the published information available relates to the

occurrence and distribution of antibiotics (human as well as animals) in the aquatic environment (Halling-Sørensen et al., 1998; Kümmerer, 2001), although few recent reviews focused on sorption and other aspects of antibiotics in the environment (Tolls, 2001; Thiele-Bruhn, 2003). Recently, Boxall et al. (2004) presented an overview of veterinary medicines as a whole in the environment. In light of this and given that the last few years have produced a number of research publications, we feel it is time to collate information from the available literature and provide a wider perspective on the issue. The following aspects are covered in this study:

- The use pattern of antibiotics, their exposure pathways, environmental occurrence are discussed from the available literature data.
- Important physico-chemical properties of the selected group of antibiotics and the factors that govern their fate processes in soil–water system are discussed.
- Effects of veterinary antibiotics on the aquatic and soil organisms, bacterial community and plants are briefly discussed in context with the increasing antibiotic resistance from the continuous use of antibiotics in animal agriculture.
- The final section constitutes concluding remarks and some recommendations for future research.

2. Usage

2.1. The USA

In the United States information on the total annual production and use of pharmaceuticals including antibiotics is generally not available. Thus, estimates on the annual production and usage of antibiotics for human health and agriculture are controversial (Mellon et al., 2001; AHI, 2002). A recent report by Isaacson and Torrence (2002) based on a colloquium held by the American Academy of Microbiology in Santa Fe, New Mexico, outlined the confusion estimating the amount of antibiotics produced and changes in their usage.

Antibiotics are routinely used at therapeutic levels in livestock operations to treat disease and at sub-therapeutic levels (<0.2 g kg^{-1}) to increase feed efficiency and improve growth rate (Kiser, 1976; Cohen, 1998). According to the UCS (Union of Concerned Scientists), in their report Hogging it, of the estimated 16 million kg of antimicrobial compounds used annually in the US, approximately 70% are used for non-therapeutic purposes (UCS, 2001). Antibiotics used in animal feeding in the US have increased from nearly 91 000 kg in 1950 to 9.3 million kg in 1999 (AHI, 2002), which is a slight increase from the 1998 total of 8.1 million kg. Of the 9.3 million kg of antibiotics used, about 8 million kg were used for treatment and prevention of disease and only 1.3 million kg were used for improving feed efficiency and enhancing growth. This increase from 1998 to 1999 is largely attributed to greater use of ionophores and arsenicals, which increased 1.1 million kg from 1998 to 1999 (AHI, 2002). While arsenicals and ionophores are classes of pharmaceuticals not used in human medicines, there are some important pharmaceuticals that are used in both animal and human medicines. Fig. 1 shows the reported pharmaceuticals in the US in 1999 by the AHI. Table 1 summarizes the pharmaceuticals registered in the US for use in livestock for treatment and prevention of diseases as well as for growth promotion and increased feed efficiency.

A USDA survey (1996) indicated that about 93% of all grower/finisher pigs in the US received antibiotics in their diets at some time during the grower/finisher period. According to Swine'95 study (NAHMS, 1996), pork pro-

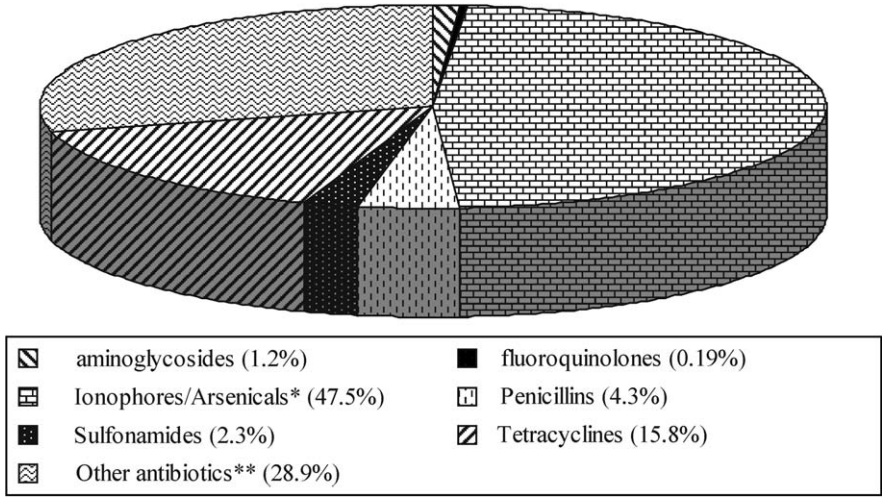


Fig. 1. Antibiotics use reported in millions of kilograms by AHI (Animal Health Institute) survey in 1999. Amounts shown in parentheses indicate percentages of total antibiotics (* denotes the antibiotics developed for animal production and not related to traditional antibiotics, ** includes cephalosporins, macrolides, lincosamides, polypeptides, streptogramins, and other minor compounds).

ducers used feed antibiotics much more commonly than antibiotics administered in water. They found that 91% of all operations used antibiotics in feed for disease prevention during the grower/finisher phase of production. Regionally, use of antibiotics in feed varied from 80.0% in the Southeast to 95.1% in the Midwest (Fig. 2). The three most frequently used antibiotics in swine productions identified in 1996 in the US were tylosin (30.4%), chlortetracycline (40%), and bacitracin (52.1%). These compounds were fed to swine for 2–2 $\frac{1}{2}$ months during their production cycle. The values in brackets in the preceding sentence indicate the percentages of producers using antibiotics for disease prevention in grower/finisher rations.

Table 1
Selected antibiotics approved for use in the US for use in livestock at therapeutic and at sub-therapeutic levels

Antibiotics	Disease prevention	Growth and feed efficiency	Type of animals
Amoxicillin[a,b]	Yes	No	Swine
Ampicillin[a,b]	Yes	No	Swine
Apramycin	Yes	No	Swine
Arsenilic acid	Yes	Yes	Swine, chicken, turkeys
Bacitracin	Yes	Yes	Swine, beef cattle, quail, pheasant, chicken, turkeys
Bambermycins	No	Yes	Swine, turkeys
Chlortetracycline	Yes	Yes	Swine, beef cattle, chicken
Efrotomycin	No	Yes	Swine
Erythromycin[c]	Yes	Yes	Swine, beef cattle, poultry
Gentamycin	Yes	No	Swine
Lincomycin	Yes	No	Swine, poultry
Neomycin	Yes	No	Swine, beef cattle
Oleandomycin	No	Yes	Swine, chicken, turkeys
Oxytetracycline	Yes	Yes	Swine
Monensin	No	Yes	Beef cattle
Penicillin	No	Yes	Swine, chicken, turkeys, quail, pheasant
Spectinomycin	Yes	No	Swine
Streptomycin	Yes	No	Swine
Tetracycline	Yes	Yes	Swine
Tiamulin	Yes	Yes	Swine
Tylosin	Yes	Yes	Swine, beef cattle, chicken
Arsanilate sodium	No	Yes	Swine
Carbadox	Yes	Yes	Swine, beef cattle
Roxarsone	Yes	No	Swine, chicken, turkeys
Sulfamethoxypyridazine[d]	Yes	No	Swine
Sulfachloropyidazine[d]	Yes	No	Swine
Sulfamethazine[d]	Yes	No	Swine
Sulfathiazole[d]	Yes	No	Swine
Virginiamycin	No	No	Swine

Source: NRC (1999) and Mellon et al. (2001).
[a] Only in combination with chlortetracycline and penicillin.
[b] Available by prescription only.
[c] In combination with arsanilic acid in poultry.
[d] Only administered in conjunction with chlortetracycline and tylosin.

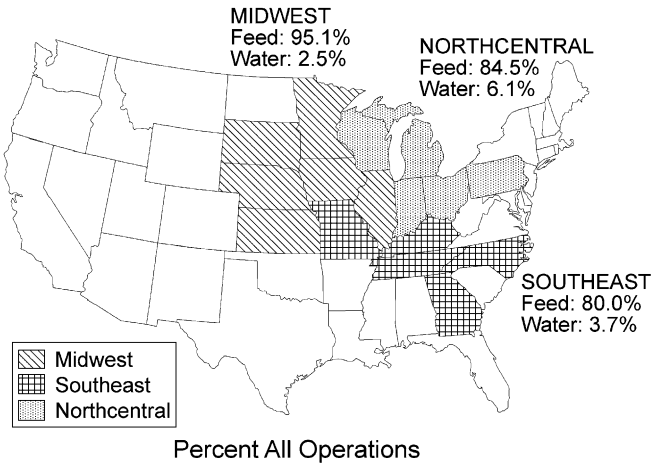


Fig. 2. Regional distribution of use of antibiotics in feed and water on a preventative basis for grower/finisher hogs. (*Source:* NAHMS, 1996.)

A 1998 survey conducted by the Animal Health Institute (AHI) reported there were 109 million cattle, 7.5 billion chickens, 92 million swine, and 292 million turkeys in the US (AHI, 2002) and a 2002 survey conducted by the National Agricultural Statistics Service (NASS) reported 104 million cattle, 8.6 billion chickens, 60 million swine, and 275 million turkeys in the US (NASS, 2002). The annual production of food-producing animals also leads to a large volume of agricultural waste. The USDA estimated that in 1997 meat-producing animals excreted approximately 1.4×10^3 billion kg of waste (Horrigan et al., 2002). A significant portion of food-producing animals in the US is raised in confined animal-feeding operations (CAFOs). CAFOs are livestock-raising operations, such as hog, cattle, dairy, and poultry farms, where animals are kept and raised in confined situations. Under the Clean Water act, CAFOs are defined as point sources of pollution and are therefore subject to National Pollutant Discharge Elimination System (NDPES) permit regulations. Under these regulations, CAFOs are defined as facilities with 1000 animal unit (AU). According to one report there are currently more than 6600 AFOs in the US that have >1000 animals and are classified as CAFOs (USDA, USEPA, 1998). In the case of matured hogs, the number is between 1250 and 2550, with each animal weighing nearly 25 kg in body weight under the EPAs two- and three-tier structures (Table 2). CAFOs are a rapidly growing sector of the US agricultural economy. An estimated 376 000 livestock operations confine animals in the US, generating approximately 128 billion pounds of manure each year (USEPA, 2000). CAFOs are the largest of these livestock operations and are regulated under the Clean Water Act. Given that the total production of antibiotics in the US now stands at more than 22 million kg annually, with about one-half being used for agriculture (Levy, 1998), and considering a significant fraction of animals are produced in CAFOs, the usage of antibiotics in CAFOs is in the order of millions of kilograms each year.

Table 2
USEPA proposed definition of CAFOs

Animal type	Two-tier structure	Three-tier structure	
	animals = 500 AU	animals = 1000 AU	animals = 300 AU
Beef cattle and heifers	500	1000	300
Veal cattle	500	1000	300
Dairy cattle (mature miled or dry)	350	700	200
Swine (≫55 lbs)	1250	2550	750
Immature swine (⩽55 lbs)	5000	10000	3000
Turkeys	27500	55000	16500
Chickens	50000	100000	30000
Horses	250	500	150
Sheep or lambs	5000	10000	3000
Ducks	2500	5000	1500

Source: USEPA (2000).

The majority of swine CAFOs and cattle feedlots store their liquid and solid waste in large lagoons or in concrete pits. The waste lagoons can cover several acres and hold millions of litres of liquid and solid manure. The majority of these operations depend on anaerobic digestion. In general, the liquid manure is pumped from the lagoons and applied to agricultural fields as fertilizer. In the US, most states now require that the lagoons are lined to prevent or minimize leakage and the levels of these waste-storage structures must also be maintained to ensure that the dams are not breached. Thus, there are times when manure may be applied that do not coincide with agricultural crop needs. In most poultry operations the litter is stored in piles to compost. The composted litter can be applied to fields at rates up to 3 tons per acre. The amount of time that the litter is composted is variable. Most of the animal waste from CAFOs is applied to fields within 10 miles of where the manure was generated. Thus, in many cases the degree of application exceeds the capacity of the soil with respect to nutrients (Kellogg et al., 2000). In addition the veterinary pharmaceuticals contained in the waste may be applied to soil, that has not fully processed the manure from the last application.

A report from the USDA (1996) indicates nearly 98% of swine operations with 300 or more hogs dispose manure on land owned or privately rented by the operation. The duration of conservation and subsequent field application standards depend on the national legislative regulations in the US. Most hog CAFOs use one of three waste handling systems: flush under slats, pit recharge, or deep under-house pits. Flush housing uses fresh water or recycled lagoon water to remove manure from sloped floor gutters or shallow pits. The flushed manure is stored in lagoons or tanks along with any precipitation or runoff that may come into contact with the manure. Flushing occurs several times a day. Pit recharge systems are shallow pits under slatted floors with 15–25 cm of pre-charge water. The liquid manure is pumped or gravity fed to a lagoon approximately once a week. Deep pit systems start with several centimetres of water, and the manure is stored under the house until it is pumped out for field application on the order of twice a year. Most large operations have 90–365 days storage, and the deep pit system uses less water, creating slurry that has higher nutrient concentrations than the liquid manure systems. This type of slurry system is more common in Midwestern states and the cooler climates in the US (USEPA, 2000). Given an estimate of 100000 million kg of feces and urine being produced annually by the 60 million hogs raised in the US (Meadows, 1999), and given the land application of animal waste as a source of fertilizer in agricultural sector is a common practice, occurrence of antibiotic residues in streams, lakes or other aquatic environment is not unlikely.

2.2. The UK/European Union (EU)

In the UK, certain classes of antibiotics are incorporated into the feed of animals in order to improve their growth rates. According to the Veterinary Medicine Directorate (VMD, 2001), the antibiotics are sold as prescription-only medicines (POMs), general sales list medicines (GSL) and pharmacy and merchant list medicines (PMLs). Table 3 summarizes the amounts of individual antimicrobial active substances sold in the UK through veterinary wholesalers for use as growth promoters or veterinary medicines. Tetracyclines are the most widely used antibacterial compounds, followed by sulfonamides, β-lactams, macrolides, aminoglycosides, fluoroquinolones and others. Sulfonamides are

Table 3
Usage of antimicrobial active substances sold in the UK in 2000

Therapeutic class	Active substance	Usage (kg)
Tetracyclines	Oxytetracycline	8495
	Chlortetracycline	6256
	Tetracycline	1517
Sulfonamides	Sulfadiazine	14224
	Sulfadimidine	4933
	Formosulphathiazole	859
	Sulfadoxine	545
β-lactams	Amoxicillin	17432
	Procaine penicillin	7223
	Procaine benzylpenicillin	2811
	Clavulanic acid	2194
	Ampicillin	1487
	Benzatine penicillin	1363
	Cloxacillin	1324
	Cephalexin	1310
	Benzylpenicillin	1273
	Phenoxylethylpenicillin	834
Aminoglycosides	Dihydrostreptomycin	5978
	Neomycin	1079
	Apramycin	466
Macrolides	Tylosin	5144
Fluoroquinolone	Enrofloxacin	799
2,4-Diaminopyrimidine	Trimethoprim	2955
Pleuromutilin derivatives	Tiamulin	1435
Lincosamides	Lincomycin	721
	Clyndamycin	688

Data source: IMS Health.

the second most widely used veterinary antibiotics in the UK, accounting for nearly 21% of total sales (Ungemach, 2000). From 1993 to 1998, sales of antimicrobial growth promoters in the UK remained largely static. However, after 1998 there was a 69% decrease in sales, and at present, out of 448 000 kg of antimicrobials, 28 000 kg are used as growth promoters in animals. Although usage data on individual antimicrobial compounds used as growth promoters in the UK are limited, according to International Medicinal Statistics (IMS), 7.5 kg of monensin was used in 2000. It is likely that this number is an underestimate of the total sales of growth promoters, as most of the products are classified as zootechnical feed additive or pharmacy and merchant only list medicine (EA, 2001). Other compounds identified as potentially major use growth promoters in the UK include flavophospolipol and salinomycin sodium.

The use of antibiotics as growth promoters in the European Union is subject to Directive 70/524/EEC, covering additives in feeding stuffs and also includes a requirement that at the level permitted in animal feed does not adversely affect human, animal health, or the receiving environment (EU Directive 70/524/EEC, 1970). Total amounts of antibiotics used for animal health in EU member states are available from respective national authorities. While usage data have been made available only in Sweden, Denmark and Finland and to a lesser extent – the Netherlands, little or no information on usage and trends of antibiotics sales is available from countries such as Austria, Belgium, France, Germany, Greece, Ireland, Italy, Luxemburg, Portugal, Spain and the UK (EMEA, 1999). Table 4 shows the usage of antibiotics as growth promoters in number of animal species in the European Union. Antibiotics together with other compounds (anthelmintics or parasiticides) are the most important groups of veterinary pharmaceuticals, both with a market volume of more than 200 million Euros alone in 1999 (Tolls, 2001). It has been reported that of the total usage of 5 million kg of antibiotics, 3.5 million kg are used for therapeutic purposes (Kay and Boxall, 2000), while the remaining 1.5 million kg are used as feed additive for growth promotion (Alder et al., 2000).

Sweden, the first to ban the use of antimicrobial growth promoters in 1986, claimed numbers of antibiotic resistant bacteria remained lower than its neighbours and other countries during the period 1986–1995 (Wierup, 2001). Following the bans on growth promoters by Sweden in 1986, Denmark banned the use of avoparcin as growth promoter in 1995. In the following years, virginiamycin, tylosin, bacitracin, spiramycin, carbadox and olaquindox were banned as growth promoters in the EU. Following the official ban on the growth promoter virginiamycin in January 1998 by the EU, the Danish food-animal industries decided to voluntarily discontinue all further use of antimicrobial growth promoters in broilers, slaughter pigs and cattle in February and March 1998 (DANMAP, 2000). This resulted in a dramatic decrease in antibiotic use and by 2000, the use of growth promoters in Danish food animals was nil (Table 5). The report of the DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Program) is available in English at www.svs.dk/uk/Organization/Frm_org.htm. Germany also banned the use of avoparcin as growth promoters in animals in 1996. According to a recent report published in the American Association of Swine Veterinarian's electronic newsletter in December 2005, the use of all growth promoters in pigs will be banned in the EU from 1st January 2006 (Burch, 2006). These growth promoters include avilamycin, flavophospholipol and the ionophores monensin for cattle and salinomycin for pigs in addition to previously banned growth promoters.

2.3. Australia

Before 2000, a number of antimicrobials, including arsenicals, glycopeptides (avoparcin), macrolides, ionophores, polypeptides, quinoxalines, streptogramins (virginiyamycin), and others, were registered in Australia as growth promoters and made available for over-the-counter sale to livestock owners, feed millers, and feed mixtures. However, after the report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR, 1999), the Australian Government accepted recommendations to review the use of growth promoters on animals. Glycopeptides were withdrawn voluntarily from the market in June 2000. The Government also recognized that curtailment of antimicrobial use in agriculture could result in economic consequences and international trade implications. Current antibiotics registered for use as growth promoters in animal industries across Australia are shown in Table 4. Because of the strict Australian regulatory system for veterinary antibiotics, fluoroquinolone or amphenicol classes of antibiotics, colistin or gentamicin (aminoglycoside) have not been registered in food-producing animals. Unlike many countries where cephalosporin antibiotics have been used for the last two decades, in Australia such antibiotics were registered in the mid-1990s. Another antibiotic carbadox, a qunioxaline derivative, was prohibited for use in animals in Australia because of its carcinogenicity. However, like Canada, there are no available data on the quantities of various growth promoters used in animals in Australia.

2.4. New Zealand

Unlike many overseas countries, New Zealand raises its large population of ruminant animals on pasture with the exception of the intensively housed fed poultry and pig industries, where antibiotics are used in feed (Sarmah, 2003). Overall, in New Zealand, animals account for about 57% of nearly 93 000 kg of antibiotics use. About 34% of these antibiotics are ionophores, which have quite a distinct mode of action from other groups. Without the inclusion of ionophores, total use of antibiotics in animals account about 47% out of the remaining 75 000 kg. The amount of non-ionophore antibiotics used as growth pro-

Table 4
Animal antibiotics registered for use as growth promoters/feed efficiency in Australia, Denmark, European Union (EU), Canada and the USA

Countries	Group	Antibiotic	Usage
Australia	Arsenicals	3-Nitro-arsonic acid	Pigs, poultry
	Glycopeptides	Avoparcin	Pigs, meat poultry, cattle
	Macrolides	Kitasamycin	Pigs
		Oleandomycin	Cattle
		Tylosin	Pigs
	Polyethers (ionophores)	Lasalocid	Cattle
		Monensin (data available)	Cattle
		Narasin	Cattle
		Salinomycin	Pigs, cattle
	Polypeptides	Bacitracin	Meat poultry
	Quinoxalines	Olaquindox (data available)	Pigs
	Streptogramins	Virginiamycin	Pigs, meat poultry
	Others	Flavophospholiphol or Bambermycin	Pigs, poultry, cattle
European Union (EU)[b]	Glycopeptides	Avoparcin	Banned, 1997
	Macrolides	Tylosin[a]	Pigs
		Spiramycin[a]	Turkeys, chickens, calves, lambs and pigs
	Oligosaccharides	Avilamycin	Pigs, chickens, turkeys
	Polyethers (ionophores)	Monensin	Cattle (fattening)
		Salinomycin	Pigs
	Polypeptides	Bacitracin[a]	Turkeys, laying hens, chickens (fattening), calves, lambs, pigs
	Streptogramins	Virginiamycin[a]	Turkeys, laying hens, cattle (fattening), calves, sows, pigs
	Others	Flavophospholipol or Bambermycin	Laying hens, turkeys, other poultry, calves, pigs, rabbits, cattle (fattening)
Canada	Aminoglycosides	Neomycin	Cattle
	Lincosamides	Lincomycin hydrochloride	Breeder
	Macrolides	Erythromycin	Breeder, broiler
		Tylosin	Sheep
	Penicillins	Penicillin G	Chicken (broiler, breeder)
		Potassium	Turkey
		Penicillin G procaine	Chicken, turkey, sheep
	Tetracyclines	Chlortetracycline	Chicken (breeder, layer)
		Oxytetracycline	Turkey, swine, cattle, sheep
	Sulfonamides	Sulfamethazine	Swine, cattle
	Ionophores	Lasolocid sodium	Cattle
		Monensin	Cattle
		Narasin	Swine
		Salinomycin sodium	Swine, cattle
	Polypeptides	Bacitracin	Chicken, swine, turkey, chicken
	Glycolipids	Bambermycin	Breeder, turkey
	Quinoxalines	Carbadox	Swine
	Others	Arsanilic acid	Broiler, turkey, swine
USA	Arsenical	Arsenilic acid	Poultry[c]
		Roxarsone, cabarsone	Poultry
	Polypeptides	Bacitracin	Cattle, swine, poultry
	Glycolipids	Bambermycins	Swine, poultry
	Tetracyclines	Tetracycline	Swine
		Chlortetracycline	Cattle, swine, poultry
		Oxytetracycline	Cattle, swine
	Elfamycine	Efrotomycin	Swine
	Macrolides	Erythromycin	Cattle
		Oleandomycin	Chicken, turkey
		Tylosin	Cattle, swine, chicken
		Tiamulin	Swine
		Lincomycin	Swine
	Ionophores	Monensin	Cattle
		Lasalocid	Cattle
	Penicillins	Penicillin	Poultry
		Arsanilic acid	Poultry
	Quinoxalines	Carbadox	Swine
		Virginiamycin	Swine

Table 4 (*continued*)

Countries	Group	Antibiotic	Usage
	Sulfonamides	Sulfamethazine[d]	Cattle, swine
		Sulfathiazole[d]	Swine

Sources: NRA (1998), Prescott and Baggott (1995), Health Canada (2002), and Mellon et al. (2001).
[a] Use banned from 1 January 1999.
[b] Under EC directive 70/24/EEC, 1998.
[c] Include chicken, turkey, quail, pheasant.
[d] Used with chlortetracycline and penicillin.

Table 5
Usage of antimicrobial growth promoters (kg active compound) in Denmark

Antibiotic group	Growth promoter	1990	1992	1994	1996	1998	1999	2000
Bacitracin	Bacitracin	3983	5657	13689	8399	3945	63	0
Flavofospholipol	Flavomycin	494	1299	77	18	6	665	0
Glycopeptide	Avoparcin	13718	17210	24117	0	0	0	0
Ionophore	Monensin	2381	3700	4755	4741	935	0	0
	Salinomycin	–	–	213	759	113	0	0
Macrolides	Spiramycin	12	–	95	15	0.3	0	0
	Tylosin	42632	26980	37111	68350	13148	1827	0
Oligosaccharides	Avilamycin	10	853	433	2740	7	91	0
Quinoxalines	Carbadox	850		10012	1985	1803	293	0
	Olaquindox	11391		22483	13486	28445	9344	0
	Virginiamycin	3837	15537	2801	5055	892	0	0
Total		79308	99650	115786	105548	49294	12283	0

Source: DANMAP (2000).

moters and prophylaxis accounts for the 24% of the total 75000 kg. Of that 24%, nearly 69% is used for growth promotion, the remainder for prophylaxis (Table 6). Because of the large-scale pastoral farming for the ruminant animals in New Zealand, only 6% of the non-ionophore antibiotics are used in feed for growth promotion and prophylaxis. Other animals, such as pig and poultry, account for 19% and 74% of the use, respectively. Table 6 shows that sheep, beef cattle and deer are not given significant quantities of feed that might otherwise contain growth promotants. Pigs receive by far the greater amount of antibiotics. Data collected from the recent survey by the Agricultural Chemicals and Veterinary Medicine Group (MAF, 1999) show the percentages of each of these antibiotics out of total portion in Fig. 3. Because of number of mergers and takeovers in the veterinary pharmaceutical industry in New Zealand, some products have been discontinued or re-marketed and this survey may therefore not give a true picture of the survey results. At this point, a number of antibiotics are under review in New Zealand.

2.5. Africa

Data on the consumption of antibiotics by food-producing animals in African countries are lacking. However, Mitema et al. (2001) assessed antimicrobial consumption in Kenya by collating data between 1995 and 1999 from the official record of the Pharmacy and Poisons Board of

Table 6
Use of orally administered antibiotics (kg/year) in New Zealand

Group	Growth promotion			Prophylaxis			Total
	Cattle	Pigs	Poultry	Cattle	Pigs	Poultry	
Ionophores	4708	–	–	9391	–	3933	18032
Polypeptides	183	1390	9270	62	–	–	10905
Macrolides	–	442	–	–	1312	2904	4658
Glycopeptides	–	–	–	–	–	1060	1060
Streptogramins	851	–	40	–	–	–	891
Tetracyclines	–	–	–	–	–	218	218
Total	5742	1832	9310	9453		7897	35764
Less ionophores	1034	1832	9310	62		3964	17732

Source: MAF (1999).

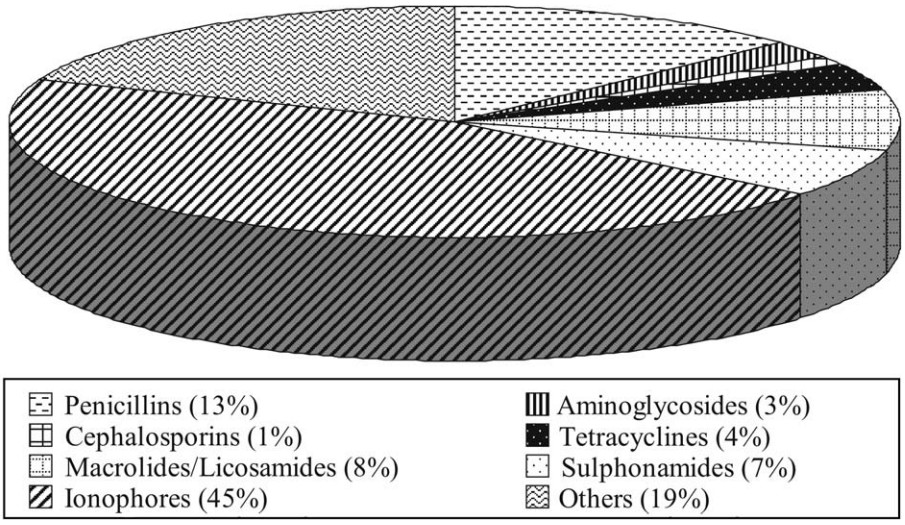


Fig. 3. Total antibiotic sales (kg) for agricultural industries in New Zealand. Amounts shown in parentheses indicate percentages of total antibiotics in the year 2000. (*Source:* ACVM Group Survey, MAF, 2001, New Zealand.)

the Ministry of Health (Table 7). Their study revealed that approximately 14 600 kg of active antimicrobials are used in animal food production in Kenya, of which, tetracyclines and sulfonamides + trimethoprim account for nearly 78% of the use (56% and 22%, respectively). The authors further concluded that no antibiotics were used as growth promoters in Kenya, although speculation suggests some soluble tetracyclines and sulfonamides soluble powders or solutions are used as growth promoters. In other African countries such as the United Republic of Tanzania and Uganda, veterinary antimicrobials are easily accessible and under low levels of control from government authorities (WHO, 2001).

2.6. Other countries

Sales and/or use data of veterinary antibiotics from other countries are currently lacking in the public domain. The situation on the use of antimicrobials as growth promoters in Canada is broadly similar to the US. Food-animal production in Canada is a large, diverse and dynamic industry. Table 4 shows the list of currently registered antibiotic compounds for use as growth promoters in different animal species in Canada (Health Canada, 2002). However, there are no comprehensive estimates of antimicrobial consumption in animal production for Canada.

The use of antibiotics in food-producing animals as growth promoters in Japan is prohibited and currently no antibiotics are registered for such use. However, antibiotics are permitted for use as a component of feed additives but only after Ministerial approval (JETACAR, 1999).

In China, the use of antibiotics in animal feeds has been regulated since 1989 and only non-medicated antibiotics are permitted as feed additives. The antibiotics that are currently registered for use in China include monensin, salinomycin, destomycin, bacitracin, colistin, kitasamycin, enramycin and virginiamycin. However, other antibiotics such as tetracyclines are also used (Jin, 1997).

In Russia, the use of antibiotics in feed is restricted mainly to non-medical drugs such as bacitracin, grizin, flavomycin and virginiamycinaics which are registered for use (Panin et al., 1997). According to a report by WHO

Table 7
Quantities (kg) of active substance of antimicrobial drugs per antimicrobial class administered in food-producing animals in Kenya during 1995–1999

Antimicrobial class	Year					Total	Mean
	1995	1996	1997	1998	1999		
Aminoglycosides	308.63	752.13	462.42	2421.52	843.88	4788.50	957.7
β-lactams	352.9	572.86	480.65	1921.90	1195.45	4523.78	904.72
Tetracyclines	3664.41	15889.35	9215.98	7782.45	3324.75	39876.91	7975.38
Nitrofurans	5244.80	1155.00	55.0	660.00	385.00	7499.80	149.96
Quniolones	25.08	7.70	6.28	177.57	252.14	468.78	93.76
Sulfonamides	6876.65	499.00	605.00	934.78	6604.40	15519.83	3103.96
Macrolides	0.00	165.00	0.00	7.79	0.00	172.79	34.56
Others (tiamulin)	24.75	69.30	23.76	0.00	0.00	117.81	23.56
Total	16497.22	19110.34	10849.09	13906.01	12605.62	72968.28	14593.66

Source: Mitema et al. (2001).

(2001), in many developing countries such as India, Thailand, Indonesia, there is a lack of control with antimicrobial use in animals intended for food and therefore there is no data available at all on the types of VAs and amounts used in various food-producing animals.

2.7. Critical comments

To date, available information on VAs use and sales trends in the US, European countries and elsewhere is poor and incomplete as there has never been systematic collection of data based on a standard procedure. Only recently have a few EU member states (the Scandinavian countries and Netherlands) started to collect data on the use of antibiotics. In the US, controversy and debate still exist about the use of VAs in animal agriculture, as discussed in the preceding sections (Isaacson and Torrence, 2002). In addition, no countries have data on the consumption of VAs per body weight of different types of animals, and this is a bottleneck to overall estimation of use data for VAs in animal agriculture. As far as a global trend in the usage and sales is concerned, no clear picture is seen because of the non-availability of information in many countries and the differences in the collection system for the VAs. It is only within the EU member states, albeit in Scandinavian countries and the Netherlands, where information on such trends over time is available (EMEA, 1999). However, this trend does not reflect the whole European community and difficult to draw proper conclusions about the actual volumes of antibiotics or different classes of antibiotics used in these countries.

3. Pathways and occurrence in the environment

Veterinary antibiotics can enter the environment through manufacturing plants, process effluents, disposal of unused or expired compounds, overland flow runoff, unsaturated zone transport from fields to which agricultural waste has been applied, and through leaky waste-storage structures (Fig. 4). The importance of the individual pathways of these compounds into the environment varies and depends primarily on the waste storage, manure field application practices and the type of antibiotic used.

Over the last decade concerns have been raised about the possibility of excreted wastes from animals getting into the environment once such wastes are spread as manure supplement in agricultural field. It has been reported that in some cases, as much as 80% of the antibiotics administered orally to livestock, pass through the animal unchanged into bacteria-rich waste lagoons and is then spread on agricultural field as a source of fertilizer (USEPA, 2000). Thus residues of the antibiotics, antibiotic resistant bacteria and R-plasmids may be readily available for transport into surface and groundwater through leaching and overland flow runoff (UCS, 2001; Jongbloed and Lenis, 1998).

The amounts of antibiotics excreted vary with the type of antibiotic, the dosage level, as well as the type and the age of the animal (Katz, 1980). Excretion amounts of as high as 95% back into the environment in active forms has also been reported (Elmund et al., 1971; Magnussen et al., 1991; Beconi-Barker et al., 1996). For instance, chlortetracycline fed to cattle at 70 mg head^{-1} day^{-1} as a

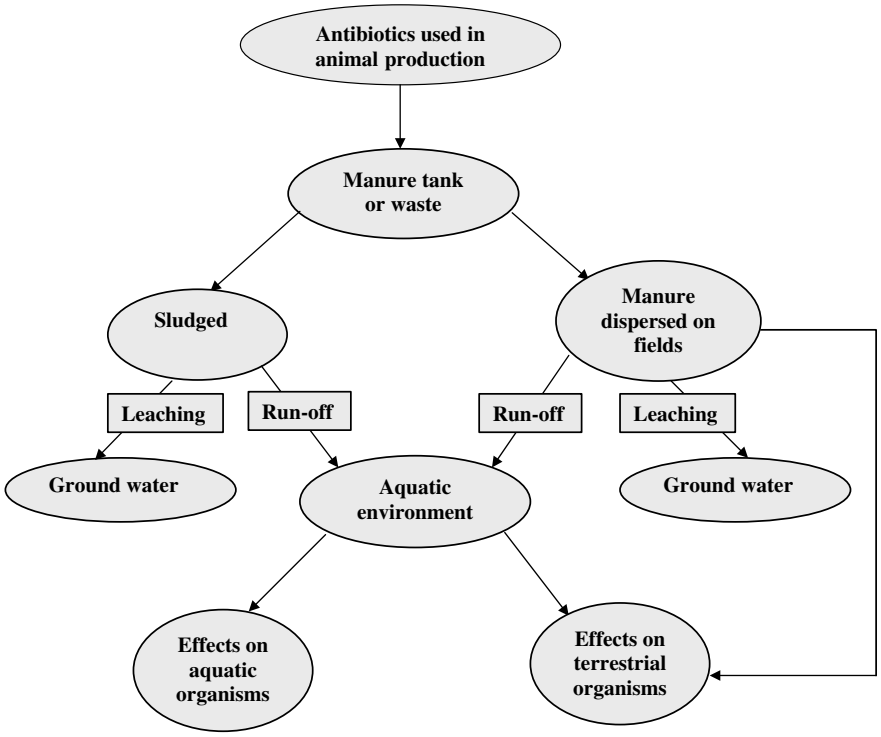


Fig. 4. Anticipated exposure pathways for veterinary antibiotics in the environment.

growth promoter and for the treatment of enteritis and leptospirosis, showed up in fresh manure at 14 μg g^{-1} (Elmund et al., 1971). Excreta containing urine and/or faeces can contain the unchanged product and its metabolites that eventually end up in a waste lagoon, where they are stored and applied to the field as an organic matter supplement or fertilizer. Thus, antibiotics and their daughter products are directly exposed to the environment and can eventually be transported to the nearby streams, lakes or other aquatic bodies or leach downward through the soil during rainfall.

Studies on the occurrence, fate, and transport of pharmaceutical compounds in the environment are of comparatively recent origin and a number of these compounds have been detected in sewage effluents and surface waters, as well as in drinking water (Heberer and Stan, 1997; Halling-Sørensen et al., 1998; Ternes, 1998; Hirsch et al., 1999; Stumpf et al., 1999; Kolpin et al., 2002; McArdell et al., 2003). Though majority of these studies reported the occurrence of human pharmaceuticals, there are instances where animal antibiotics have been found in surface and groundwaters, and in marine sediments, and these are discussed below.

3.1. Surface waters

The first reported case of surface water contamination by antibiotics was in England more than two decades ago, when Watts et al. (1982) detected at least one compound from the macrolide, sulfonamide, and tetracycline group of antibiotics in river water at concentrations of 1 μg l^{-1}. Following this, a variety of other antibiotics were also detected in surface water in concentrations up to 1 μg l^{-1} (e.g. Richardson and Bowron, 1985; Pearson and Inglis, 1993; Ternes, 1998; Hirsch et al., 1999). For example, a German group detected residues of chloramphenicol in one sewage treatment plant effluent and one small river in southern Germany at concentrations of 0.56 and 0.06 μg l^{-1} respectively (Hirsch et al., 1999). Chloramphenicol is used to treat human in extremely rare cases such as severe meningitis, and its veterinary use in the European Community has been banned since 1995. The occurrence of this compound has been linked to its sporadic use in some fattening farms (BGVV, 1996).

Veterinary antibiotics have also been measured in groundwater, sediments, slurry/manure, as well as in soil biota (e.g. Hamscher et al., 2000, 2001; Meyer et al., 2000, 2003; Campagnolo et al., 2002; Kolpin et al., 2002; Yang and Carlson, 2003), and in dust originating from a pig-fattening farm in Germany (Hamscher et al., 2003). Meyer et al. (2003) found that chlortetracycline (total), sulfamethazine, and lincomycin were the most frequently detected antibiotics, respectively, in liquid waste at hog and poultry AFOs, from six states in the US. In this study, the estimated concentrations of individual antibiotic compounds from the hog-lagoon waste ranged from <1 to more than 1000 μg l^{-1}. In the vicinity of the hog CAFOs in Iowa, one or more antibiotic compound (chlortetracycline, oxytetracycline, lincomycin, sulfamethazine, trimethoprim, sulfadimethoxine, and the dehydrated metabolite of erythromycin) were detected in four groundwater samples, 1 of 2 tile-drain inlets, and 3 of 4 tile-drain outlets. Antibiotics such as tylosin, oleandomycin and spiramycine have also been found in the river waters of Italy (Zuccato et al., 2000). Elsewhere, Alder et al. (2001) detected sulfamethazine and other groups of antibiotics used in veterinary medicine in Swiss surface waters, and attributed these residues to runoff from land-applied manure.

More recently, the USGS reported the occurrence of 21 antibiotic compounds in samples collected from 139 streams across a number of US sites. Of these, large proportions were antibiotics used in animals as growth promoters, such as tylosin, tetracyclines, sulfonamides and carbadox. The frequency of detection was highest for sulfonamides and lincomycin, followed by tylosin. The concentrations of the individual compounds detected in this study were generally less than 1.0 μg l^{-1}. Only a few of the 95 compounds measured in this study have drinking water guidelines and drinking water health advisory levels.

3.2. Groundwater and marine sediments

The occurrence of veterinary antibiotics in groundwater has also been reported (Holm et al., 1995; Hirsch et al., 1999; Hamscher et al., 2000). Although most antibiotics detected in groundwaters were from use in agricultural areas with a large number of fat stock farms or sewage irrigation fields, they did not exceed the limit of quantitation (0.02–0.05 μg l^{-1}; Hirsch et al., 1999). However, residues of sulfonamide antibiotics were detected in four samples collected from an agricultural area, with two samples showing sulfamethazine at concentrations of 0.08 and 0.16 μg l^{-1}. The authors attributed the finding of these compounds in the groundwater to veterinary applications as the compounds are not used for human medicines. In a separate study carried out elsewhere in Germany, Hamscher et al. (2000) reported chlortetracycline, oxytetracycline, tetracycline and tylosin at the limit of detection of 0.1–0.3 μg l^{-1} in soil water samples collected from agricultural land. Multiple classes of antimicrobial compounds (tetracycline, macrolide, β-lactam, sulfonamide) were also detected in and groundwater samples collected in nearby swine farms in the US (Campagnolo et al., 2002). Furthermore, residual oxytetracycline at concentrations ranging from 500 to 4000 μg kg^{-1}were observed in marine sediment following chemotherapy treatment in fish farms in the US (Capone et al., 1996).

3.3. Dung, manure and agricultural soils

The intracorporal administration of antibiotics inevitably leads to residual concentrations in excrements (Thiele-Bruhn, 2003). It is therefore not surprising to find residues of antibiotics either as metabolite or parent

compound in dung, manure and subsequently in agricultural fields (Patten et al., 1980; Hamscher et al., 2002; Höper et al., 2002). For instance, from a field study where soil had been fertilized with liquid manure, Hamscher et al. (2002) reported the presence of 4.0 and 0.1 mg kg^{-1} of TC and CTC in liquid manure, while in the soil samples the concentrations of these compounds varied from an average 86.2 μg kg^{-1} in the top soil (0–10 cm) to as high as 171.7 μg kg^{-1} in the 20–30-cm layer. When data from Hamscher et al. (2002) were plotted (Fig. 5), an apparent increase in the concentration of TC and CTC was observed with depth, especially in the last sampling period. A possible explanation of higher concentrations at greater depths has been attributed to the additional release of bound residues in the form of 4-epi-tetracycline (4-epi TC), a metabolite of TC, and the authors concluded that 4-epi TC is transferred from the liquid manure into the soil (Hamscher et al., 2002). TCs are known to degrade abiotically in pharmaceutical solutions (discussed later) depending on pH, redox and light conditions (Clive, 1968), and degradation products such as 4-epi TCs are formed, albeit only at few percent relative to the parent compound (Mitscher, 1978). It is also conceivable that variation in microorganism population, density, and types, as well as the existing pH and redox potential, can also greatly influence the persistency of TCs in soil; this area therefore warrants further investigation before we can elucidate the mechanisms surrounding the persistency of these compounds in the natural environment. A recent survey of the occurrence of various TCs and sulfamethazine (sulfonamide group) in sandy soils fertilized with liquid manure was carried out in northwestern Germany by Pawelzick et al. (2004). The reported maximum concentrations for the compounds screened in this study were 27 μg kg^{-1} (OTC), 443 μg kg^{-1} (TC), 93 μg kg^{-1} (CTC), and 4.5 μg kg^{-1} (sulfamethazine) in the top 0–30-cm soil. At least 3 of the 14 total agricultural fields used in this study had higher than EMEA (European Agency for the Evaluation of Medicinal products) trigger values of 100 μg kg^{-1} for TCs (Pawelzick et al., 2004). Elsewhere in Germany, Winckler and Grafe (2000) also found TCs to persist in agricultural soils at concentrations of 450–900 μg kg^{-1}. In contrast to some of these findings, an early study by Runsey et al. (1977) could not detect any residue of antibiotics in manure applied to pasture and soil, probably due to non-availability of proper analytical methods at that period.

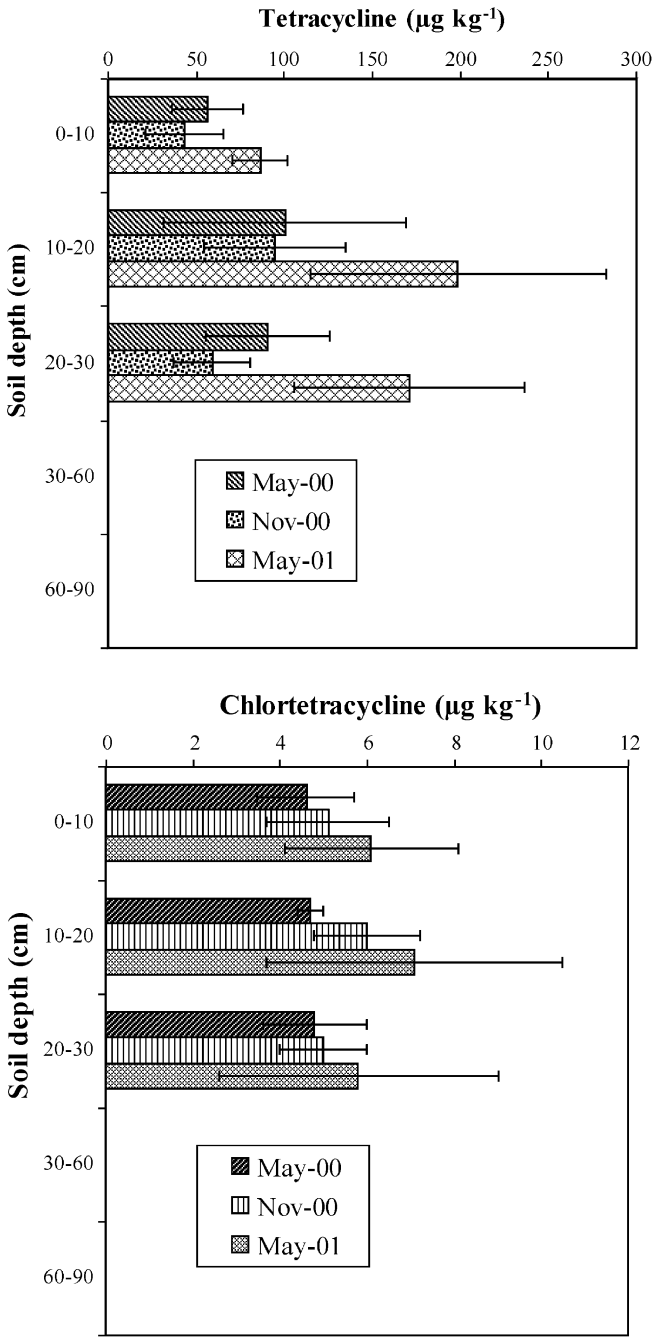


Fig. 5. Concentration of tetracycline residues as a function of depth under field conditions. (*Data source:* Hamscher et al., 2002.)

Nevertheless, the foregoing sections reveal that a growing number of studies worldwide provide evidence of the presence of numbers of VAs in animal wastes, surface and ground waters, river sediments and in soils at concentrations that could have potential impacts on the ecosystems. While most of the studies represent a single survey of the samples, it is conceivable that contamination due to the application of manure to the land and subsequent degradation is a cyclic event as new quantities of antibiotics are continually released. In view of this, understanding the fate and transport mechanism of these compounds in soil–water system is of utmost importance.

4. Fate and transport

Although it has been more than five decades since the first use of antibiotics in feedlots, (Addison, 1984), scientific research in this area is still in its infancy. Most of the work on this aspect, to date, has been done in the UK and other European countries, primarily Denmark and Germany. Important information on the fate and behavior of antibiotics in soils and water is lacking.

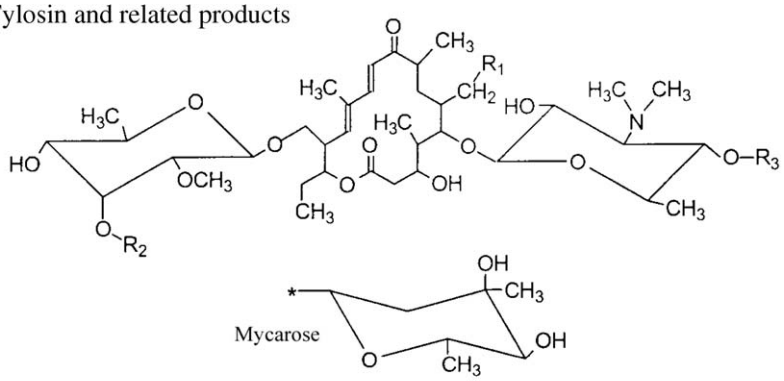
On release via urine and faeces into the environment, antibiotics disperse through a variety of transport mechanisms. A number of physical and chemical processes are responsible for the antibiotics moving through the feedlot or the open pasture into the environment; sorption, leaching and degradation being the three important processes in the soil–water systems. These processes are driven by the physico-chemical properties of the antibiotics, such as their molecular structure, size, shape, solubility, speciation, and hydrophobicity. Before discussing their fate and transport in the environment, the basic chemistry of these compounds should be understood. While VAs can be classified into several categories, it is beyond the scope of this paper to address the chemistry behind each of them. We therefore focus on only on the few selected groups of antibiotics (Fig. 6) most commonly used in animal industries worldwide.

4.1. Chemistry of selected VAs

4.1.1. Tylosin

Tylosin (Fig. 6a) falls within the macrolide group of antibiotics, and is a broad-spectrum antibiotic with a good antibacterial activity against most pathogenic organism such as gram-positive bacterium, some gram-negative bacterium, vibrio, spirochete, coccidian etc. (McGuire et al., 1961). It consists of a substituted 16-membered lactone ring, an amino sugar (mycaminose), two neutral sugars (mycinose and mycarose), and is produced by fermentation of streptomyces strains (McGuire et al., 1961). Tylosin consists of a mixture of the macrolides Tylosin A, Tylosin B (desmycosin), Tylosin C (macrocin), and Tylosin D (relomycin), all of which contribute to the potency of the antibiotic. Apart from these other minor constituents, it includes lactenocin (TL), 5-0-mycaminosyltylonolide (OMT), and desmycinosyl tylosin (DMT). Mycaminose is present in all the related substances and is attached to the lactone ring at position 5 via a β-glycosidic linkage. TA, TC and TD all contain mycinose, attached at position 14 of the ring, and mycarose, which is attached at position 4 of the mycaminose moiety, also via glycosidic linkages. The remaining related substances contain either one or neither of these two sugars. About 80–90% of the parent compound is composed of Tylosin A (Horie et al., 1998; European Pharmacopoeia, 1999). Tylosin is unstable in

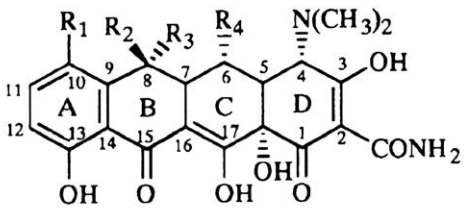
(a) Tylosin and related products



	Tylosin A	Tylosin B	Tylosin C	Tylosin D
R_1	-CHO	-CHO	-CHO	$-CH_2OH$
R_2	$-CH_3$	$-CH_3$	-H	$-CH_3$
R_3	-Mycarose	-H	-Mycarose	-Mycarose

(b) Tetracyclines

Tetracyclines



	R_1	R_2	R_3	R_4
Tetracycline (TC)	H	CH_3	OH	H
Chlortetracycline (CTC)	Cl	CH_3	OH	H
Oxytetracyline (OTC)	H	CH_3	OH	OH

Fig. 6. Molecular structure of some antibiotics commonly used in animal husbandry.

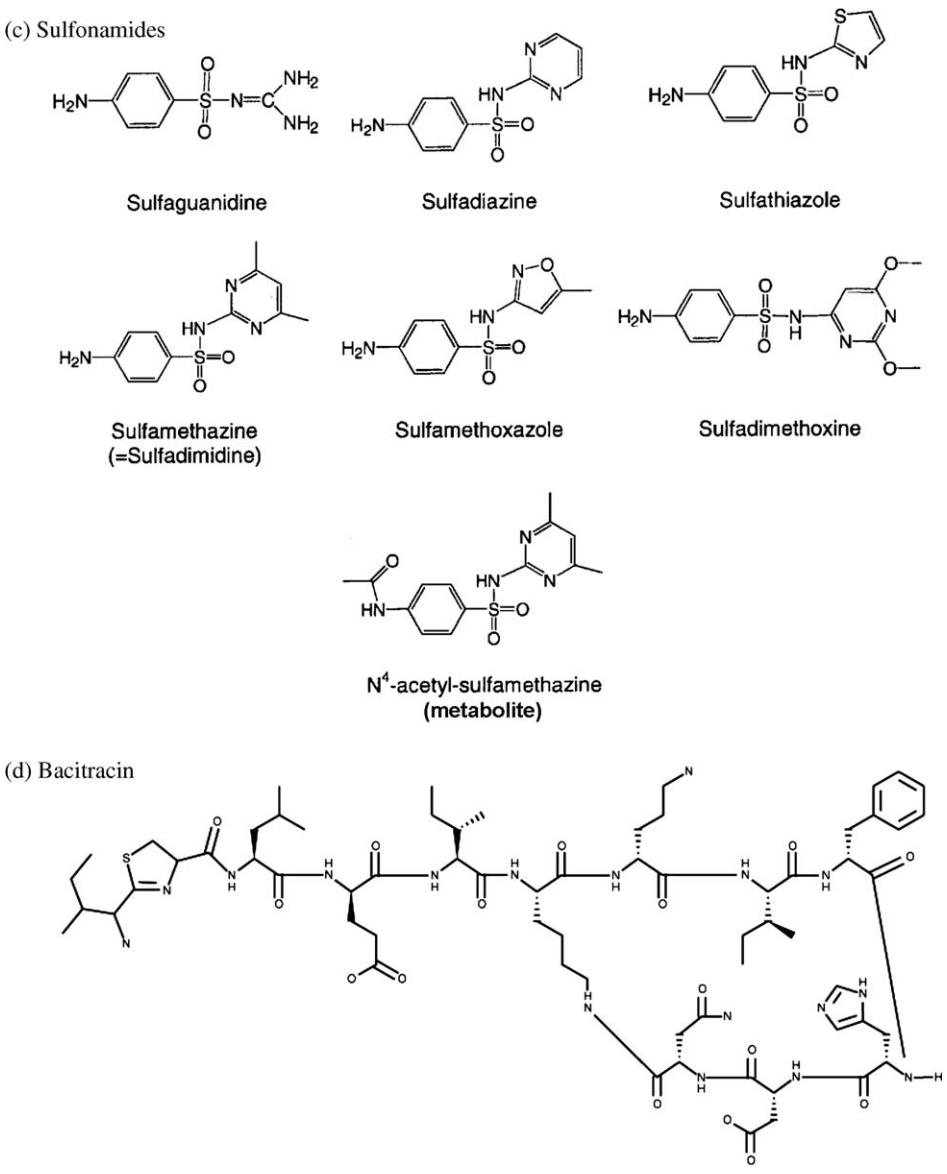


Fig. 6 (*continued*)

acidic and alkaline media and relatively stable under neutral pH conditions (pH 7). The solubility of most of the macrolide group of antibiotics is high and has been found to increase with an increase in solvent polarity (Wilson, 1981; Salvatore and Katz, 1993).

4.1.2. Tetracyclines

The tetracyclines (TCs) are broad-spectrum antibacterials widely used in veterinary medicine. They are active against a range of organisms such as Myco-plasma and Chlamydia, as well as a number of gram-positive and gram-negative bacteria. Tetracycline (TC), oxytetracycline (OTC) and chlortetracyclines (CTC) are widely used in animal feeds to maintain health and improve growth efficiency in many countries. These chemicals are characterized by a partially conjugated four-ring structure with a carboxyamide functional group (Mitscher, 1978). The molecule of tetracycline has several ionizable functional groups of a rather unusual type, and the charge of the molecule depends on the solution pH (Fig. 6b). An examination of their pK_a values (Table 8) suggests that TC, OTC and CTC have similar pH dependent speciation, which is also consistent with their structural relationship. Therefore, assigning pK_as in any one of the antibiotics, a similar relationship can be assumed for the other two (Stephens et al., 1956). There are three distinct acidic functional groups for tetracycline: tricarbonyl methane (pK_a 3.3); dimethyl ammonium cation (pK_a 9.6); and the phenolic diketone (pK_a 7.7). However, for conventional designation of the functional group, one should consider only the neutral form, i.e. the basic dimethyl ammonium cation (Sassman, pers. comm.). The multiple ionizable functional groups present in TCs suggest that at environmentally relevant pH values, they may exist as a cation (+ 0 0), zwitterion

Table 8
Selected examples of commonly used veterinary antibiotics in animal agriculture and their important physical/chemical properties

Group	Antibiotic (s)	pK_a, 25 °C	pK_b, 25 °C	Solubility[a] (mg l^{-1})	Vapour pressure[a] (Torr)	Henry's law constant[a] (Pa m^3 mol^{-1})	Proton acceptors	Proton donors	Log K_{ow}	MW (g mol^{-1})
Aminoglycosides	Neomycin	12.9	9.52	na	na	8.5×10^{-12}–4.1×10^{-8}	19	19	−3.70	614.6
	Streptomycin	na	na	na	na		na	na	na	581.6
	Kanamycin	7.2	na	na	na		na	na	na	484.5
β-lactams	Penicillins G	2.62	na	22–10 100	1.69E−18	2.5×10^{-19}–1.2×10^{-12}	6	2	1.67	334.4
	Ampicillin	2.61	na		1.21E−19		na	na	1.35	349.4
	Ceftiofur	2.62	na		na		na	na	0.54	523.6
Macrolides	Tylosin	13	7.37	5000	na	7.8×10^{-36}–2.0×10^{-26}	18	5	3.41	917.1
	Tilmicosin	13.16	9.81	566 000	na		15	4	5.09	869.1
	Erythromycin	8.8	na	na	na		na	na	na	733.9
	Oleandomycin	7.7	na	na	na		na	na	na	785.9
Sulfonamides	Sulfamethoxine	6.69	1.48	340	1.05E−11	1.32×10^{-12}	7	3	0.42	310.3
	Sulfamethazine	7.45	2.79	1500	3.64E−11	na	6	3	0.80	278.3
	Sulfanilamide	10.6	1.9	7500	na	1.52×10^{-8}	na	na	−0.62	172.2
	Sulfadimidine	7.6	2.8	1500	na	3.09×10^{-11}	na	na	0.89	278.3
	Sulfadiazine	6.4	1.6	77	na	1.6×10^{-8}	na	na	−0.09	250.3
	Sulfapyridine	8.4	2.9	270	na	1.09×10^{-11}	na	na	0.35	249.3
Tetracyclines	Chlortetracycline	4.5	9.26	600	1.57E−28	1.7×10^{-23}–4.8×10^{-22}	10	7		478.9
	Oxytetracycline	4.5	9.68	1000	6.27E−30		11	8		460.4
	Tetracycline	3.3–9.6	na	1700	na		na	na		444.4
Lincosamides	Lincomycin	12.9	8.78	900	1.85E−19	na	8	5	0.86	406.5
Fluoroquinolones	Enrofloxacin	2.74	7.11	130 000	2.10E−13	5.2×10^{-17}–3.2×10^{-8}	6	1	2.53	359.4
	Danofloxacin	2.73	9.13	na	8.41E−14		6	1	1.85	357.4
	Sarafloxacin	6.0	na	100	na		na	na	na	385.4
	Oxolinic acid	6.9	na	4	na		na	na	na	261.2

pK_a = acidity constant; pK_b = basicity constant; Log K_{ow} = octanol–water partition coefficient; MW = molecular weight.
Source: CAS (2004), Thiele-Bruhn (2003), and Hirsch et al. (1999).
[a] When individual values are not available, a range is given for the compound group.

(+ − 0), or as a net negatively charged ion (+ − −) (Figueroa et al., 2004; Sassman and Lee, 2005). Therefore, it can be envisaged from these ionization schemes that in the pH regime of environmental interest (pH 4–8), the antibiotics would be dominated by the zwitterionic species and would reach maximum concentration at pH 5.5. TCs are relatively stable in acidic media, but not in alkaline conditions, and form salts in both media (Halling-Sørensen et al., 2002). They have been found to form complexes with chelating agents such as divalent metal ions and β-diketones and strongly bind to proteins and silanol groups (Oka et al., 2000). In general, these compounds are sparingly soluble in water (Florence and Attwood, 1981); however, solubility of the corresponding hydrochlorides is reported to be much greater (Thiele-Bruhn, 2003).

4.1.3. Sulfonamides

The sulfonamides (Fig. 6c) are synthetic bacteriostatic antibiotics with a wide spectrum against most gram-positive and many gram-negative organisms. Sulfonamides inhibit multiplication of bacteria by acting as competitive inhibitors of *p*-aminobenzoic acid in the folic acid metabolism cycle (O'Neil et al., 2001). The sulfonamides consist of a benzene ring, an amine moiety (–NH_2), and a sulfonamide group (–SO_2NH_2). The amine and sulfonamide groups must be para to one another for the sulfonamide to possess antibacterial properties (Hardman et al., 2001; Beleh, 2003). Sulfonamides are often discussed as if they were a homogeneous group of compounds. Although this may be reasonable for their antimicrobial activity, it is not true for their pharmacokinetics. The main veterinary compounds within this group are sulfadiazine-trimethoprim, sulfadimethoxine, sulfamethazine, sulfathiazole and sulfadimethoxine-ormetoprim (Beville, 1988). However, there are others that have been used in the livestock include sulfamethoxazole and sulfachloropyridazine. Although the sulfonamides are amphoteric, they generally function as weak acids at physiologic pH range. They are therefore usually seen as sodium salts that have increased solubility as pH increases. The solubility of sulfonamides can range in the order of 0.1–8 g l^{-1} and is compound specific within this group (Halling-Sørensen, pers. comm.). The pK_a values of various derivatives range from 5.4 for sulfacetamide to 10.4 for sulfanilamide. Most sulfonamides used for veterinary purposes have at least two nitrogen functions (Fig. 6c), with the amide attached to the sulfur referred to as N^1 and deprotonated at pH > 5.5–7. The amine attached to the aromatic cycle is referred to as N^4 and is protonated at pH 2.5. For this reason, most sulfonamides are positively charged under acidic condi-

tions, neutral between pH 2.5 and 6 (approx.), and negatively charged at alkaline conditions (Haller et al., 2002).

4.1.4. Bacitracin

Bacitracin (BC) is part of the peptide group of antibiotics (Fig. 6d) and one of the most commonly used antibiotics in the world as an animal feed additive. BC consists of more than 20 components with different antimicrobial activities, of which BC-A and BC-B are the main components, while the main degradation product BC-F possesses no antimicrobial activity (Oka et al., 1989). While the compound is highly soluble in water, in solution it looses its antibacterial activity at room temperature. Historically, because of commercial requirements to institute economic recovery operations, a bacitracin base for animal feed use has been superceded by two relatively water-soluble forms: bacitracin methylene disalicylate (BMD) and bacitracin zinc. Solubility of BMD and bacitracin zinc is 50 and 5.1 mg ml^{-1} respectively, though at lower pHs (3–4), BMD is as insoluble as the zinc salt (Weiss et al., 1957). As these peptides possess high molecular weights and are typically ionic, they are expected to exhibit infitesimally low vapour pressures over the temperature range at which they are stable. The values of dissociation constant (pK_a) for this group of compounds are not available in the literature. However, given their low stability constant, bacitracin zinc would be expected to dissociate into zinc ions and free bacitracin under environmental conditions (Craig et al., 1969). Similarly, BMD is expected to dissociate into methylene disalicylic acid and bacitracin.

4.2. Sorption of VAs by soils and clay minerals

Given the variation in the chemical nature of these antibiotics, their sorption mechanism onto soil or other environmental matrices is likely to be different. Tolls (2001) presented a critical analysis of sorption mechanism of few selected groups of VAs. Our focus in this section is to present an overview and, where available, add new information to existing literature data.

A literature search revealed that earlier sorption studies reported antibiotic sorption as % release of the compound by soils or at best the amounts adsorbed per gram of soil (Siminoff and Gottileb, 1951; Gottileb et al., 1952; Martin and Gottileb, 1952; Pinck et al., 1961a,b). It is only in the last decade that efforts have been made to measure partitioning coefficient (K_d) values for certain VAs in soils (Yeager and Halley, 1990; Rabølle and Spiild, 2000; Thiele, 2000; Boxall et al., 2002; Sassman et al., 2003; Thiele-Bruhn et al., 2004) and clay minerals (Figueroa et al., 2004; Kim et al., 2004; Kulshrestha et al., 2004).

Veterinary antibiotics react in varying degrees to form complexes with clay minerals montmorillonite, vermiculite, illite, and kaolinite (Pinck et al., 1961a,b). Both bacitracin and chlortetracycline have been shown to be unstable in the presence of alkaline clays, while oxytetracycline is found to be stable (Pinck et al., 1961a,b). The low values of adsorption of bacitracin by vermiculite and illite have been attributed to the anionic behavior resulting from the clay alkalinity at pH range of 7.9–8.2. Bacitracin being a neutral substance (Johnson et al., 1945; Robinson, 1952) as well as a polypeptide may exist as a dipolar molecule, like many other amino acids (Pinck et al., 1961a). In acid solution it can act like a cation, while under basic solution it acts like an anion and this is why probably only 8 mg of the compound is being sorbed by the Orella soil compared with >300 mg by the non-basic montmorillonite clays in earlier studies of Pinck et al. (1961a,b). The low adsorption capacity of illite and kaolinite for other basic antibiotics such as tylosin has been also observed (Ghosal and Mukherjee, 1970; Bewick, 1979). This is mainly due to the non-expanding lattice in these clays with the consequent restriction of cation exchange to the outer surfaces of the clay particles (Bewick, 1979). On the other hand, bentonite and montmorillonite have an expanding lattice, resulting in greater exchange capacity compared with illite and kaolinite (Hillel, 1980).

Sithole and Guy (1987a) studied the interactions of tetracycline with model clay adsorbents as a function of suspension pH, ionic strength, and adsorbate concentration using Na, Ca, and dodecyltrimethylammonium forms (C_{12}-TMA) of bentonite and a tannic acid covered bentonite. The purpose of using C_{12}-TMA was to reduce the surface area accessible to TC. Their study showed that the adsorption isotherms followed a Langmuir type, suggesting the occurrence of sorption at limited number of sites. The resultant adsorption capacity decreased and followed an order of tannic acid-clay > Ca-clay > Na-clay > dodecyltrimethylammonium-clay, with tannic acid-clay having maximum adsorptive capacity at pH 4.6–6.0. The authors postulated three mechanisms based on the interaction of each form of clay used in the study: an interaction between TC and clay due to the ion exchange between the clay surface and the protonated amine group of the TC; complexation reactions between the divalent cations on the clay and TC; and a mechanism where there is interaction between TC with the exposed Al ions on the edges of clay. It has been however, argued that hydrophobic interactions are not effective in counteracting the effect of the reduced surface area as done by Sithole and Guy (1987a) in their sorption studies, and therefore mechanisms such as cation exchange, cation bridging at clay surfaces, surface complexation, and hydrogen bonding are also likely to be involved in sorption of TCs by soils (Tolls, 2001). Under pH regime of environmental interest (pH 4–8), these antibiotics have zwitterionic behavior with increasing net negative charge above pH 6 (Colaizzi and Klink, 1969). Therefore, strong adsorption through the ion exchange process would be expected to occur only if solution pH is less than the pK_a value of the compound, where most of the basic groups are protonated and the molecule is positively charged. For TC, this form predominated below pH 3.3 (Colaizzi and Klink,

1969). In contrast, recent studies have shown that the surface acidity of clays can also be responsible to cause sorption by cation exchange well above the pK_a (Figueroa et al., 2004; Sassman and Lee, 2005). Study by Sithole and Guy (1987b) showed that adsorption of tetracycline onto humic acid and peat followed the Freundlich model (Sithole and Guy, 1987b), suggesting the adsorption of tetracycline onto organic matter-rich soil or manure would depend on the pH and ionic strength of the suspension, with greater sorption occurring mainly within the pH range of 4.0–7.0, a range within the pH regime of environmental interest. From their study, Sithole and Guy (1987a,b) suggested that because of the hydrophobic interaction of tetracycline with bentonite clays, there was less sorption, and the interaction between the molecules of tetracycline and the divalent cations at the clay surface dominated the sorption process.

More recently, Kulshrestha et al. (2004) investigated the interaction of OTC with model clay sorbents and postulated that at lower pH values, when OTC has a net positive charge, they tend to have greater sorption affinity with cation exchange as the dominant mechanism. On the other hand, the opposite is true when OTC molecules are present in zwitterionic form (pH 5.0), and hydrophobic mechanism prevails over other mechanisms. Elsewhere, Figueroa and Mackay (2005) showed that for OTC, there is a general trend of cation plus zwitterionic species interaction with soil or sediment clay components. Furthermore, the authors suggest that antibiotic sorption interactions with clays are controlled by the ionic functional groups of the base compound structure within an antibiotic class, although there may be only little influence of other non-ionic substituents on the base structure. Further insight to the mechanisms of TC sorption by soil and its constituents was recently provided by Sassman and Lee (2005), who investigated the sorption of three TCs (TC, OTC, and CTC) in several soils varying in pH, CEC, AEC, clay content and type, and OC content under various background electrolyte concentrations. They conclude that although several processes may influence the sorption of TCs, batch studies and empirical modelling supported their hypothesis that pH and CEC play an important role in TC sorption. A study by Jones et al. (2005) demonstrated poor correlation between %OC and OTC sorption on 30 soils, presumably due to the fact that the authors used CEC values that were measured at pH 7, and not at the isotherm pH (Sassman and Lee, 2005). Given that TCs exist in an environmentally relevant pH regime as cations, zwitterions, and anions, predicting sorption and transport of this group of antibiotics can be often complicated and difficult. Clearly, much research is therefore warranted before we fully understand the over-riding mechanisms responsible for their ultimate fate in the environment.

Efrotomycin, a fermentation product isolated from *Nocardia lactamdurans* (formerly *Streptomyces lactamdurans*), is a member of kirromycin family of antibiotics, which, apart from its therapeutic use, is often used as a growth promoter in swine (Maehr et al., 1980). From a sorption study, Yeager and Halley (1990) showed that efrotomycin was highly sorbed in four soils having a pH range of 5.0–7.5. The estimated partitioning coefficient (K_d) for efrotomycin ranged from 8 to 290 l kg^{-1} in the four soils used in the study. However, the authors reported there was no single correlation ($p < 0.05$) between K_d and any of the soil parameters such as pH, % organic matter, cation exchange capacity (CEC), and the % silt, clay and sand. In contrast, an earlier study by Tate et al. (1989) showed that organic matter and clay fractions have strong influence on the sorption of efrotomycin.

Rabølle and Spiild (2000) reported a laboratory sorption study on four VAs (metronidazole, olaquindox, oxytetracycline and tylosin) using four Danish soils. These antibiotics were commonly used as growth promoters in swine production in Denmark (although they have subsequently been banned there); some are still being used, however, in many other countries including US. The study showed that the partitioning coefficients (K_d) for metronidazole and olaquindox ranged from 0.54 to 1.67 ml g^{-1}, while that of oxytetracycline and tylosin were a few orders of magnitude higher (Table 9). None of the soil properties showed positive correlation with the estimated partitioning coefficients for the compounds, although there appeared to be some correlation for tylosin. The non-linear trend of the isotherms were clear from the reported N values, and it was more prominent for tylosin data, as the values of K_d and K_f (Freundlich's coefficient) in all four soils were several orders of magnitude difference. The authors attributed this to their inability to measure the K_d values with sufficient accuracy, citing stronger sorption affinity for tylosin molecules to the soils. Elsewhere, Sassman et al. (2003) reported similarly high values for tylosin and tylosin A-aldol on several US soils (Table 10), with respective isotherms exhibiting strong non-linearity (N 0.27–0.65 for tylosin A and 0.52–0.75 for tylosin A-aldol). However, there was good positive correlation between the measured partitioning coefficients and OC, CEC and clay content of soils. The authors postulated that likely mechanisms for tylosin and its metabolite could involve cation exchange, hydrophobic partitioning and hydrogen bonding.

Boxall et al. (2002) investigated the sorption behavior of sulfonamide antibiotics in UK soils and soil/manure mixtures in order to assess the likely potential for these compounds to pollute surface and groundwaters. Sorption coefficients (K_d) for sulfachloropyridazine ranged from 0.9 to 1.8 l kg^{-1} for sandy loam and clay loam soils respectively, suggesting that the compound would be highly mobile in the environment. Elsewhere, a similar range of K_d values (4.9 and 0.6–3.2 l kg^{-1}) was also reported for sulfathiazole (Thurman and Lindsey, 2000) and sulfamethazine (Langhammer, 1989). More recently, Thiele-Bruhn et al. (2004) studied sorption of a range of sulfonamide antibiotics in whole soils and particle-size fractions in two topsoils (fertilized and unfertilized) from Germany. The authors reported K_f values to range from 0.5 to

Table 9
Available literature values for partitioning coefficients of selected VAs in various environmental matrices

Compound (s)	Matrices	pH	OC (%)	K_d (l kg^{-1})	K_{oc} (l kg^{-1})	References
Sulfachloropyridazine	Clay loam, sandy loam	6.5–6.8	NR	0.9–1.8		Boxall et al. (2002)
Sulfadimidine	Sand, loamy sand, sandy loam	5.2–6.9	0.9–2.3	0.9–3.5	80–170	Langhammer and Buening-Pfaue (1989)
Sulfamethazine	Sand, loamy sand, sandy loam	5.2–6.9	0.9–2.3	0.6–3.2	82–208	Langhammer (1989)
Sulfapyridine	Silty loam	6.9–7.0	1.6–2.4	1.6–7.4	101–308	Thiele (2000)
Sulfanilamide	Whole soil, clay, sand fraction	6.7–7.0	1.6–4.4	1.5–1.7	34–106	Thiele-Bruhn et al. (2004)
Sulfadimidine	Whole soil, clay, sand fraction	6.7–7.0	1.6–4.4	2.4–2.7	61.0–150	Thiele-Bruhn et al. (2004)
Sulfadiazine	Whole soil, clay, sand fraction	6.7–7.0	1.6–4.4	1.4–2.8	37–125	Thiele-Bruhn et al. (2004)
Sulfadimethoxine	Whole soil, clay, sand fraction	6.7–7.0	1.6–4.4	2.3–4.6	89–144	Thiele-Bruhn et al. (2004)
Sulfapyridine	Whole soil, clay, sand fraction	6.7–7.0	1.6–4.4	3.1–3.5	80–218	Thiele-Bruhn et al. (2004)
Sulfathiazole	Topeka clay loam	NR	1.0	0.6	NR	Thurman and Lindsey (2000)
Tylosin	Loamy sand, sand	5.6–6.3	1.1–1.6	8.3–128	553–7990	Rabølle and Spiild (2000)
	Silty clay, clay, sand	5.5–7.4	0.4–2.9	5.4–6690	1350–95532	Sassman et al. (2003)
Tylosin A-aldol	Silty clay, clay, sand	5.5–7.4	0.4–2.9	516–7740	1290–266896	Sassman et al. (2003)
Tylosin	Pig manure	NR	NR	45.5/270	110	Loke et al. (2002)
Tylosin	Clay loam, sandy loam	NR	2.2–4.4	66–92	NR	Gupta et al. (2003)
	Pig manure	9.0[a]	0.13–0.16	38.6–107.5	241–831	Kolz et al. (2005a)
Oxytetracycline	Loamy sand, sand	5.6–6.3	1.1–1.6	417–1026	42506–93317	Rabølle and Spiild (2000)
	Pig manure	NR	NR	83.2/77.6	195	Loke et al. (2002)
	Marine sediment	NR	NR	663, 2590	NR	Smith and Samuelsen (1996)
Tetracycline	Clay loam	NR	1.0	>400	NR	Thurman and Lindsey (2000)
Tetracycline	Clay loam, sandy loam	NR	2.2–4.4	1147–2370	NR	Gupta et al. (2003)
Chlortetracycline	Clay loam, sandy loam	NR		1280–2386		Gupta et al. (2003)
Olaquindox	Pig manure	NR	NR	20.4/9.8	50	Loke et al. (2002)
	Loamy sand, sand	5.6–6.3	1.1–1.6	0.69–1.7	46–116	Rabølle and Spiild (2000)
Efrotomycin	Loam, silt loam, sandy loam, clay loam	5.0–7.5	1.1–4.6	8.3–290	580–11000	Yeager and Halley (1990)
Ciprofloxacin	Sewage sludge	6.5	37	417	1127	Halling-Sørensen (2000)
	Loamy sand	5.3	0.7	427	61000	Nowara et al. (1997)
Enrofloxacin	Clay, loam, loamy sand	4.9–7.5	0.73–1.63	260–5612	16510–99980	Nowara et al. (1997)
Metronidazole	Loamy sand, sand	5.6–6.3	1.1–1.6	0.54–0.67	39–56	Rabølle and Spiild (2000)
Fenbendazole	Silty loam	6.9–7.0	1.6–2.4	0.84–0.91	35–57	Thiele-Bruhn and Leinweber (2000)

NR = not reported; K_d = soil partition coefficient; K_{oc} = organic carbon normalized partition coefficient.
[a] pH values were after sorption experiment.

6.5 l kg^{-1} among the compounds studied, with strong sorption non-linearity ($N = 0.31$–0.76), presumably due to interaction of polar organic compounds with different functional group of soil organic matter and sorption to mineral surfaces (Chiou et al., 2000). The concept of assuming organic carbon normalization employed in sorption studies of organic compounds is an old paradigm and recent work has suggested that the K_{oc} concept attributing linear sorption solely due to hydrophobic partitioning to soil organic matter may not be suitable for VAs (Tolls, 2001; Thiele-Bruhn et al., 2004). However, more work is needed on this aspect.

It is noteworthy that in most of the earlier studies, K_d estimation was done from sorbed antibiotic concentrations through the difference between initial and equilibrium solution concentrations. This can often lead to an overestimation of sorption if loss from solution is due to processes other than sorption, such as biotic/abiotic degradation and/or volatilization. In view of this, K_d determination from sorption isotherm constructed by extraction method (e.g. Thiele-Bruhn et al., 2004; Sassman and Lee, 2005) would help eliminate these effects and not bias results. Most sorption studies also reveal that although the majority of the antibiotics used in animal production are strongly sorbed to soil and clay particles (Table 9), whether they may still be biologically active and can influence the selection of antibiotic resistant bacteria in the terrestrial environment are some areas where future research should be directed (Chander et al., 2005).

4.3. Transport of VAs in soil

While the literature is replete with published information on the mobility of pesticides as well as inorganic compounds in the environment, there is a paucity of data on transport characteristics of VAs in general. It is only in the last few years that studies have begun to emerge in the scientific literature (Rabølle and Spiild, 2000; Boxall et al., 2002; Kay et al., 2004). Rabølle and Spiild (2000) conducted packed soil column studies under saturated steady-state conditions and the relative mobility of four antibiotics was determined using the LC-MS technique. Most of the antibiotics remained in the top few centimetres of the soil column, indicating the high sorptive affinity of these compounds for the soils used; the order of mobility for the compounds followed metronidazole > olaquindox > tylosin > oxytetracycline. The study demonstrated that the risk of soil water/groundwater quality

Table 10
Available literature values (HL = half-life) for degradation of veterinary antibiotics in various environmental matrices

Compound (s)	Matrices	Temperature (°C)	% Degraded	Time (days)	References
Tetracycline	Pig manure (ventilated, non-ventilated)		50	4.5–9	Kühne et al. (2000)
	Water (ventilated, non-ventilated)		50	15–30	Kühne et al. (2000)
	Pig manure	8	50–70	48	Winckler and Grafe (2001)
Chlortetracycline	Sandy loam soil + cattle faeces	4	0	30	Gavalchin and Katz (1994)
		20	12	30	
		30	56	30	
Oxytetracycline	Sediment slurry (aerobic)	15	50	42–46 (HL)	Ingerslev et al. (2001)
	Soil, slurry	NA	50	18–79 (HL)	Kay et al. (2004)
	Soil + cattle manure	NA	0	180	Van Gool (1993)
	Bedding + pig manure	NA	50	30 (HL)	De Liguoro et al. (2003)
Tylosin	Sandy loam soil + manure	4	60	30	Gavalchin and Katz (1994)
		20	100	30	
		30	100	30	
	Pig manure (aerobic)	20	50	>2 (HL)	Loke et al. (2000)
	Sand + slurry, sandy loam + slurry	NA	50	3.3–8.1 (HL)	Ingerslev and Halling-Sørensen (2001)
	water, water + sediment (aerobic)	15	50	9.5–40 (HL)	Ingerslev et al. (2001)
	Liquid manure	23	50	2.4 (HL)	Oliveira et al. (2002)
	Bedding + pig manure	NA	50	3.6 (HL)	De Liguoro et al. (2003)
Sulfonamides*	Activated sludge	6, 20	50	0.4–4.1[a] (HL) 0.3–0.7[b] (HL)	Ingerslev and Halling-Sørensen (2000)
	Soil, slurry	NA	50	3.5 and 127	Kay et al. (2004)
Erythromycin	Sandy loam soil + cattle faeces	4	0	30	Gavalchin and Katz (1994)
		20	75	30	
		30	100	30	
	Soil	20	50	11 (HL)	Schlüsener and Bester (2004)
Ceftiofur	Soil (clay loam, sand, silty clay loam)	22	50	22–49 (HL)	Gilberstson et al. (1990)
^{14}C-Sarafloxacin	Soil (sandy loam, loam, silty loam)	22	0.5–0.6	80	Marengo et al. (1997)
Oleandomycin	Soil	20	50	23 (HL)	Schlüsener and Bester (2004)
Salinomycin				5 (HL)	
Tiamulin				26 (HL)	
Bacitracin	Sandy loam soil + cattle faeces	4	77	30	Gavalchin and Katz (1994)
		20	67	30	
		30	77	30	
Monensin	Manure (aerobic)	NA	60–70	70	Donoho (1984)
Olaquindox	Sand + slurry, sandy loam + slurry	NA	50	5.8–8.8 (HL)	Ingerslev and Halling-Sørensen (2001)
	Sediment slurry (aerobic)	15	50	4–8 (HL)	Ingerslev et al. (2001)
	Sediment slurry (anaerobic)	15	50	22 (HL)	Ingerslev et al. (2001)
Metronidazole	Sand + slurry, sandy loam + slurry	NA	50	13–27 (HL)	Ingerslev and Halling-Sørensen (2001)
	Sediment slurry (aerobic)	15	50	14–104 (HL)	Ingerslev et al. (2001)
	Sediment slurry (anaerobic)	15	50	3–75 (HL)	Ingerslev et al. (2001)
Bambermycin	Sandy loam soil + cattle faeces	4	0	30	Gavalchin and Katz (1994)
		20	100	30	
		30	100	30	
Virginiamycin	Silty sand	25	50	87–173 (HL)	Weerasinghe and Towner (1997)

HL = half-life; a = first spike, b = second spike; NA = not available.
* Sulfacetamide, sulfabenzamide, sulfamethoxypyridazine, carbutamide, sulfamerazine, sulfameter, sulfadoxine, sulfanilamide, sulfadimidine, sulfadiazine, sulfadimethoxine, sulfapyridine, sulfachloropyridazine.

contamination by tylosin and oxytetracyclines would be much lower compared with olaquindox and metronidazole. However, more work is needed to clearly understand the transport behavior of VAs under realistic long-term field experiments. It was recently demonstrated through field studies in the UK that weak acid such as sulfonamide and OTC has high potential to be transported to surface waters (Boxall et al., 2002; Kay et al., 2004). In contrast, tylosin was not detected, perhaps due to rapid degradation in slurry (Loke et al., 2000) and soil (Ingerslev and Halling-Sørensen, 2001).

Like any other organic chemical, transport of VAs in the environment can depend on several factors. Chemical properties, temperature and moisture content of the soil, the timing of manure application, as well as prevailing weather conditions can determine the overall degree of

mobility of antibiotics in the environment. Other factors such as water solubility, dissociation constants, and sorption–desorption processes, as well as the stability and binding to the soils and the partitioning coefficients at various pH values can all affect the mobility of antibiotics range in the soil environment. For example, a lysimeter study in Germany showed no clear indication of mobility of tetracycline hydrochloride on a humous sandy soil when applied with liquid manure (Engels and Winckler, 2004), perhaps owing to higher sorption coefficient values for this compound (Tolls, 2001). In contrast, the presence of dissolved organic matter (DOM) in liquid manure showed increased mobility for tetracycline antibiotics as recently observed in soil column studies (Aga et al., 2003). Other factors that can influence the mobility of VAs are preferential flow via desiccation cracks and worm channels to the tile drains, as recently demonstrated in a UK field study (Kay et al., 2004).

4.4. Biodegradation of VAs

On release into the environment through animal excretion and subsequent use in the field as a supplement to fertilizer, the excreted compounds can be adsorbed, leached, biaccumulated, degraded through biotic or abiotic processes, and in some cases may revert back to the parent compound. Bioavailability of VAs is often thought to be simple; however, it has been reported that this is not necessarily true (Henschel et al., 1997; Halling-Sørensen et al., 1998). In the next sections, biological degradation of some of the common VAs in various environmental media (Table 10) is discussed, along with their potential risks to the environment.

4.4.1. Soil

While a number of studies on the biodegradation of VAs in the soil environment have been performed (Gonsalves and Tucker, 1977; Donoho, 1984; Gilberstson et al., 1990; Gavalchin and Katz, 1994; Loke et al., 2000; Ingerslev and Halling-Sørensen, 2001), most of them are difficult to compare, as no two studies were similar in terms of the antibiotics used and the experimental conditions. For instance, a study by Gonsalves and Tucker (1977) showed that even after repeated application of oxytetracycline (OTC) in the form of drench, residues were not found below 20 cm in a Florida sandy soil. Residues of OTC were found at measured concentration of >25 μg g^{-1} for at least 40 days after application; however, it declined steadily and persisted up to 18 months after application when concentration of OTC reduced to <1 μg g^{-1} in the soil. The apparent immobilisation of OTC in the soils to a greater depth was attributed to the presence of higher percentages of clay and organic matter in the surface soils with residues of OTC bound strongly to soil particles. Gilberstson et al. (1990) studied ceftiofur sodium, a wide-spectrum cephalosporin antibiotic, in the urine and faces of cattle and in three soils (pH range 6.9–8.0), as well as in buffers of pH 5, 7 and 9. Their study showed that ceftiofur sodium (^{14}C) degraded to microbiologically inactive metabolites, with half-lives ($T_{1/2}$) of >49, 22 and 41 days in three soils collected from California (pH 8.02), Florida (pH 6.96) and Wisconsin (pH 7.37). The effect of sterilizing the faeces of cattle was clearly demonstrated by the marked decline in the rate of degradation of the compounds compared with non-sterilized samples, thus indicating the important role of microorganisms in the degradation of the antibiotics. Although the metabolite could not be identified, the authors also observed similar results for pig faeces. Gavalchin and Katz (1994), studied degradation of a range of VAs (bacitracin, penicillin, streptomycin, tylosin, bambermycins, erythromycin and chlortetracycline) as a function of temperature in a sandy surface soil (pH 6.0–6.3) from New Jersey, US, mixed with chicken faeces. Their study showed that persistence of these fecal-borne antibiotics varied according to their chemical structure and the incubation temperature. Persistence under field conditions is also likely to be affected by interplay of several factors such as temperature, humidity, rainfall, and the nature of soil properties as demonstrated by Donoho (1984) who reported degradation of monensin, (growth promoter used in pigs) being faster under field conditions than observed under laboratory study.

4.4.2. Manure/slurry

Earlier incubation studies of antibiotics reported in the literature used soil mixed with either animal faeces or urine to which a known quantity of antibiotic was added and the inactivation was observed through periodic sampling analysis either by HPLC/microbiological assay. While the laboratory incubation studies with soil are easy to perform as many of the parameters can be controlled, the real challenge would be to conduct biodegradation tests under realistic situations such as in the manure tank or field where the factors that influence the degradation processes are difficult to control.

Of late, a number of such attempts have been made to study the biodegradability of a range of VAs in the laboratory using manure and/or slurry mixtures (Loke et al., 2000; Ingerslev and Halling-Sørensen, 2001; Kolz et al., 2005b). For instance, the use of methanogenic manure containing test system to study tylosin A degradation is a good example (Loke et al., 2000). The authors reported the half-lives of tylosin A to be <2 days under methanogenic conditions, which increased with the addition of more manure particles. However, the authors failed to support the concomitant decrease in the concentration of tylosin A with an increase in more manure to the system, was the result of sorption, abiotic or biotic degradation. It is conceivable that in a manure tank there would be a much greater concentration of colloid and particulate matter than in the laboratory test systems. This may increase the fraction of antibiotic that is sorbed and hence influence the overall rate of degradation. Published information on the formation of tylosin metabolite during degradation studies is scarce.

From a laboratory microcosm study of tylosin in aqueous manure soil systems, Oliveira et al. (2002) observed that degradation was rapid during the first 10 days and slowed to a steady rate through the formation and accumulation of metabolites in subsequent sampling events. The authors reported an initial half-life of 2.4 days for tylosin based on a 10 day pseudo first-order kinetics data (Oliveira et al., 2002). This half-life of tylosin was similar to that reported earlier by Loke et al. (2000). Similarly, a recent study by Kolz et al. (2005b) found that tylosin degradation in manure–lagoon slurries (incubated at 22 °C) exhibited biphasic kinetics with 90% disappearance occurring within <5 days. The authors also observed the formation of tylosin degradates (tylosin B and D, dihydrodesmycosin and an unknown product) in anaerobic condition during their 8-month incubation study. The formation of degradates after an incubation period of 8 months suggested that degradation in lagoon slurries is not complete and there is a likelihood of the residues entering nearby agricultural fields (Kolz et al., 2005b).

Ingerslev and Halling-Sørensen (2001) simulated the biodegradability of three VAs in soil–manure slurries under aerobic laboratory conditions using aniline as the benchmark chemical and found that degradation half-lives for the compounds (4.1–8.1 days for tylosin, 5.9–8.8 days for olaquindox, and 9.7–26.9 days for metronidazole) did not seem to be influenced by the varied nature of soils and was not concentration dependent in the test system. Given the complex nature of real-world situations where soil pH, redox conditions, temperature, prevailing soil water conditions, wetting and drying cycles, as well as the fact that the size and type of bacterial populations can vary, biodegradability of VAs may likely to be different in the field than what has been observed under controlled conditions in the laboratory. For example, under field condition, Halling-Sørensen et al. (2005) found average degradation half-lives of chlortetracycline and tylosin A to vary between 25–34 days and 49–67 days in two Danish sandy soils, respectively. These half-lives in field soils were substantially higher than the reported values for these compounds when experiment was conducted in the laboratory.

4.4.3. Surface waters and sediments

Information on biodegradation of VAs used for livestock purposes in both surface waters and sediments (freshwater and marine) is lacking. However, a large body of data exists on this aspect for VAs used specifically for aquaculture, which has been covered in a recent paper by Boxall et al. (2004). Some common VAs that are used in both animal and fish farms include OTC, sarafloxacin, sulfadiazine, sulfamethoxine and oxonilic acid. Biodegradation studies conducted on these compounds showed significant variation in the reported half-lives, and were often difficult to compare with one another for a single compound due to differences in experimental protocol and adopted laboratory conditions (e.g. Pouliquen et al., 1992; Samuelsen et al., 1994; Hektoen et al., 1995; Lai et al., 1995). For example, from a laboratory incubation study of OTC in marine sediment, no degradation was observed after 6 months of incubation period (Samuelsen et al., 1994). In contrast, in an earlier laboratory study by Samuelsen (1989), OTC was found to have a half-life of 30–64 days in sediment from a fish farm. Similarly, there are many other instances that show the degree of variation observed in the degradation rate of VAs in these matrices.

4.5. Abiotic degradation of VAs

Degradation of VAs in water can also occur through abiotic processes such as photodegradation and/or hydrolysis. These processes often play an important role in the overall dissipation and elimination of VAs in the environment. Several studies are available in the literature on the abiotic degradation of VAs (e.g. Oka et al., 1989; Gilberstson et al., 1990; Lunestad, 1992; Paesen et al., 1995a,b), and all of these show great variation in the degradation rate. For instance, study by Gilberstson et al. (1990) showed little photodegradation for ceftiofur sodium, and hydrolysis half-life for the compound varied from about 4 days to about 100 days within a pH range of 5–9. There was an increase in the rate of hydrolysis

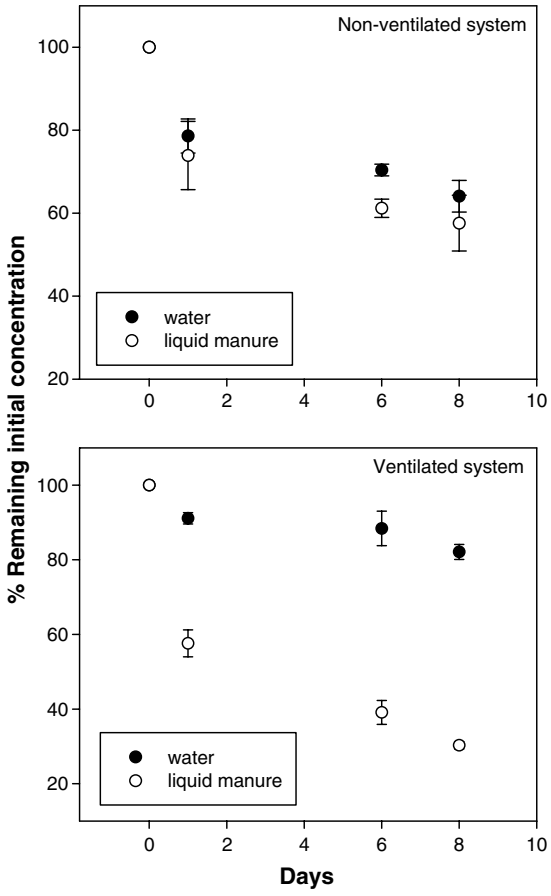


Fig. 7. Degradation of tetracycline under controlled laboratory conditions. (*Data source:* Kühne et al., 2000.)

Table 11
Field-scale and column studies into the fate and transport of veterinary medicines

Study	Location	Study substances	Study scale	Application	Manure type	Manure storage	Matrices analysed	Sampling regime	Application rate	Soil data	Climate data
Aga et al. (2003)	Illinois – US	Tetracycline	Column	Natural	Pig	U	S, L	Set times	Y	Detailed	Continuous irrigation
Boxall et al. (2005)	Derbyshire – UK	Lincomycin Oxytetracycline Sulfadiazine Trimethoprim	Field	Natural	Pig	Y	S, SW	Set times SW – continuous	Calculated	Detailed	Y
Blackwell et al. (2005)	Derbyshire – UK	Oxytetracycline Sulfachloropyridazine Tylosin	Plot	Spiked (except tylosin)	Pig	Y	S, IW	Set times	Y	Detailed	Y
Burkhardt et al. (2005)	Zurich, Switzerland	Sulfadiazine Sulfadimidine Sulfathiazole	Plot	Spiked manure or aqueous solution	Pig	U	OF	Continuous	Y	Detailed	Irrigation
Gupta et al. (2003)	Minnesota, USA	Tetracycline Chlortetracycline Tylosin	Plot	Natural	Pig	Y	OF, DW	Continuous	Y	Some data	N
Halling-Sørensen et al. (2005)	Askov and Lundgaard, Denmark	Chlortetracycline Tylosin	Field	Natural	Pig	Y	S	Set times	Calculated	Detailed	Y
Hamscher et al. (2005)	Lower Saxony – Germany	Tetracycline Chlortetracycline Sulfamethazine Sulfadiazine	Field	Natural	Pig	Y	S, GW	Set times	Y	Y	N
Krapac et al. (2005)	Illiniois – US	Tetracycline Chlortetracycline Oxytetracycline Anhydrotetracycline B-apooxytetracycline Anhydrochlortetracycline	Field	Natural	Pig	Y	GW, M	Grab	N	Limited	N
Kay et al. (2004)	Leicestershire – UK	Oxytetracycline Sulfachloropyridazine Tylosin	Field	Spiked manure (except tylosin)	Pig	Y	DW, S	S – set times DW – continuous	Y (except tylosin)	Detailed	Y
Kay et al. (2005a)	Leicestershire – UK	Oxytetracycline Sulfachloropyridazine Tylosin	Lysimeter	Spiked (except tylosin)	Pig	Y	S,L	Continuous	Y (except tylosin)	Detailed	Y
Kay et al. (2005b)	Leicestershire – UK	Oxytetracycline Sulfachloropyridazine Tylosin	Plot	Spiked (except tylosin)	Pig	Y	OF	Continuous	Y (except tylosin)	Detailed	Y
Kreuzig and Holtge (2005)	Lower Saxony – Germany	Sulfadiazine	Plot and lysimeter	Spiked	Pig	NA	S, L	Set times	Y	Detailed	Irrigation
Kreuzig et al. (2005)	Lower Saxony – Germany	Sulfadiazine	Plot	Spiked	Pig	NA	OF	Continuous	Y	Detailed	Irrigation

Y = yes, N = No.
M = manure, S= soil, IW = interstitial water, GW = groundwater, SW = surface water, DW= drainage water, OF = overland flow water, L = leachate, NA = not available.

Table 12
Summary of results from column, lysimeter and field studies with veterinary medicines

Study substance	CAS	K_{oc}	DT_{50} (d)	Maximum measured concentrations
Macrolides				
Lincomycin	154-21-2	59	–	8.5 μg kg^{-1} (S)[b] 21.1 μg l^{-1} (SW)[b]
Tylosin	1401-69-0	7988	<2 (pig slurry) 95–97 (soil)	50 μg kg^{-1} (S)[e] ND (S)[c] ND (S)[h] ND (L)[c] ND (DW)[h] ND (OF)[j] ND (L)[i]
Sulfonamides				
Sulfadiazine	68-35-9		–	0.8 μg kg^{-1} (S)[b] 27.6% (OF, grass)[l] 2.5% (OF, arable)[l] 4.1% (L)[k] 0.57% (OF)[d] 4.13 μg l^{-1} (SW)[b]
Sulfachloropyridazine	80-32-0	3.3–8.1	16–18 (soil) 70 (pig slurry)	0.78 μg l^{-1} (L)[c] 613 μg l^{-1} (DW)[h] 416 (OF)[j] 0.77 μg l^{-1} (L)[i]
Sulfadimidine	57-68-1	–	–	2.09% (OF)[d]
Sulfathiazole	72-14-0			1.11% (OF)[d]
Sulfamethazine	57-68-1	60	–	2 μg kg^{-1} (S)[f] 0.24 μg l^{-1} (GW)[f]
Tetracyclines				
Tetracycline	60-54-8	40000		225 μg kg^{-1} (S)[a] 295 μg kg^{-1} (S)[f] 0.4 μg l^{-1} (GW)[g] ND (GW)[f] 2% (L over 30 d)[a]
Oxytetracycline	6153-64-6	27792–93317	18 (soil)	305 μg kg^{-1} (S)[b] ND (L)[c] 36 μg l^{-1} (DW)[h] 0.13 μg l^{-1} (GW)[g] 32 μg l^{-1} (OF)[j] ND (L)[i] 4.49 μg l^{-1} (SW)[b]
Chlortetracycline	64-72-2	–	–	20–30 μg kg^{-1} (S)[e] 39 μg kg^{-1} (S)[f] ND (GW)[g] ND (GW)[f]
Anhydrotetracycline	–	–	–	0.1 μg l^{-1} (GW)[g]
B-apoxytetracycline	–	–	–	0.3 μg l^{-1} (GW)[g]
Anhydrochlortetracycline	–	–	–	0.3 μg l^{-1} (GW)[g]
2,4-Diaminopyrimidines				
Trimethoprim	738-70-5	1680–3990	110 (soil)	0.5 μg kg^{-1} (S)[b] 0.02 μg l^{-1} (SW)[b]

S = soil, GW = groundwater, SW = surface water, DW = drainage water, OF = overland flow water, L = leachate, ND = not detected.

[a] Aga et al. (2003).
[b] Boxall et al. (2005).
[c] Blackwell et al. (2005).
[d] Burkhardt et al. (2005).
[e] Halling-Sørensen et al. (2005).
[f] Hamscher et al. (2005).
[g] Krapac et al. (2005).
[h] Kay et al. (2004).
[i] Kay et al. (2005c).
[j] Kay et al. (2005b).
[k] Kreuzig and Holtge (2005).

for ceftiofur with a concomitant decrease in pH. A study by Paesen et al. (1995a) showed that tylosin A hydrolyses into tylosin B under acidic condition, while in neutral and alkaline medium, the compound produces tylosin A-aldol, along with number of other relatively polar decomposition products. Given the high values of pH in swine manure, understanding the hydrolysis behavior of the compound under alkaline conditions is important. The rate of decomposition of tylosin A depends largely on pH, buffer type and concentration, as well as on ionic strength (Paesen et al., 1995a). A clear degradation well seems to form upon hydrolysis (rate constants vs pH) of tylosin A within a pH range of 2.0–12.8 as reported by Paesen et al. (1995a). It is therefore conceivable that, based on the propensity of non-ionic and anionic species of tylosin A to hydrolyse, an empirical functional relationship could be developed to describe the dependence of rate constant on pH. While this has been demonstrated for weak acids such as sulfonylureas (Sarmah et al., 2000), tylosin, being a weak base, could also have a similar relationship; however, this area needs further investigation. Development and incorporation of empirical functional relationships can help predictive models ability to determine the fate of these compounds in the environment. Other works on the abiotic degradation of VAs include hydrolysis studies involving oxytetracycline (Vej-Hansen et al., 1978), and tetracycline (Vej-Hansen and Bundgaard, 1978), and are discussed below.

From a laboratory study of tetracycline stability in water and liquid swine manure, Kühne et al. (2000) reported a significant reduction in the concentration of tetracycline and formation of an optical isomer (epimer) of tetracycline, 4-epi-tetracycline. The authors carried out a number of small experiments using non-ventilated/ventilated, and control experiments. When data from this study were plotted in Fig. 7, a biphasic degradation of tetracycline was observed both in water and in liquid swine manure under the two systems. Degradation was rapid on day 1 under both systems and slowly decreased at a steady rate. The loss was more rapid under the ventilated than the non-ventilated system, and the measured DT_{50} values in water ranged from 15 and 30 days (non-ventilated) to 9 and 4.5 days (ventilated) respectively. The authors speculated that faster degradation in manure compared with water was probably due to higher pH values in manure (with 1 unit increase) where pH increased significantly from 7.6 and 7.7 to 8.3 and 8.7, respectively in unventilated and ventilated manure. An interesting finding of this study was the apparent formation of 4-epi-tetracycline in all samples, with concentration being relatively higher in liquid manure than in water samples. The tetracycline group of antibiotics is known to possess limited stability in aqueous solutions. Up to pH 5–6, reversible epimerization to 4-epi-tetracycline is the predominant reaction, as indicated in previous studies of this group of compounds (Vej-Hansen and Bundgaard, 1978; Khan et al., 1989). Beyond pH 6 the oxidation process seems to play a major role in the degradation of tetracycline. However, the formation of 4-epi-tetracycline was also reported previously in weakly alkaline solutions (Vej-Hansen and Bundgaard, 1978).

The discussion in the preceding sections revealed that over the years a number of studies have begun to investigate the fate and transport of VAs in the environment. These studies could provide valuable information on those factors and processes that should be considered in the risk assessment of veterinary medicines and feed additives, and it is possible to develop a dataset for evaluation of exposure assessment models for use in the environmental risk-assessment process. This could provide reassurance if existing modelling approaches for e.g., pesticides, are to be applied to veterinary medicines and feed additives.

We have identified and summarized a number of recent investigations into the fate and transport of VAs and feed additive in the environment (Tables 11 and 12). These studies were identified from the available scientific literature and internet. A total of 13 studies were identified that focused on antibacterial substances (macrolides, sulfonamides, tetracyclines and trimethoprim) and covered 11 active ingredients and three metabolites. Available data indicated the substances varied in their sorption behavior and persistence in manure and the environment, with maximum concentrations for the study substances in individual environmental matrices provided in Table 12. The aim of the individual studies varied, as did the study designs and the amount of detail provided (Table 12). Overall, the dataset provides useful information on a range of factors, and many of the studies appear to have the necessary information required for any model evaluation process.

5. Environmental effects of VAs

Veterinary antibiotics are designed to affect mainly microorganisms and bacteria found in animals. This therefore makes them potentially hazardous to other such organisms found in the environment (Warman, 1980). In general, toxic levels of antibiotics for microorganisms, bacteria and micro-algae present in the environment are 2–3 orders of magnitude below the toxic values for higher trophic levels (Wollenberger et al., 2000). In the recent past, their effects on soil and aquatic organisms, and plant species have been studied under controlled laboratory conditions (e.g. Batchelder, 1981, 1982; Brambilla et al., 1994; Migliore et al., 1995, 1996, 1997; Bauger et al., 2000; Halling-Sørensen, 2000, 2001; Halling-Sørensen et al., 2003). Excreted antibiotics may also partially inhibit methogenesis in anaerobic waste-storage facilities commonly used at CAFOs and thus decrease the rate at which bacteria metabolize animal waste products (Loftin et al., 2005).

5.1. Plant uptake, and effects on soil organisms, aquatic species and bacteria

On release into the environment through manure application, antibiotics may end up on arable land and can be

taken up by plants. Batchelder (1981) tested the effects of CTC and OTC on pinto bean plants gown in aerated nutrient media and showed that relatively low antibiotic concentrations can markedly affect the plant growth and development in nutrient solution (Table 13). When soil was used as a growth media, there was a large variation in the sensitivity among the species, with pinto beans being more sensitive than the edible radish at a concentration of 160 mg l^{-1} of OTC and CTC (Table 13). Elsewhere, Migliore et al. (1995) showed bioaccumulation of sulfamethoxine antibiotics by roots and stems of certain plant species, albeit at much higher dose levels (13 to >2000 mg kg^{-1}), and bioaccumulation was often higher in the roots than in the stems (Migliore et al., 1995, 1996). However, such high concentrations are unlikely to occur in soil (Jjemba, 2002) and therefore investigation with realistic environmental concentrations should be used while carrying out toxicity studies using these compounds. For more information on the effect of antibiotics on plants, readers may refer to a recent review by Jjemba (2002).

Reproductive effects and adverse impacts on early life stages of different aquatic organisms may be caused by the presence of antibiotic residues in the environment (Kümpel et al., 2001). A number of studies have investigated the toxic effects of VAs on aquatic species (e.g. Dojmi di Delupis et al., 1992; Brambilla et al., 1994; Lanzky and Halling-Sørensen, 1997; Migliore et al., 1997; Wollenberger et al., 2000), most of which used a concentration range of mg l^{-1} (Table 13). For example, Wollenberger et al. (2000) studied the acute and chronic toxicity effects of nine commonly used VAs on the freshwater crustacean *Daphnia magna* through a reproduction test, and showed that the acute toxicities (48-h EC_{50} value, mg l^{-1}) were lowest for oxolinic acid (4.6), but highest for OTC (~1000). Earlier, Migliore et al. (1997) showed the toxicity of several antibiotics to *Artemia* species, while Dojmi di Delupis et al. (1992) showed that aminosidine, bacitracin, erythromycin and lincomycin all showed slight toxicity to *D. magna*, with EC_{50} values after 48 h ranging from 30–500 mg l^{-1}, with bacitracin as the most toxic. Other studies on antibiotic toxicity examined effects on soil or sewage sludge bacteria and insects (Bauger et al., 2000; Halling-Sørensen, 2001; Halling-Sørensen et al., 2003), as shown in Table 13.

Data relating to the effects of veterinary antibiotics on aquatic organisms, bacteria, macro-invertebrates, and plants are currently available for a range of compounds, although the majority relate to short-term acute responses such as lethality. Since experimental parameters often influence the results of a toxicity investigation, some times by orders of magnitude (Koller et al., 2000), exact/precise operating conditions such as temperature, pH, time duration, etc., have to be taken into account in order to estimate their effects on the environment. The majority of toxicity studies available in the literature was undertaken at higher than environmentally relevant concentrations and was performed for a short duration. Nevertheless, indirect effects resulting from adverse alterations of natural balance due to the impact VAs on lower trophic levels cannot be excluded (Kümpel et al., 2001). With the exception of a few studies, the potential environmental impacts of metabolites of VAs have not been extensively studied. Although it is accepted that metabolites are generally less toxic than the parent compound, they often have significant activity, as reported for enrofloxacin (Burhene et al., 1997) and the tetracycline degradation product anhydrotetracycline (Halling-Sørensen et al., 2002). For example, anhydrotetracycline (ATC) had an EC_{50}value for sewage sludge bacteria approximately three times lower than the EC_{50} value of the parent compound tetracycline. It is also important to note that although studies have shown that direct effects of VAs on soil fauna are not likely at environmentally relevant concentrations, the influence of the food web on the overall impact on micro- and macro-fauna should be considered. Since soil ecosystems contain many interactions both in spatial and temporal scales within food webs, and because of the complexity, interactions are not well described or understood at present, and links between the community structure and essential soil functioning are not always straightforward (Jensen, 2001).

Earlier (Sections 3 and 4), we discussed concentration levels reported for a range of veterinary antibiotics in environmental matrices such as soil, water, and manure, and their fate and transport in the environment. The above section briefly discussed the effects of some of these compounds on certain aquatic organisms, plants and bacteria. We now raise an important question – how relevant are the effects observed at the concentration used and the one that we have observed in the environment? A comparison of available ecotoxicity data on standard organisms for some commonly used VAs with some monitoring data on soil, water, and dung samples suggests environmental concentrations are more than an order of magnitude lower for those compounds, with the exception of ciprofloxacin (Boxall et al., 2003). There was also exception for monensin (growth promoter) in soil. Under certain circumstances, therefore, VAs could have an effect on the terrestrial and aquatic ecosystems. In combination with direct effects on micro-flora and other standard organisms, another possibility is undesirable changes in natural populations of microbiota through the emergence of resistant bacteria in the environment, and this is discussed below.

5.2. Antibiotic resistance

The frequent use of antibiotics either to treat diseases or as animal feed supplements has raised concerns about the potential for to the rise of populations of new strains of bacteria resistant to antibiotics (McDonald et al., 1997; Witte, 1998). Bacterial populations isolated from the gut of animals exposed to antibiotics were found to be five times more likely to be resistant to any given antibiotic resistant microbial populations. This can be further enhanced in animal manure through excretion and through

Table 13
Selected examples of literature data on toxicity effects of commonly used animal antibiotics on soil organisms and plants

Compound (s)	Test organisms	Toxicity (effect/inhibition %)	Concentration ($mg\ l^{-1}$)	References
Bacitracin	*Daphnia magna*	LC_{50} (24 h)	126	Brambilla et al. (1994)
		LC_{50} (48 h)	30	Migliore et al. (1997)
	Artemia salina	LC_{50} (24 h)	34	
		LC_{50} (48 h)	21.8	
	Daphnia magna	NOEC	5	Dojmi di Delupis et al. (1992)
		EC_{50} (24 h)	126	
		EC_{50} (48 h)	30	
Chlortetracycline, oxytetracycline	*Phaseolus vulgaris* (pinto bean plants)	Root dry weight reduced (66–94%)	160	Batchelder (1981)
	Raphnus sativas L. (edible radish)	Growth stimulation and N uptake	~160	Batchelder (1982)
	Fungal hyphae	48%	10	Colinas et al. (1994)
Oxytetracycline + penicillin	Bacteria (sandy soil)	71%	10	
Oxytetracycline	Springtails	LC_{10}/EC_{10}	>5000/>5000 $mg\ kg^{-1}$	Bauger et al. (2000)
	Earthworms	LC_{10}/EC_{10}	>5000/1954 $mg\ kg^{-1}$	
	Enchytreids	LC_{10}/EC_{10}	>5000/3000 $mg\ kg^{-1}$	
	Sewage sludge bacteria	EC_{50}	1.2	Halling-Sørensen (2001)
	Sewage sludge bacteria	EC_{50} 0/10 h	0.12/0.27	Halling-Sørensen et al. (2003)
Tetracycline	Sewage sludge bacteria	EC_{50}	2.2	Halling-Sørensen (2001)
Tylosin	Springtails	LC_{10}/EC_{10}	>5000/149	Bauger et al. (2000)
	Earthworms	LC_{10}/EC_{10}	>5000/3306	
	Enchytreids	LC_{10}/EC_{10}	2501/632	
	Sewage sludge bacteria	EC_{50}	54.7	Halling-Sørensen (2001)
		EC_{50} 0/10 h	17.5/24.9	Halling-Sørensen et al. (2003)
Tylosin, oxytetracycline, tiamulin, metronidazole, olaquindox	Springtails	LD_{10}	>1000	Jensen (2001)
	Enchytreids	LD_{10}	>1000	
	Springtails reproduction	EC_{10}	100	
Sulfamethoxine	Roots and stems (*Panicum miliaceum*)	Bioaccumulation in plants	110–2071 $mg\ kg^{-1}$	Migliore et al. (1995)
	Roots and stems (*Pisum sativum*)		60–178 $mg\ kg^{-1}$	
	Roots and stems (*Zea mays*)		13–269	
	Root/stem/leaf (carrot)	Inhibition	1 mM	Migliore et al. (1996)
	Root/stem/leaf (corn)		1 mM	
	Root/stem/leaf (millet)	No effect	1 mM	
	Root/stem/leaf (pea)	Inhibition	1 mM	
Sulfadiazine	Sewage sludge bacteria	EC_{50} 0/10 h	15.9/16.8	Halling-Sørensen et al. (2003)
		NOEC	60	Halling-Sørensen (2001)
Streptomycin	Sewage sludge bacteria	EC_{50}	0.47	Halling-Sørensen (2001)
Metronidazole		NOEC	100	
Tiamulin		EC_{50}	14	
Oxonilic acid		EC_{50}	0.10	
Olaquindox		EC_{50}	96	
Penicillin		EC_{50}	85	
Ciprofloxacin		EC_{50}	0.61	Halling-Sørensen (2000)

the sharing of extrachromosal antibiotic resistance plasmids (R-plasmids) with non-resistance microbes. Widespread use of antibiotics and the land application of manure have resulted in multiple strains of antibiotic resistant bacteria in the intestinal flora of untreated pigs (Berger et al., 1986). Kelly et al. (1997) reported the findings of percentage of multiple antibiotic resistant microbial populations in litter from broiler houses. Nearly three decades ago it was reported that continued application of manure from animal waste onto arable land could lead to build up and extended bacteria survival (Dazzo et al., 1973). Earlier cases of increasing antibiotic persistence and changes in microbial resistance patterns associated with medicated feeds have been linked to aquaculture (Husevåg et al., 1973; Nygaard et al., 1992; Samulesen et al., 1992; Sandaa et al., 1992; Attarassi et al., 1993; Leff et al., 1993). Elsewhere, there was a 70% increase in resistance to certain VAs (penicillin, tetracycline, streptomycin) when manure from a dairy farm was applied to a garden soil (Esiobu et al., 2002). Similarly, Van den Bogaard et al. (2000) reported the presence of resistance to a range of VAs in the faeces of pigs in the Netherlands and Sweden. Elsewhere, Halling-Sørensen et al. (2005) showed that there was initial increase in the level of both chlortetracycline

and tylosin resistant aerobic bacteria in the manure amendment field soil, however it declined to the same level as observed during the beginning of the trial. Similar pattern of decreasing level for resistant bacteria was also reported by Sengeløv et al. (2003b). For information about the occurrence and transfer of antibiotic resistant genes in the environment, readers may refer to a review by Seveno et al. (2002).

It is generally believed that consumption of tainted food is the main transmission pathway of drug resistance, and as a result other possible means of antibiotic resistance dissemination (such as fate of antibiotics and potential link to the emergence of resistant genotypes) have received little attention (Chee-sanford et al., 2001). Chee-sanford et al. (2001) reported the occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine-production facilities in the US. Their study suggests there is a possibility that other resistance genes could potentially occur in the environment as a result of the direct use of antibiotics in animal agriculture, and groundwater may be a likely source of antibiotic resistance in the food chain. There have also been reports on the occurrence of specific antibiotic resistance characteristics in the environment (McKeon et al., 1995; Goni-Urriza et al., 2000). However, a number of questions remain unanswered – what are the environmental and human health consequences of the presence of resistant bugs in the environment? How and at what rate can these bacteria transfer their genes to the naturally occurring microbiota after discharge onto arable land? How much impact does resistance to veterinary antibiotics have on human health concerns if different antibiotics are used to treat human diseases?

6. Concluding remarks and way forward

Veterinary pharmaceuticals including antibiotics have become an integral component in maintaining animal health. The use and sales data of VAs worldwide revealed that in general there is lack of systematic collection of data. Better estimates of VA use are needed through a system of data collection that involves a standardized protocol that will enable properly designed and science-based effective intervention and mitigation strategies. The tiered approach recommended by WHO (2001) could be adopted by countries for systematic data collection, which are as follows:

- Each country should establish a national monitoring programme of the usage of antimicrobials in food animals through the involvement of a competent regulatory authority in that country. This can be done by collecting data from Veterinarians, farmers, animal producers, importers and exported as well as production data from manufacturers; data on intended and actual usage from manufacturers, distributors including feed mills, pharmacies and veterinary prescription records.
- Each country should have a regulatory approval and control system for antimicrobial agents and products containing antimicrobials agents.
- Countries should collect data on the total amounts of each compound and report these data in kilograms of active ingredient on an annual basis.

Environmental consequences resulting from the use of manure produced at the animal farms (CAFOs) for fertilizer supplement in agricultural land is an area requiring urgent attention. The widespread practice of using subtherapeutic doses of antibiotics to promote growth and improve feed efficiency has become one of the more controversial practices in CAFO management. Recent studies have shown that antibiotic compounds administered to food-producing animals occur in stored liquid and solid manure of CAFOs, are applied to fields through the application of manure, and that residues can persist in the soil and may be transported to surface and groundwater. Despite considerable efforts to enhance understanding of the fate and behavior of VAs the environment, a large knowledge gap still exists with respect to their microbial degradability and in particular to their metabolic pathway. Available literature data often contradict results from one experiment to another, or make it difficult for a valid comparison to be made due to different experimental protocols and laboratory conditions adopted during studies. Others argue that laboratory degradation studies often have a limited relevance to the environment due to changes in temperature, concentration, moisture content, pH, and other environmental factors (Ingerslev and Halling-Sørensen, 2001). These difficulties make the choice of data obtained from degradation studies less reliable for environmental risk-assessment purpose.

This review has shown that the fate of specific antibiotics in soil–water systems and their effects on plants and soil organisms are beginning to be addressed. The multianalyte methods using SPE, LC/MS, LC/MS/MS and ASE that have been developed since 1998 have begun to show the occurrence and transport of antibiotics from their sources into the environment and are also being used to try and identify environmental degradation processes. Efforts are also being made to understand the environmental dissemination of antibiotic resistant bacteria from CAFOs. The development of antibiotic resistant microbes and their connection to human health are issues that need to be investigated in greater depths by health and regulatory bodies so that a compromise can be made when it comes to the prudent use of VAs and their risk to human health and the environment in general. However, several significant issues to be addressed:

- Whether or not antibiotics have a significant role in maintaining or developing antibiotic resistant and multiple antibiotic resistant bacterial populations, particularly pathogenic bacteria, after excretion and in soil amended with manure from CAFOs.

- Whether there is a relationship between antibiotic residues and antibiotic resistant bacteria in the environment.
- Whether exposure to low levels of complex mixtures of antibiotics has deleterious effects on the quality of water and ecosystem health.

For the agricultural industry and government oversight agencies to make informed management and policy decisions on the use of VAs, interdisciplinary research needs to be conducted to address these issues. Microbial, human, and ecosystem health, and fate and transport problems require microbiologists, toxicologists, environmental and agricultural engineers, organic chemists, geochemists, risk assessment and industry scientists to work together. A variety of studies are required to address the issues, including CAFO farm and field studies, soil and sediment sorption and degradation studies, and overland flow and unsaturated zone flow path studies. In addition, studies to identify degradation pathways for "important" antibiotic compounds and metabolites need to be identified and measured at source and in the environment to fully understand their impact in our water resources.

Currently available information on VAs in the environment allows us to begin identifying the risks they may pose to the environment. A comparison with the results obtained under standard laboratory protocol and the available environmental concentration data from the literature indicate that, for the majority of the compounds, the effective concentrations used on target species were significantly higher than environmentally relevant concentrations, implying that significant impact on terrestrial ecosystems is not likely and so is the associated risk. At the same time, there were instances where the opposite was true. Little is known currently about the chronic subtle effects from long-term, low-level exposures of veterinary antibiotics to different species. Often several antibiotics are used to treat a livestock herd, and it is also likely that other chemical application, such as pesticides, may be used at the same site, which has been demonstrated before (Kolpin et al., 2002). This can lead to additivity, antagonism, synergism, eventual interactive effects on terrestrial and aquatic organisms, and hence a possible increase or decrease in the compound effects in the ecosystem as a whole (Boxall et al., 2003). One important issue to consider is the relationship between the standard tests adopted and the more subtle longer term effects of mixed compounds in the environment, so that a rationale decision can be established when it comes to the addition of an unknown compound to one already in existence. In addition, primary focus should be on collating better information on the quantity and use of VAs in different countries, their use per body weight of animals, excretion pattern, and the development of sensitive analytical methods capable of routine analysis of multiple compounds and their metabolites in environmental samples. Attention should also be given to their release pathways and their emissions into the atmosphere, if any.

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