Impact of Veterinary Pharmaceuticals on the Agricultural Environment: A Re-inspection

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Contents

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1 Introduction

Soil is undoubtedly one of the most important natural resources of the Earth. It is not only a habitat for many organisms, but also a platform for human activities and a supplier of many raw materials and foods (Glasener 2002). However, intensive development of the veterinary industry and agriculture, excessive fertilization and inappropriate use of pesticides is causing the entry of large amounts of pollutants into the soil (Poskrobko et al. 2007). Wastes (from wastewater treatment plants WWTP and biosolids from farmlands) are used more extensively, because the growing number of soils utilized agriculturally are now arid, and will be so even more in the future, because of climate change. These streams of wastes, raw or treated by fermentation, are rich in new classes of pollutants—i.e. pharmaceuticals, the residues of which are an emerging problem for the agricultural environment. The reasons for this will be presented below.

It is believed that residues of pharmaceuticals in the environment can pose a large problem (Andreu et al. 2009; Zuo et al. 2006; Zuo and Lin 2007). The basis for this concern is the fact that veterinary pharmaceuticals (VP_S) after administration are not completely metabolized by organisms and are excreted with urine and feces either in their native form or in the form of metabolites (Martínez-Carballo et al. 2007). Increased fertilization of farmland with natural fertilizers or sewage sludge contributes to the introduction of antibiotics into soil, surface water (via surface runoff), groundwater (through leaching), plants or other living organisms, where these pharmaceuticals can generate a number of negative consequences (Andreu et al. 2009; Beausse 2004; Chenxi et al. 2008; Ding et al. 2011; Hammesfahr et al. 2011; He et al. 2012; Hu et al. 2010a; Jacobsen et al. 2004; Kong et al. 2007; Kwon et al. 2011; Thiele-Bruhn and Peters 2007). It is believed that increased levels of antibiotics in the environment contribute, among other things, to the development of microorganisms resistant to these antibiotics (Chen et al. 2014; Kwon et al. 2011). There is also a risk that some plants are able to transfer the antibiotics from the soil into the food chain (Kong et al. 2007). Some veterinary medicines can be toxic to humans or cause allergies, thus their presence in plant food is undesirable (Lillenberg et al. 2009). VPs are quasi-persistent in the environment, because they possess degradation abilities (biotic and abiotic, dependent on compound structure and environment conditions), and are continuously entering the environment. The fate of VPs in soil is complex, including sorption, accumulation, leaching, degradation, transformation, and finally plant and organism intake. All these processes work together and can both decrease and intensify the negative effect in soil of VPs such as xenobiotics. A scheme for optimistic and worst-case scenarios resulting from VP presence in soil is shown in Fig. 1. It should be noted that some processes work in both cases, but their effects can differ. A good example of this is sorption, which can decrease toxicity, plant uptake and leaching, while also increasing the accumulation and permanence of pharmaceuticals.

VPs are one of the emerging contaminants (Campo 2015) investigated in food products, because of their potential adverse health effects in humans (Baynes et al.

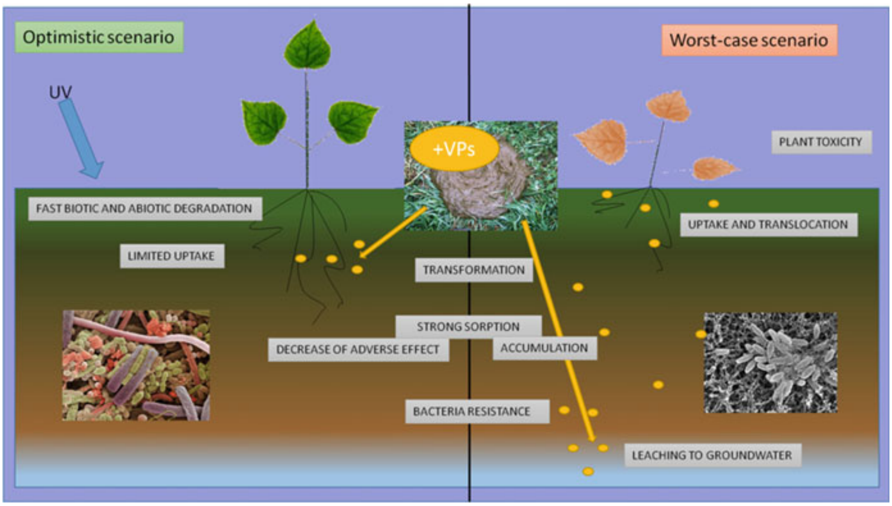

Fig. 1 The optimistic and worst-case scenarios resulting from the presence of veterinary pharmaceuticals in manure used as fertilizers

2016). In 2003 Boxall et al. posed the question "Are veterinary medicines causing environmental risk?" (Boxall et al. 2003). After 13 years, knowledge regarding this topic has increased. The influence of VPs on the soil environment has been investigated by many groups. There are ample instances in the literature concerning VPs use, sale, environmental fate, transport (sorption and leaching), stability, as well as toxicity and bacterial resistance concerning the main groups of veterinary products. Reviews of this topic are also available (Boxall et al. 2003; Kemper 2008; Sarmah et al. 2006), but new information is being reported every year. Some of these new reports show a different aspect of the presence of VP$_{\mathrm{S}}$ in natural soil and their impact on the organisms living there. The aim of this review is a re-assessment of the influence of VP$_{\mathrm{S}}$ introduced by manure fertilization on the agricultural environment.

1.1 *Antibiotics and Anti-parasitic Pharmaceuticals: Presentation and Production*

VPs are commonly used at therapeutic levels in livestock breeding for treating various diseases, as well as in food additives to promote animal growth. Some are also used to prevent human diseases. VPs are a broad range of compounds, including anti-parasitic drugs, anti-inflammatory medications, anesthetics, pain medications, antibiotics and specialized products used to manage reproductive, cardiovascular or metabolic conditions (Table 1). Tetracyclines (TCs),

Table 1 Most investigated VPs in environmental components

Group	Representative	Group	Representative
Antimicrobials, antibiotics (substances that kill microorganisms or suppress their multiplication or growth, treatment and prevention of bacterial diseases)			
Tetracyclines (TC$_S$)	Chlortetracycline (CTC) Doxycycline (DC) Oxytetracycline (OTC) Tetracycline (TC) Methacycline (MTC) Demeclocycline (DMLC) Anhydrotetracycline (AHTC) Anhydrochlortetracycline (AHCTC) Dihydrodesmycosin (DDM) 4-epi-tetracycline (4-epi-TC) 4-epi-oxytetracycline (4-epi-OTC) α-apo-oxytetracycine (α-apo-OTC) β-apo-oxytetracycline (β-apo-OTC) 2-Acetyl-2-Decarboxamido-Oxytetracycline (ADOTC)	Sulfonamides (SA$_S$)	Sulfadiazine (SDZ) Sulfadimidine (SMD) Sulfamethoxazole (SMX) Sulfamethizole (SMZ) Sulfadimethoxine (SDM) Sulfamethazine (SMT) Sulfachloropyridazine (SCP) Sulfaquinoxaline (SQX) Sulfathiazole (STZ) Sulfadoxine (SDX) Sulfameter (SMR) Sulfaguanidine (SGD) Sulfamerazine (SMR) Sulfacetamide (STD) Sulfamethoxypyridazine (SMXP) Sulfapyridine (SPY) Sulfisoxazole (SSX) Sulfanilamide (SFL)
Macrolides (MQ$_S$)	Tylosin (TYL) Azithromycin (AZM) Clarithromycin (CAM) Clindamycin (CLI) Erythromycin (ERY) Roxithromycin (ROX) Spiramycin (SPM) Vancomycin (VAN) Tilmicosin (TIL) Leucomycin (LUM) Oleandomycin (ODM)	Fluoroquinolones (FQ$_S$)/ quinolones (Q$_S$)	Ciprofloxacin (CIP) Enrofloxacin (ENR) Ofloxacin (OFN) Pefloxacin (PEF) Levofloxacin (LF) Clinafloxacin Lomefloxacin (LOM) Flumequine (FLU) Difloxacin (DFX)

β-Lactams (B-LA$_S$)	Amoxicillin (AMO) Ampicillin (APM) Cephotaxim (CTX) Cloxacilin (CLX) Cephalexin (CPX) Ceftiofur (CFT) Penicilin (PEN) Benzylpenicillin (BEN)	Aminoglycosides (AG$_S$)	Dihydrostreptomycin (DHS) Neomycin (NEO) Apramycin (AP) Paromomycin (PRM) Streptomycin (STP)
Polyether ionophores (PEI$_S$)	Salinomycin (SAL) Monensin (MON) Maduramycin (MAD) Lasalocid (LAS)	Phenicols (PQ$_S$)	Chloramphenicol (CAP) Florfenicol (FF) Thiamphenicol (TAP)
Other antibiotics	Trimethoprim (TMP) Novobiocin (NB) Bacitracin (BC) Virginiamycin (VG) Tiamulin (TAM) Nalidixic acid (NA) Narasin (NR)	Quinoxalines (QXL$_S$)	Olaquindox (OLA) Carbadox (CBX)
		Lincosamides (LINS$_S$)	Lincomycin (LIN) Clindamycin (CLIN)
Antiparasitics (BNZ$_S$), including anthelmintics (treatment of parasitic diseases, those caused by helminths, amoeba, ectoparasites, parasitic fungi, and protozoa, among others)			
Benzimidazoles (BNZ$_S$)	Albendazole (ALB) Oxfendazole (OFZ) Fenbendazole (FBZ)	Avermectins (AVR$_S$)	Doramectin (DOR) Ivermectin (IVM)
Imidazoles (IMD$_S$)/ nitroimidazoles (NID$_S$)	Metronidazole (MTZ)	Tetrahydropyrimidines (THPM$_S$)	Pyrantel pamoate (PM)
Pyrethroids (PRD$_S$)	Flumethrin (FL)	Triazines (TZ$_S$)	Toltrazuriln (TZL)

sulfonamides (SAs), macrolides (MQ$_S$), benzimidazoles (BNZ$_S$), fluoroquinolones (FQ$_S$) and β-lactam antibiotics (B-LA$_S$) belong to the group of antimicrobial and antiparasitics drugs (BNZ$_S$) in use for more than 50 years. These drugs have stood the test of time, because of their broad spectrum of activity, low cost and satisfactory effectiveness even in small doses. They are used to treat, for example, bacterial infections or are administered prophylactically to animals (Anderson et al. 2005; Andreu et al. 2009; Białk-Bielińska et al. 2009; Jacobsen et al. 2004; Nebot et al. 2014; Fritz and Zuo 2007). Some of these pharmaceuticals, despite the restrictions introduced in 2006 by the EU to ban all use of antibiotics in animals as growth promoters, are still being added to fodder (Dzierżawski 2012; Raich-Montiu et al. 2010).

After administration to an animal body (oral, dermal or injection), VP behavior is similar to that of human pharmaceuticals, i.e. a certain portion is metabolized, while others are eliminated unchanged. Following treatment, livestock will excrete 50–90% of the administered dose (with the parent pharmaceuticals constituting 9–30%), usually within several days. For example, SA biotransformation mainly occurs by phase I oxidation and phase II acetylation (García-Galán et al. 2008), and new types of metabolites are still under investigation (Hiba et al. 2016). Due to incomplete absorption in the animal gut and/or unmetabolized excretion [excretion rates of 30–90% of the mother compound (Sarmah et al. 2006)], the substances can enter the environment via the use of manure as a soil fertilizer, as well as via the anaerobic fermentation process in biogas plants when manure is used as a substrate (the elimination rate differs between compounds and conditions).

Annual growth rates (%) of total livestock production are set to increase, especially in developing countries (Steinfeld 2004). The Asian pharmaceutical market is growing at a rate of 10–15% annually, compared to a 5–7% growth in G7 countries (Rehman et al. 2013). The Food and Agriculture Organization of the United Nations (FAO) indicates that the value of global aquaculture production increased from approximately \$50 billion to nearly \$140 billion in the years between 2003 and 2012 (Lillicrap et al. 2015). In 2013, 1452 tons of VPs were supplied with TC$_S$ and penicillins (PEN$_S$) being the most distributed active compounds (454 tons and 473 tons, respectively), followed by SA$_S$ (152 tons) (Spielmeyer et al. 2015). Almost 100,000 different chemicals are registered in the EU, of which 30,000 are sold in quantities above 1 ton (Beausse 2004). It is estimated that more than 20,000 tons of antibiotics are produced annually, of which more than half are used in veterinary medicine (Li et al. 2011; O'Connor and Aga 2007). According to a report of the American Association of Concerned Scientists, 11.2–12.8 million kilograms of antibacterial substances were used on farm animals for medicinal purposes in 2001 alone (Dzierżawski 2012). In 2004, pharmaceutical wholesalers in Denmark sold 114 tons of veterinary drugs (not counting those available without a prescription), Finland reported 13.3 tons, Sweden-16.1 tons, while the amount of sales of veterinary medicines in Germany and France stood at respectively 668.8 and 1270 tons (Kools et al. 2008).

In Europe, the most widely marketed antibacterial agents are TC$_S$, followed by PEN$_S$, SA$_S$, MQ$_S$, FQ$_S$ and third-and fourth-generation cephalosporins (CLS$_S$), but patterns vary between countries (Grave et al. 2014). In 2012 in Poland, it was established that the total sales of antibacterial veterinary medicinal products amounted to 519 tons, of which the share of TC_S, PEN_S and SA_S was, respectively, 41, 25, and 10% (Ministry of Agriculture and Rural Development 2013).

All these facts indicated that the amount of VPs which reach the environment is substantial and will increase every year. Although VPs do not persist in the environment (their stability depends on several factors), their continuous supply to natural matrices makes them semi-persistent pollutants. The concentration of VP_S already present in the environment (water system and soils) is already worrying.

1.2 Occurrence of VP_S in Manure and Soil

The development of the veterinary industry and the intensification of agriculture are the main causes of the presence of veterinary antibiotics in almost every component of the environment (Dghrir and Drogui 2013; Homem and Santos 2011; Maia et al. 2014; Solliec et al. 2016; Thiele-Bruhn 2003). While there is a significant amount of literature data on the occurrence of pharmaceuticals in surface waters, knowledge of the solid components, particularly including soil, is limited (Andreu et al. 2009). It is a disturbing fact that every year considerable amounts of bio-fertilizers (e.g. manure and sludge) are applied to fields. In 2006 alone, the United States produced about 8 million tons of sludge, of which 50% was introduced into the soil (Chenxi et al. 2008). In contrast, five times the amount of manure—41 million tons—was generated in Korea, of which almost 81% was used as compost or manure on croplands (Kwon et al. 2011). In the EU, about 37% of the 6.6 million tons of sewage sludge is used annually for soil fertilization (Jjemba 2002). Via the fertilization of farmland with manure, a lot of contaminants, including VPs, are introduced into the soil. The amount of antibiotics entering fields in fertilizers are estimated at kilograms per hectare (Kemper 2008; Li et al. 2011; Thiele-Bruhn 2003). The amount of antibiotics contained in manure, which is considered the main source of these substances (Beausse 2004; Kummerer 2003; Li et al. 2011), may remain constant or increase as a result of the re-transformation of metabolites to their native form (Kemper et al. 2008). An example of this are metabolites in the form of conjugates (acetylated metabolites). These substances show no activity, but after entry into fertilizer the acetyl group may detach, which will cause the release of the active substance (Christian et al. 2003; Kemper et al. 2008). Furthermore, transformation products may have different physico-chemical properties than the parent compound and can exhibit greater toxicity in the environment and higher mobility (García-Galán et al. 2009; Mitchell et al. 2014; Solliec et al. 2016). Dust escaping from stables or barns and being deposited on the surface of the ground, or wastewater discharges from veterinary clinics are considered to be further sources of veterinary pharmaceuticals (Kemper 2008; Le-Minh et al. 2010; Masse et al. 2014; Sarmah et al. 2006; Thiele-Bruhn 2003; Chen et al. 2013).

An increasing number of reports associated with the presence of pharmaceuticals in the environment are appearing in the literature. It is believed that the most frequently detected veterinary antibiotic groups in fertilizers and soils are TC_S, SA_S, FQ_S, MQ_S and PEN_S (Beausse 2004; Picó and Andreu 2007; Tadeo et al. 2012). Information on the occurrence of anthelmintics is very limited (Horvat et al. 2012). Examples of detected concentrations of veterinary drugs in various environmental samples are presented in Table 2.

Generally, the concentration levels of veterinary compounds in solid components are in the range of μg kg^{-1}–mg kg^{-1}. However, the determined quantities are significantly lower in soils (ppb range), probably due to degradation and leaching or water uptake (Hammesfahr et al. 2011; Hu et al. 2010b; Masse et al. 2014; Rabølle and Spliid 2000; Ramaswamy et al. 2010a; Wu et al. 2010a, b). The following review of the literature (Table 2) confirms that the most frequently detected and determined compounds are TC_S, which is undoubtedly related to their leading position in terms of sales and consumption. In contrast, much less information can be found on the presence of VPs from the MQ_S group or LCS_S. Their concentrations in both manure and soil are usually at μg kg^{-1}. Pan et al. described the frequency of appearance of the most widely used group of antibiotics in samples of pig manure. According to the results, TCs are found in 85–97% of samples, SAs in 52%, while MQs in only 5% (Pan et al. 2011). TCs and SAs are commonly determined in soils and fertilizers. It is stated that the concentration of these pharmaceuticals in pig manure is 4 mg kg^{-1} for TCs and 3.5 mg kg^{-1} for SAs (Thiele-Bruhn 2003). In agricultural soils in Denmark, the concentration of OTC is in the range of 2.5–50.0 μg g^{-1}, while in pig manure the amount of this compound is much greater: 33–2000 μg g^{-1} (Kong et al. 2007). In Germany, the concentration of TCs is 450–900 μg kg^{-1} (Sarmah et al. 2006). In Turkey, the maximum concentration of OTC was reported to be 500 μg kg^{-1} in fertilized agricultural soils (Li et al. 2011). Examining the residues of TCs in 100 Spanish soil samples, Andreu et al. noted OTC, TC and CTC in 25 samples, and the most commonly detected pharmaceutical was OTC (15.7–105.4 μg kg^{-1}) (Andreu et al. 2009). In a study conducted by Hu et al., the most commonly determined group of veterinary medicines in Chinese agricultural soils were FQ_S (19–120 μg kg^{-1}). The concentrations of other pharmaceuticals were 12–46 μg kg^{-1} for TCs and 2–9 μg kg^{-1} for SAs (Hu et al. 2012). Higher concentrations of SA_S are recorded in the work by Garcia-Galan et al., wherein SMT and STZ are determined at the levels of 8.7 and 12.4 mg kg^{-1}, respectively (García-Galán et al. 2009). On the other hand, the number of MQs measured in these soils has been established at the level of 13–67 μg kg^{-1} (Thiele-Bruhn 2003).

The detected amount of the compounds largely depends on the sorption capacity of the VPs, the type of fertilizer used and the depth from which soil samples were collected. In the case of natural fertilizers (pig and poultry), it is estimated that the concentrations of the most commonly used antibiotics are up to 216 mg L^{-1} (Masse et al. 2014), where according to Karci et al. higher amounts of antimicrobial agents are detected in samples of fresh poultry manure (Karci and Balcioğlu 2009). Some literature data show that VPs (particularly TCs) can be found up to 40 cm below the

Table 2 Occurrence of VP$_S$ in soils, manure and biosolids (Andreu et al. 2009; Boxall et al. 2006; Campagnolo et al. 2002; Christian et al. 2003; Ding et al. 2011; García-Galán et al. 2009; Haller et al. 2002; Hammesfahr et al. 2011; Hamscher et al. 2002; Hu et al. 2010a, 2010b, 2012; Jacobsen et al. 2004; Kong et al. 2007; Li et al. 2011; Martínez-Carballo et al. 2007; Qiao et al. 2012; Sarmah et al. 2006; Shelver et al. 2010; Thiele-Bruhn 2003; Uslu et al. 2007; Winckler et al. 2003; Zhou et al. 2012)

Group of veterinary pharmaceuticals	Matrix	Determined Concentration	References
TC$_S$			
TC OTC CTC	Animal manure	0.36–23 mg kg^{-1} 0.21–29 mg kg^{-1} 0.10–46 mg kg^{-1}	(Martínez-Carballo et al. 2007)
OTC CTC		1.6–136 mg kg^{-1} 1.1–26 mg kg^{-1}	(Winckler et al. 2003)
CTC OTC TC DC MTC		35,500 ng g^{-1} 661 ng g^{-1} 821 ng g^{-1} 296 ng g^{-1} 4.02 ng g^{-1}	(Zhou et al. 2012)
CTC TC OTC		68.0–1000 μg L^{-1} 25–410 μg L^{-1} 25–410 μg L^{-1}	(Campagnolo et al. 2002)
OTC		33–2000 mg g^{-1}	(Kong et al. 2007)
OTC TC CTC		5.3–183.5 mg kg^{-1} 8.3–43.5 mg kg^{-1} 0.4–26.8 mg kg^{-1}	(Hu et al. 2010b)
CTC TC		0.1 mg kg^{-1} 4.0 mg kg^{-1}	(Hamscher et al. 2002)
TC OTC CTC DC MTC		15,264 μg kg^{-1}	(Qiao et al. 2012)
CTC TC		0.15–14.7 mg kg^{-1} 0.18–0.84 mg kg^{-1}	(Hu et al. 2010a)
TC CTC		1.1 mg kg^{-1} 1.7 mg kg^{-1}	(Martínez-Carballo et al. 2007)
OTC CTC TC DC	Soil	15.7–105.4 μg kg^{-1} 5.8–34.4 μg kg^{-1} 18.8–64.3 μg kg^{-1} 12.1–45.7 μg kg^{-1}	(Andreu et al. 2009)
TC CTC		86.2–198.7 μg kg^{-1} 4.6–7.3 μg kg^{-1}	(Hamscher et al. 2002)
CTC		10–15 μg kg^{-1}	(Jacobsen et al. 2004)
OTC		305 μg kg^{-1}	(Boxall et al. 2006a, b, c)
OTC TC CTC		124–2683 μg kg^{-1} 20.9–105 μg kg^{-1} 33.1–1079 μg kg^{-1}	(Hu et al. 2010b)

(continued)

Table 2 (continued)

Group of veterinary pharmaceuticals	Matrix	Determined Concentration	References
TC CTC OTC		12–46 μg kg^{-1}	(Hu et al. 2012)
OTC		2.5–50 μg g^{-1}	(Kong et al. 2007)
TC		450–900 μg kg^{-1}	(Thiele-Bruhn 2003) (Sarmah et al. 2006)
OTC TC CTC		79.7 μg kg^{-1} 74.4 μg kg^{-1} 104.6 μg kg^{-1}	(Li et al. 2011)
CTC DMLC DC OTC TC	Treated sewage sludge	69.6–346.6 μg kg^{-1} 36.6–131.2 μg kg^{-1} 149.6–291.2 μg kg^{-1} 51.9–743.6 μg kg^{-1} 281.9 μg kg^{-1}	(Ding et al. 2011)
SAs			
SMX SDX SCP	Animal manure	2.0–5.7 mg kg^{-1} 0.1–32.7 mg kg^{-1} 0.3–2.4 mg kg^{-1}	(Hu et al. 2010b)
SMD		1 mg kg^{-1}	(Christian et al. 2003)
SMR TMP		47 ng g^{-1} 6.26 ng g^{-1}	(Zhou et al. 2012)
SGD SDZ SMD SMX SDM		20 mg kg^{-1}	(Haller et al. 2002)
SMT STZ		8.7 mg kg^{-1} 12.4 mg kg^{-1}	(García-Galán et al. 2009)
SMT SDM TMP		2.5–400 μg L^{-1} 2.5 μg L^{-1} 2.5 μg L^{-1}	(Campagnolo et al. 2002)
SMT STZ		2250–5060 ng L^{-1} 785–1700 ng L^{-1}	(Shelver et al. 2010)
SDM SDZ TMP		20 mg kg^{-1} 51–91 mg kg^{-1} 17 mg kg^{-1}	(Martínez-Carballo et al. 2007)
SMD	Soil	15 μg kg^{-1}	(Christian et al. 2003)
SAs		90 μg kg^{-1}	(Hammesfahr et al. 2011)
SMX SDX SCP		0.1–0.9 μg kg^{-1} 1.2–91 μg kg^{-1} 1.3–2.5 μg kg^{-1}	(Hu et al. 2010b)
SDZ TMP		0.8 μg kg^{-1} 0.5 μg kg^{-1}	(Boxall et al. 2006a, b, c)

(continued)

Table 2 (continued)

Group of veterinary pharmaceuticals	Matrix	Determined Concentration	References
STD SCP SDM SMR SMD SMX STZ SMZ SMXP SPY SSX		2–9 μg kg^{-1}	(Hu et al. 2012)
SMR SMT SMR SMX SDM		114.8–321.4 μg kg^{-1}	(Li et al. 2011)
SDZ SMR SMT SMX	Treated sewage sludge	562 μg kg^{-1} 112–668.9 μg kg^{-1} 127.8–131.8 μg kg^{-1} 4.8–35.9 μg kg^{-1}	(Ding et al. 2011)
FQs			
CIP	Animal manure	0.1 mg kg^{-1}	(Hu et al. 2010b)
ENR OFN		16.5 ng g^{-1} 8.15 ng g^{-1}	(Zhou et al. 2012)
OFN CIP PEF		1.2–15.7 mg kg^{-1} 0.1–4.3 mg kg^{-1} 3.3–24.7 mg kg^{-1}	(Hu et al. 2010b)
ENR		2.8–8.3 mg kg^{-1}	(Martínez-Carballo et al. 2007)
CIP NOR ENR LOM	Soil	13.7–1347.6 μg kg^{-1}	(Li et al. 2011)
FQs		6–52 μg kg^{-1}	(Thiele-Bruhn 2003)
NOR CIP ENR OFN		19–120 μg kg^{-1}	(Hu et al. 2012)
OFN CIP		0.1 μg kg^{-1} 10.3–30.1 μg kg^{-1}	(Hu et al. 2010b)
CIP		0.37 mg kg^{-1}	(Martínez-Carballo et al. 2007)
NOR CIP		0.29–0.40 mg kg^{-1}	(Golet et al. 2002)
ENR		0.013–0.204 mg kg^{-1}	(Uslu et al. 2007)

(continued)

Table 2 (continued)

Group of veterinary pharmaceuticals	Matrix	Determined Concentration	References
MQ_S and LCS_S			
LUM	Animal manure	15.2 ng g^{-1}	(Zhou et al. 2012)
ERY LIN		2.5 μg L^{-1} 2.5–240 μg L^{-1}	(Campagnolo et al. 2002)
LIN		0.12–3.8 mg kg^{-1}	(Hu et al. 2010b)
TYL		<110 μg kg^{-1}	(Jacobsen et al. 2004)
LIN	Soil	8.5 μg kg^{-1}	(Boxall et al. 2006a, b, c)
TYL A		10–20 μg kg^{-1}	(Jacobsen et al. 2004)
LIN		1.1–11.7 μg kg^{-1}	(Hu et al. 2010b)
MQ_S		13–67 μg kg^{-1}	(Thiele-Bruhn 2003)
ERY LIN	Treated sewage sludge	10.4–62.8 μg kg^{-1} 2.6–8.7 μg kg^{-1}	(Ding et al. 2011)

surface of soil fertilized with animal slurry. There are no signs of the elution of these substances to deeper levels (Andreu et al. 2009). For example, in experiments conducted in Germany the presence of TC and CTC in slurry was reported in amounts of 4 and 1 mg kg^{-1}. The concentration of these pharmaceutical in soil samples averaged 86.2 μg kg^{-1} in the 0–10 cm layer and 171.7 μg kg^{-1} at 20–30 cm (Sarmah et al. 2006). Zhang et al. found TCs in a layer of soil (0–20 cm) in concentrations of 3.9–43.4 μg kg^{-1}, while at a depth of 20–30 cm the concentration of these compounds was 2.8 μg kg^{-1} (Zheng et al. 2012). Other assays confirmed the presence of antibiotics in sandy soils fertilized with slurry, where OTC, TC, CTC and SMT were detected at maximum concentrations equal to, respectively, 27, 443, 93 and 4.5 μg kg^{-1} in the 0–30 cm layer (Sarmah et al. 2006). Other sources indicate that SMT is detected only in the top layer of the soil (15 cm) (Shelver et al. 2010).

Some antibacterial agents (above all, TCs and FQ_S) may remain in soils for many years (Beausse 2004; Chen et al. 2014; Dı́az-Cruz et al. 2003; Jechalke et al. 2014; Karci and Balcioğlu 2009; Kemper 2008; Masse et al. 2014; Rabølle and Spliid 2000), and this is associated with their strong sorption on the surface of the soil (Picó and Andreu 2007; Wang and Yates 2008). For example, Tamtam et al. describe the presence of veterinary antibiotics in agricultural soils near Paris after 4 years of long-term wastewater irrigation (Chen et al. 2014; Tamtam et al. 2011), while SAs have been determined in soils after a year of fertilization (Shelver et al. 2010). Most antibiotics are adsorbed very quickly. When the frequency of soil fertilization with manure exceeds the degree of degradation of the antibiotics, they can be expected to accumulate in soils (Białk-Bielińska et al. 2011; García-Galán et al. 2009; Kemper 2008; Qiao et al. 2012). The above research results show that VPs are a major environmental problem worldwide, and that their detection in sediments, soils and waters raises concern about the possible adverse effects of these compounds on natural ecosystems (Andreu et al. 2009). However, more research is needed to understand the behavior of VPs in soils and fertilizers (Masse et al. 2014) and to assess their potential risk to human health (Liu et al. 2014).

2 Stability of VPs in Manure and Soil

The large consumption of a veterinary antibiotic results in its presence in the environment. Despite the fact that pharmaceuticals in manure or soil occur in low concentrations (ppb–ppm range) and can undergo processes of degradation, their continuous introduction into the ecosystem may be dangerous (Białk-Bielińska et al. 2011; García-Galán et al. 2009; Homem and Santos 2011; Jjemba 2002; Schlusener and Bester 2006). Both biotic and abiotic processes determine the environmental fate of pharmaceuticals (Montesdeoca-Esponda et al. 2012), as is discussed in further sections. Abiotic degradation processes of VPs are dependent on pH, redox conditions and exposure to light.

2.1 Biodegradation in Soil

It is believed that the biodegradation of chemicals is probably one of the most important environmental processes, and where a greater amount of manure is placed on fields, its intensity is greater (Kemper 2008; Sittig et al. 2014). During biodegradation, a chemical substance may be mineralized or transformed into a decomposition product (Barra Caracciolo et al. 2015; Ingerslev and Halling-Sørensen 2001).

It is believed that the amount of organic matter in soils can both increase and reduce the rate of biodegradation (Ingerslev and Halling-Sørensen 2001). In the case of FQ_S and TCs, which strongly bind to the surface of the soil, it is suspected that the sorption process can delay biotic and abiotic degradation, which is why they are persistent in sediments, soils and manure (Lillenberg et al. 2009; Uslu et al. 2007).

SAs, FQ_S and TMP are considered to be compounds which are resistant to microbial degradation (Baran et al. 2006; Białk-Bielińska et al. 2011; Le-Minh et al. 2010; Montesdeoca-Esponda et al. 2012; Sittig et al. 2014; Van Doorslaer et al. 2014). However, various data can be found in the literature concerning their durability. For example, the constant biodegradation rate of ciprofloxacin in soil is 0.39 d^{-1}. The half-life period of this compound is longer (19 days) in sterilized soil than in non-sterilized soil (9 days) (Zhang et al. 2012). Nevertheless, it has also been proven that this compound does not degrade under anaerobic conditions (Chenxi et al. 2008; Thiele-Bruhn 2003). In the case of SAs (SMD), which do not bind too strongly to the surface of the soil, there is information about their stability in both the slurry and in the soil (Christian et al. 2003). The persistence of VPs from the TC_S group, particularly CTC, in Danish soils is established at 25–34 days

(Daghrir and Drogui 2013). According to reports in the literature, VPs from the group of MQs and AG$_S$ decompose well in the environment (Haller et al. 2002). MQ$_S$ (especially TYL) are stable in neutral conditions, but under acidic conditions TYL A degrades to TYL B (Sarmah et al. 2006; Thiele-Bruhn 2003). The half-life of this compound in sandy soil is 49–67 days (Sarmah et al. 2006). Different values were presented by Schlusener et al. where, during a 120-day experiment of the oxygen degradation of five MQ$_S$ antibiotics in soil (TYL, ERY, ODM, SAL and TAM), it was shown that the half-life of these compounds is 8, 20, 27, 16, and 5 days, respectively (Schlusener and Bester 2006). B-LA$_S$ antibiotics are hydrolytically and biologically degradable in a matter of hours or days depending on the soil moisture. The rate of degradation of these compounds has been assessed as 5–67 days (Carlson and Mabury 2006; Halling-Sørensen et al. 2005; Jechalke et al. 2014). This is due to the structure of B-LA$_S$ antibiotics (such as PEN, BEN or CLX), consisting of a β-lactam ring, which contributes to the rapid degradation of these compounds in the environment (Kemper et al. 2008).

2.2 *Abiotic Degradation in Soil*

Among many processes, photodegradation contributes to the decomposition of pharmaceuticals on the surface of soils (Jechalke et al. 2014; Chen et al. 2012). Fertilizers spread on soils contain pharmaceuticals that are exposed to sunlight, but the process of photolysis may be significant only when the pharmaceuticals are located in a thin layer of distributed manure. SAs, TCs or FQ$_S$ tend to undergo photolysis in aqueous solutions, but information on the degradation of these compounds on the surface of the soils is not only limited but also inconsistent (Martínez-Carballo et al. 2007; Thiele-Bruhn and Peters 2007).

It is believed, however, that in the case of FQ$_S$ the rate of photodegradation in soil is lower than in water, which may be related to the presence of humic acids (Picó and Andreu 2007). However, according to Beausse et al., the photodegradation of FQs in soils is incomplete, which results in the detection of these compounds in soil samples—0.3 mg kg^{-1}, even 8–21 months after fertilization (Beausse 2004; Jechalke et al. 2014; Picó and Andreu 2007). Similar observations were made by Kemper, who believes that the effect of light is negligible when these compounds are located in a sediment or suspension (Kemper 2008). The photolytic and chemical stability of FQs is conditioned by the presence and durability of the quinolone ring (Babić et al. 2013). It is known that in aqueous conditions degradation products of TCs are formed by epimerisation, dehydration or proton transfer. In pH 2–6 4-epi-TCs can be created, which in special alkaline conditions revert to an active form (Halling-Sørensen et al. 2003a, b; Jia et al. 2009; Solliec et al. 2016). In acidic conditions ($pH < 2$) AHTC and AHCTC are created, of which only AHTC is stable. AHCTC is transformed to α and β-apo-OTC forms (Halling-Sørensen et al. 2003a, b; Jia et al. 2009; Solliec et al. 2016; Wu et al.

2011). However, literature data on products of transformation in solid environments (especially in soils) are limited.

The durability of antibiotics in soils is highly dependent not only on their susceptibility to degradation, but also on leaching in water, the structure of the compound, the physico-chemical properties and type of soil, and the climatic conditions, in particular the temperature (Boxall et al. 2004; Díaz-Cruz et al. 2003; Horvat et al. 2012; Picó and Andreu 2007), which accelerates the decomposition of compounds. For example, studies on the stability of CTC in soil after 30 days of incubation have shown the presence of 44% of the starting concentration of the compound at 30 °C, 88% at 20 °C and the lack of any degradation of CTC at 4 °C (Hamscher et al. 2002). It has also been proven that the time of the use of manure on the field can affect the degradation rate of compounds. It has been shown that, in soil fertilized with manure, the half-life of IVM in winter ranges from 91 to 217 days, while in the summer it is much shorter (7–14 days) (Boxall et al. 2004).

2.3 *Half-Lives in Manure*

Half-lives of many antibiotics in solid components often vary from a few days to several weeks (Díaz-Cruz 2007; Masse et al. 2014), but their degradation in manure, soil or sediment proceeds according to the same mechanisms. Boxall et al. presented a summary of the half-lives of veterinary antibiotics in manure (Boxall et al. 2004). According to these data, the most persistent groups of pharmaceuticals are TC_S and Q_S ($t_{1/2} > 100$ days). In the case of SA_S, AG_S and MQ_S their half-lives are respectively <8–30 days, 30 days, <2–21 days. The least durable compounds are pharmaceuticals from the group of $B\text{-}LA_S$; their half-life is only 5 days. Other sources say that AVR_S (belonging to the MQ_S) remain in manure for a long time (Raich-Montiu et al. 2011). However, according to Wang et al. the half-life of TYL in the feces of animals (cattle, chicken and swine) is 6.2, <6.2 and 7.6 days, respectively (Teeter and Meyerhoff 2003; Wang and Yates 2008).

The degree of VP degradation in manure is connected with aerobic conditions; however, manure can also be composted (anaerobic conditions). In the case of TYL, $t_{1/2}$ in veal manure is <2 days (under methanogenic conditions) (Liguoro et al. 2003; Loke et al. 2000), so degradation is faster than in soil. After 8 months of incubation in conventional-lagoon slurry (22 °C, anaerobic conditions), Kolz et al. reported the presence of degradation products of TYL-primarily TYL B, D and DDM (Kolz et al. 2005), which proves the incomplete degradation of TYL in lagoons. Moreover, other sources indicate that, in the case of fertilizers stored in lagoons, concentrations of antibiotics can be stable for up to 150 days (Kuchta and Cessna 2009; Ramaswamy et al. 2010b).

In the case of TC_S, it is considered that they are more rapidly decomposed in liquid porcine manure under aerobic than anaerobic conditions (Thiele-Bruhn 2003; Wang and Yates 2008). During laboratory tests on the stability of TC in liquid manure, a significant reduction of the concentration and the creation of an optical isomer of 4-epi-TC was reported (Sarmah et al. 2006). The same study also observed that the degradation of TC_S in the fertilizer was completed more quickly because of the higher pH. O'Connor et al. showed that after 6 days 29–64% TCs were found in manure, while no degradation products were identified (O'Connor and Aga 2007). On the other hand, Storteboom showed that OTC remains longer in dairy manure (9.8d or 17.7d-depending on intensity management) than in horse manure (Masse et al. 2014; Storteboom et al. 2007). In the case of OTC, it is estimated that the half-life of this compound in calf fertilizer is 30 days; however, this compound is detected after 5 months (820 μg kg^{-1}) (Andreu et al. 2009; Liguoro et al. 2003). According to Halling-Sørensen (2001), the half-life of MTZ, OLA and TYL in soil-manure slurries is respectively 9.7–26.9 days, 5.8–8.7 days and 3.3–8.1 days (Ingerslev and Halling-Sørensen 2001; Li 2014). A similar half-life (8.3 days) was recorded by Schlusener and Bester (2006). According to Wang et al., OTC degrades faster (during laboratory aerobic incubation) in manure at a temperature of 35–45 °C than at 15–25 °C (Wang and Yates 2008); after 64 days 59% was degraded (anaerobic digestion); also products of the degradation of 4-epi-OTC α-apo-OTC, and β-apo-OTC were detected (Wang and Yates 2008). It is believed that up to 75% of TCs (OTC) are removed at during anaerobic digestion (Masse et al. 2014), although information on this topic is still limited (Arikan et al. 2006). The significant deviations in half-life times of VPs degradation are connected with the variability of chemical structures and properties in this group of pharmaceuticals.

According to reports in the literature, composting can significantly reduce levels of veterinary antibiotics (Zhang et al. 2013a) (Liguoro et al. 2003). Composting is a controlled aerobic process, in which diverse groups of microorganisms degrade organic matter. In the composting process, temperatures often exceed 40 °C as a result of great biological activity (Dolliver et al. 2008). In the manure of calves after 35 days of composting, OTC concentration decreased by 95% (Arikan et al. 2007). A reduction in concentration was also observed in the case of CTC in poultry manure—90% after 42 days of composting, while in pig manure only 27% of the compound was reduced (Ho et al. 2013). Dolliver et al. reported a 99% decrease in the concentration of CTC in turkey manure over 35 days (Dolliver et al. 2008; Ho et al. 2013). Speltini et al. provided information on the durability of CIP during composting, suggesting it was greater than the durability of other compounds such as SDZ and CTC (Speltini et al. 2015). In the case of MON and TYL, after 35 days of composting in turkey manure concentrations of these compounds decreased by 54 and 76%, respectively (Ho et al. 2013), but no SMT degradation was observed during 35 days of turkey manure composting (Ho et al. 2013). Nevertheless, the use of manure after composting as a fertilizer is safer for the soil (Ho et al. 2013; Ramaswamy et al. 2010b).

An example summary of the half-lives of selected veterinary medicines in various environmental matrices has been presented in Table 3. The data are diverse, so the comparison of results and the drawing of clear conclusions is difficult. However, it can be observed that the degradation of drugs occurs faster in aerobic

Table 3 Half-lives of selected veterinary medicines in various environmental matrices (Angenent et al. 2008; Arikan et al. 2006; Boxall et al. 2004; Carlson and Mabury 2006; Dolliver et al. 2008; Halling-Sørensen et al. 2003a, b, 2005; Ho et al. 2013; Ingerslev and Halling-Sørensen 2001; Ingerslev et al. 2001; Kay et al. 2004; Liguoro et al. 2003; Loke et al. 2000; Pan and Chu 2016a; Schlusener and Bester 2006; Storteboom et al. 2007; Teeter and Meyerhoff 2003; Wang and Yates 2008; Winckler and Grafe 2001; Zhang et al. 2012)

Process	Compound	Half-life (days)	Ref.
Soil			
Degradation in sandy loam soil (aerobic conditions)	ERY ROX SAL TAM ODM TYL	20 >120 5.0 16 27 8.3	(Schlusener and Bester 2006)
Degradation in soil (aerobic and anaerobic conditions)	CIP	19.1 (anaerobic) 9.2 (aerobic)	(Zhang et al. 2012)
Degradation in soil	OTC SCP	18.2 3.5	(Kay et al. 2004)
Degradation in soil	TYL CTC	49–67 25–34	(Halling-Sørensen et al. 2005)
Degradation in soil (aerobic and anaerobic conditions)	TC	31.5–57.8 (aerobic) 43.3–86.6 (anaerobic)	(Pan and Chu 2016a)
	SMT	24.8–49.5 (aerobic) 34.7–57.8 (anaerobic)	
	NOR	2.91–40.8 (aerobic) 5.60–53.4 (anaerobic)	
	ERY	6.4–40.8 (aerobic) 11.0–57.8 (anaerobic)	
	CAP	6.70–43.3 (aerobic) 8.60–53.3 (anaerobic)	
Degradation in soil (aerobic conditions)	OTC	56 Days in non-amended soil	(Wang and Yates 2008)
Manure			
Degradation in broiler manure compost (aerobic conditions)	DC ENR ERY FLU NOR SDZ TIL TMP TYL	3.8 2.8 1.4 1.3 2.1 1.4 2.0 3.7 2.2	(Ho et al. 2013)
Degradation in cattle, chicken and swine manure (aerobic conditions)	TYL	6.2 (cattle) <7.6 (chicken) 7.6 (swine)	(Teeter and Meyerhoff 2003)

(continued)

Table 3 (continued)

Process	Compound	Half-life (days)	Ref.
Degradation in manure-amended and manure free	TYL	4.5–6.1	(Carlson and Mabury 2006)
	CTC	21–24	
	MON	3.3–3.8	
Degradation in pig slurry	OTC	79	(Kay et al. 2004)
	SCP	127	
Degradation in spiked turkey litter during composting (aerobic conditions)	CTC	1	(Dolliver et al. 2008)
	MON	17	
	SMT	No biodegradation	
	TYL	19	
Degradation in pig manure	TC	55–105	(Winckler and Grafe 2001)
Degradation in Bedding + pig manure	OTC	30	(Liguoro et al. 2003)
Degradation in dairy manure, horse manure, feedlot manure (aerobic conditions)	TYL	Horse manure: 4.2–9.8	(Storteboom et al. 2007)
	MON	Horse manure: 14.7–30.1	
	CTC	Horse manure: 5.1–8.4 Dairy manure: 5.8–6.8 Feedlot manure: 13.4–13.5	
	OTC	Dairy manure: 9.8–17.7 Feedlot manure: 15.2–31.1	
	TC	Feedlot manure: 6.5–17.2	
Degradation in manure (anaerobic conditions)	OTC	56	(Arikan et al. 2006)
Degradation in swine waste (anaerobic conditions)	TYL	2.49 h	(Angenent et al. 2008)
Degradation in animal manure (aerobic conditions)	OTC	8.1	(Wang and Yates 2008)
Degradation in aqueous phase in manure	TYL	<2	(Loke et al. 2000)
Others			
Degradation in soil-manure slurries (aerobic conditions)	MTZ	13.1–26.9	(Ingerslev and Halling-Sørensen 2001)
	OLA	5.8–8.8	
	TYL	3.3–8.1	
Degradation in sediment slurry (aerobic and anaerobic conditions)	OTC	42–46 (aerobic)	(Ingerslev et al. 2001)
	OLA	3–8 (aerobic), 21.5 days (anaerobic)	
	MTZ	14–104 (aerobic), 3–75 (anaerobic)	
	TYL	9.5–40 (aerobic)	
Degradation in soil/feces mixtures (summer and winter)	IVM	7–14 (summer) 91–217 (winter)	(Boxall et al. 2004)
Degradation in soil interstitial water (anaerobic conditions)	OTC	38.6 (light), 29.6 (dark)	(Halling-Sørensen et al. 2003a, b)
	α-apo-OTC	2.3 (light), 15.4 (dark)	
	β-apo-OTC	270 (light), 90.5 (dark)	
	4-epi-OTC	142.4 (light), 29.7 (dark)	
	ADOTC	41.7 (light), 38.2 (dark)	
Degradation in manure-amended soil (aerobic conditions)	OTC	33	(Wang and Yates 2008)

conditions. The fastest degradable group of drugs (among those presented) in soil and manure are MQ_S. Additionally, one can claim that composting is an effective process for eliminating the residues of veterinary antibiotics from manure.

3 Leaching from Soil to Groundwater

Sorption to soil can be considered to be an elimination process; thus, it affects the bioavailability of pollutants in the environment. It is, therefore, an immensely important process in terms of its potential hazardous effect on organisms living in both soil and water compartments. This phenomenon is based on various interactions of sorbates with soil particles including weak (e.g. van der Waals, electrostatic) or strong interactions (e.g. covalent bonding). Depending on the reversibility of the sorption process, we can distinguish equilibrium sorption (reversible, pollutant considered bioavailable), and kinetic (entrapped) adsorption known as sequestration (temporarily decreased bioavailability due to diffusion into micro-and nanopores). If sequestered residues are released, they can become a bioavailable fraction, whereas the irreversible parts of sequestered pollutants are considered non-extractable residues and therefore not bioavailable (Jechalke et al. 2014). Although both physicochemical properties of chemicals, and soil properties are crucial in the evaluation of sorption mechanisms, an assessment of the fate of chemical compounds in soil environments should also take into account the methodological approach. Therefore, in this review the authors focus on a comparison of the leaching data of veterinary pharmaceuticals obtained according to different procedures.

Generally, laboratory leaching tests can be divided into static and dynamic experiments. Static tests are commonly used when the objective of the study is to calculate the distribution coefficient K_d [L kg^{-1}], in equilibrium time, which is specific to every chemical. Dynamic tests e.g. column tests, on the other hand, enable time-dependent monitoring of contaminant leaching from soil and waste materials; in addition, the flow-through pattern of such tests resembles actual environmental conditions. Although both column and batch tests can be used to assess the possible leaching/release potential of contaminated materials on the soil–groundwater pathway (Delay et al. 2007; Grathwohl and Susset 2009; Grathwohl and van der Sloot 2007), a batch test only provides a snapshot of a particular liquid-to-solid ratio, whereas during a column leaching test the release of a contaminant depends on the local equilibrium time and advection conditions (Lopez Meza et al. 2008). Such an assessment provides more environmentally relevant results eliminating the possible overestimation of sorption present in batch tests. Therefore, the dynamic test seems to be more appropriate in the groundwater contamination risk assessment of VPs.

3.1 Literature Data on VP Leaching

The trend of shifting from batch leaching tests towards column experiments was noticed more than a decade ago. Grathwohl and Susset reported that batch tests are not a good tool to mimic environmental scenarios of leaching behavior due to under-or over-predicted concentrations in water phases (Grathwohl and Susset 2009). However, current understanding of the leaching potential of veterinary antibiotics into groundwater is still incomplete. Due to its simple experimental setup, the batch test has frequently been used and equilibrium sorption coefficients for various VPs have so far been determined.

For the following groups of VP_S, the sorption coefficients are well known: TC_S, SA_S, AG_S, MQ_S, FQ_S, IMD_S, polypeptides, polyethers, glycopeptides and QXL_S (Song and Guo 2014). Although their distribution coefficients (K_d) depend strongly on a number of factors (e.g. soil parameters like organic matter content, physico-chemical properties of the chemical compound, and external factors such as pH, ionic strength or temperature) on the basis of the presented ranges a strong interaction with soil particles is noticeable for TC_S and FQ_S (420–1030 and 260–6310 L kg^{-1}, respectively) whereas relatively weak interactions are exhibited by e.g. SA_S [0.6–107.5 L kg^{-1} (Białk-Bielińska et al. 2012)] and IMD_S (0.54–0.67 L kg^{-1}) (Song and Guo 2014). Therefore, SA_S and IMD_S are likely to migrate out of a field in runoff water or can be leached down through the soil profile by percolation water. On the other hand, TC_S are considered strongly sorbed by soil particles with K_d, reported to be as much as >300,000 L kg^{-1} for clay soil-and thus are frequently treated as scarcely mobile in this compartment of the environment (Sassman and Lee 2005; Schlabach et al. 2007). Several studies have reported small amounts of pharmaceuticals or even their lack in leachates, whereas OTC and TC have been detected in soil (Popova et al. 2014; Kay et al. 2005a; Kim et al. 2010). However, strongly sorbed chemicals can also move to other locations together with associated soil particles when eroded by runoff water. Indeed, Davis et al. reported very low aqueous concentrations of TC and CTC during a runoff study; however, their relative losses including particle facilitated transport were 65 and 34%, respectively (Davis et al. 2006). This means that sorption in this regard does not make chemicals immobile in the environment.

Aust et al. observed particle-facilitated transport and macropore flow of CTC resulting in translocation from manure layers into mineral soil. They also indicated that horizontal transport of SMT and CTC is possible due to surface runoff. Moreover, both horizontal and vertical flow within feedlots may cause the dislocation of antibiotic residues into both surface and groundwater resources (Aust et al. 2008). Another study reported that, although veterinary antibiotic residues (*i.a.* TC_S and their degradation products) mainly stayed on the surface after the spreading of swine manure and a subsequent rainfall, these residues were to some extent also distributed in the various soil depth layers of the field, signifying possible translocation in the nearby environment via drainage waters (Solliec et al. 2016).

In their recent study, Sura et al. indicate bulk density as a crucial factor affecting the surface runoff of veterinary antimicrobials. They examined the transport of CTC, SMT and TYL, which are commonly used in beef cattle production, in simulated rainfall runoff from feedlot pens and observed that increased bulk density lowered infiltration and finally caused a higher runoff volume (Sura et al. 2015). Surface water contamination results from surface runoff or drain-flow; hence, it is possible to mimic this process in the field, as described above. However, it is much more complicated to observe leaching to groundwater via infiltration through soil profiles under field conditions. Although such scenarios can be simulated in the laboratory with batch and column tests, there are discrepancies in the results obtained according to different methodological approaches. For example, the results obtained in batch and column tests for NA showed a lack of agreement (Clervil et al. 2013). Although the order of affinity determined by the batch results was consistent with that observed in the column system, the retardation factor derived from batch data was higher than that determined from the column breakthrough curves for all the sediments tested. Moreover, a discrepancy in terms of the total sorbed amount was also observed. The authors highlighted that this could be attributed to several factors linked to the differences between the experimental conditions of batch and column investigations: solid/liquid ratio, the loss of sorbent particles through transport, variations in column flow and moisture content, column flow channeling and the presence of immobile water regions as well as the kinetic behavior of adsorption (Clervil et al. 2013). Liu et al. also reported that, in the case of weakly sorbed compounds, the failure to incorporate sorption kinetics into pharmaceutical transport during water quality modeling leads to a significant underestimation (80%) of dissolved-phase concentrations, whereas for compounds exhibiting fast sorption, an overestimation of up to 150% may occur (Liu et al. 2013b). Although the leaching of SA_S was comparable in batch and column tests in the study performed by Maszkowska et al., the authors observed slight differences in leaching determined within batch testing in comparison to column testing (Maszkowska et al. 2013). Greater leaching was observed for the column test in the case of soil with a considerably higher clay fraction content. This has been explained by the different test procedures and the possibility to produce more fine particles during tumbling in the batch test and thus enhanced sorption. For coarse-grained soil, greater leaching was observed in the case of the batch test. This could have arisen from the low probability of producing more very fine particles and hence no possibility of reduced leaching via colloid sorption. A correlation between hydrophobicity and leaching potential was also observed. The slowest release was reported for SDM—the most hydrophobic among the tested compounds (24.5% decrease in concentration to L/S 1.22 L kg^{-1}).

A comparison of batch and dynamic tests was also performed by Kurwadkar et al. A column test showed that antimicrobials such as the selected SA_S, TYL and CBX achieved only a nominal 40–50% of equilibrium capacity. The results in the column tests therefore reflect transport under conditions of partial equilibrium, as may occur under typical storm conditions in the field (Kurwadkar et al. 2007, 2011). Among the investigated compounds, SA_S were more mobile than TYL and CBX, which in contrast were considered immobile with a low risk of reaching the groundwater. However, relatively mobile SA_S also turned out to be immobile in slightly acidic soils with greater organic carbon and a greater cation-exchange capacity (Kurwadkar et al. 2011).

As already mentioned above, TC_S exhibit the potential to be translocated via macropore flow, though their K_d coefficients are relatively high. Ostermann et al. also confirmed this conclusion (Ostermann et al. 2013). Although only TC and DC among the investigated TC_S occurred in the leachate at a single event, an initial preferential flow was reported to be probable for these compounds under field conditions. Preferential flow comprises the physical phenomena of the rapid transport of water and solutes in soil bypassing other volume fractions of the porous soil matrix and is attributed to flow through cracks, fissures, and biophores, e.g. earthworm burrows and root channels. Additionally, preferential flow can arise from non-homogenous infiltration or wetting flow instabilities (Bundt et al. 2001; Gerke 2006). Thus, even highly sorbed compounds such as TC_S may be more mobile than anticipated and pose a contamination risk to surface or ground waters. Nevertheless, the occurrence of TC and DC in the leachate was considerably lower than the concentration of SA_S (Ostermann et al. 2013).

Blackwell et al. showed that OTC is unlikely to move to groundwater, but has some potential to move to surface water within a short period after application. Moreover, the concentrations of OTC in runoff were at sub μg L^{-1} levels and these would drop significantly when the runoff was diluted in surface water bodies (Blackwell et al. 2007). The conclusion of Popova et al. about the relatively low risk of the significant transport of CTC, OTX, and IVM to surface-and ground waters from cattle manure on irrigated pasture tallies with this (Popova et al. 2014). The leaching of SA_S via preferential flow paths is in agreement with previous data for sulfachloropyridazine (SCP) which indicate a preferential flow for this SA in both undisturbed clay loam, where macropores are likely to exist (Kay et al. 2005b), and homogeneous sandy loam (Blackwell et al. 2009). SCP showed the potential to move to both groundwater and surface water in the study of Blackwell et al. (2007), but at low or sub μg L^{-1} concentrations before dilution into the receiving water (Blackwell et al. 2007). Ostermann et al. also determined only small portions of antibiotics, mainly SA_S, in the leachates. However, taking into consideration the fact that their concentrations in leachates constantly exceeded the threshold-value for groundwater contamination in the worst-case scenario, they indeed pose a risk for gradual groundwater contamination in the long run (Ostermann et al. 2013).

Despite all the advantages of column leaching tests, especially more environmentally relevant experimental conditions ensuring leaching data is not underestimated due to overestimated sorption results, their weakness also needs to be pointed out. For example, Kay et al. emphasized several factors leading to great discrepancies between a lysimeter study and a field study, such as a low representation of the spatial heterogeneity of the field soil in lysimeters in terms of hydrology, a lack of backfill in the lysimeter, and a different temperature (Kay et al. 2005b). Moreover, the influence of temperature on the sorption potential of ionizable pharmaceuticals onto soil particles has already been proved in the literature (i.a. SA_S) (Maszkowska et al. 2014). Although lysimeters may not be subject to all of the processes occurring in the field, according to Kay et al. this problem may be solved by collecting relatively large lysimeters and/or incorporating important hydrological pathways, such as drain backfill and desiccation cracks, into the lysimeters (Kay et al. 2005b). Also, test material has a strong influence on the obtained results. According to Oppel et al., topsoil and subsoil may differ significantly in terms of organic carbon, bacterial community, and further properties. Therefore, the results from leaching tests performed with topsoil have only a limited transferability for subsoil where there may be a source of groundwater contamination (Oppel et al. 2004). Moreover, in natural soil environments, when unsaturated flow conditions as well draught periods may lead to the drying out of the soil, leaching can be decreased by moving the chemicals back towards the soil surface as a result of capillary forces (Rabølle and Spliid 2000).

3.2 Occurrence of VPs in Ground Waters and Comparison to Leaching Data

The fast leaching of SA_S in laboratory tests or field studies is supported by the results of groundwater monitoring studies. A range of these antibiotics, e.g. STD, SMT, SDM and SMX, have been detected in different studies in groundwaters in a concentration of up to 3461 ng L^{-1} (Barnes et al. 2008; Bartelt-Hunt et al. 2011; Diaz-Cruz et al. 2008; Estévez et al. 2012; García-Galán et al. 2010; Lapworth et al. 2012; Lindsey et al. 2001; Sui et al. 2015; Teijon et al. 2010). Moreover, García-Galán et al. detected 18 out of the 19 target SA_S in two groundwater bodies from Catalonia. The highest frequency of detection was observed for SMT and SDM (89.4%); however, an acetylated metabolite of SMT also occurred frequently in the collected samples (82%) (García-Galán et al. 2010). These SA antimicrobials have also been detected by Batt et al. in groundwater samples of private water wells in USA. The concentration ranges were 76–215 and 50–68 ng L^{-1} for SMT and SDM, respectively. Thus, the negative impact of a concentrated animal feeding operation (CAFO) on the quality of the local groundwater has been proved (Batt et al. 2006).

While the presence of SA_S in water compartments, including groundwater, is justified, the leaching of TC_S is generally considered in the literature as being unlikely to occur. However, López-Serna et al. reported the occurrence of TC and OTC in groundwater underlying the city of Barcelona in Spain. Moreover, the concentrations determined were comparable to those obtained for SA_S (López-Serna et al. 2013). In the same study, the fluoroquinolone antibiotic—NOR, occurred in groundwater in the relatively high concentration of 462 ng L^{-1}, although its sorption coefficient indicates low mobility in soil (Conkle et al. 2010). However, mobility studies are normally performed in laboratory conditions while in a real environmental situation the sorption can be disturbed by the other matrix components obtained in the soil and transmitted water. Other VP_S, the presence of which in groundwaters has been determined, are as follows: TMP, ROX, SPM, MTZ, AZM, ERY, LIN, and MON (Barnes et al. 2008; Bartelt-Hunt et al. 2011; K'oreje et al. 2016; López-Serna et al. 2013; Sui et al. 2015).

As has already been mentioned above, the potential transport of veterinary medicines into groundwater is recognized by EU guidance documents. Therefore, in order to ensure data for a large set of chemicals and various scenarios, different models for the estimation of the predicted exposure concentrations (PEC) in relevant environmental compartments (e.g. groundwater) are available. The VetCalc model and the Forum for the co-ordination of pesticide fate models and their use (FOCUS) such as PEARL (Pesticide Emission Assessment at Regional and Local scales), PELMO and MACRO are recommended for such assessments of VP_S (Metcalfe et al. 2008). Concentrations in groundwater are approximated by pore water concentrations (i.e. $PEC_{groundwater} = PEC_{porewater}$), and they can be derived according to equations provided in the guidelines on the basis of predicted environmental concentrations in soil (PEC_{soil}). Although such models often use real experimental data instead of predicted data (e.g. sorption coefficients on the basis of octanol-water partition coefficients in PEC_{soil} calculations), discrepancies and gaps concerning the fate of VPs sometimes cause these results to diverge from reality.

Blackwell et al. evaluated the predictive capability of the PEARL leaching model. A comparison of the experimental measurements with simulations from this model demonstrated that it greatly underestimates the transport of antibiotics to groundwater. SCP, which is recognized as a mobile compound, and the occurrence of which in groundwater has been reported in many experimental studies, is considered by the model to be not leachable (Blackwell et al. 2009). Thus, leaching models can strongly underestimate the leaching behavior of VPs, probably due to their inability to consider factors affecting leaching in the field [e.g. different degradation rates due to temperature changes or differences in bioavailability (Blackwell et al. 2009)]. On the other hand, the study of Boxall et al. indicates the greatly overestimated risk of pharmaceuticals the occurrence of which in groundwater has already been reported at much lower concentration levels. The $PEC_{groundwater}$ for MON (326 $\mu g\ L^{-1}$) investigated in this study was revealed to be overestimated around 800-fold in comparison to concentrations seen in the field (0.39 $\mu g\ L^{-1}$) (Boxall et al. 2006b). Moreover, even an additional study determining VPs in groundwater impacted by a large CAFO detected MON in much lower concentrations (2.35 $\mu g\ L^{-1}$) than was the case for $PEC_{groundwater}$ (Bartelt-Hunt et al. 2011).

An overestimated PEC_{soil} has also been highlighted by Metcalfe et al. If concentrations of veterinary medicines in manure were either measured or spiked, there was better agreement between predicted and measured concentrations in soil (Metcalfe et al. 2008). A possible explanation for this lay in the overestimated animal husbandry scenarios and manure application scenarios in comparison to actual inputs to soils. In contrast, Blackwell et al. showed that the PEARL model seemed to work well in identifying compounds that do not leach (i.e. TC_S). However, further investigation of groundwaters demonstrated OTC occurrence in groundwater at a concentration of 41 $ng\ L^{-1}$ (López-Serna et al. 2013). A possible reason for this could be attributed to the inappropriately low limit of detection/quantification of analytical methods used so far for groundwater monitoring. Sensitivity is, therefore, one of the most critical parameters in order to obtain unequivocal and reliable determinations for groundwater risk assessment. Moreover, due to analytical constraints, the concentrations used in sorption studies are often significantly higher than those that would normally be encountered in the environment. Under field conditions, where concentrations of VPs are expected to be at the ng L^{-1} level, greater sorption capacities may be exhibited due to e.g. binding to specific and rare high-energy adsorption sites, which cannot be observed under laboratory conditions with relatively high concentrations of sorbate (Borgman and Chefetz 2013; Srinivasan et al. 2014). Therefore, even if in leaching modeling the sorption coefficient determined in batch testing (not the predicted one) is used, the leaching modeling could under or over–estimate the leaching behavior of VP_S. Srinivasan et al. proposed the concentration-dependent effective distribution coefficient (K_d^{eff}) as the basic tool for leaching estimations, as it provides a more realistic field situation (Srinivasan et al. 2014).

Another reason for underestimated modeling results for strongly sorbing compounds could be particle-facilitated transport, which is not considered in the simple algorithms suggested by the Committee for Veterinary Medicinal Products (Metcalfe et al. 2008). Possible discrepancies between modeling and field studies may also arise from differences in the scenario that is modeled and the systems where the monitoring has been done. Taking all the above mentioned into account, there is still work to be done to improve existing models as well as the analysis which is necessary for the sensitive detection of VPs at trace levels in complex matrices. Moreover, laboratory leaching experiments still need to be conducted in order to provide large sets of experimental data, especially regarding factors influencing the sorption and mobility of VPs in soil. It is also worth stressing at this point that it seems invaluable to combine data from models and monitoring studies including climate factors and regional scenarios. One such comprehensive approach recently proposed for groundwater risk assessment from pesticides (Di Guardo and Finizio 2016) would also greatly improve risk assessment related to the leaching of VP_S.

4 VPs vs. Soil Microorganisms

Among all the groups of VPs, antibiotics exert significant influence on soil microorganisms. As they are designed to selectively affect microorganisms, once introduced to soil they might then affect the structure and function of bacterial communities as well as the development and spread of antibiotic resistance. TC_S (including CTC, OTC, and TC) and SA_S (including SMT, SMX and SDZ) are typical antibiotics that are widely used in animal husbandry; thus, most literature data on the impact of veterinary antibiotics on bacteria in soil environments concern SA_S and TC_S.

4.1 Toxicity Toward Soil Bacteria and Fungi

The available data on the toxic effect of VPs on the environment and, in particular, soil bacteria are scarce. It has been documented that, given the nature of the soil environment, it is impossible to evaluate toxicity toward soil bacteria based on results obtained in tests for single species (such as growth inhibition tests with *Pseudomonas putida* or bioluminescence inhibition tests with *Vibrio fischeri*) and environments other than soil. For example, the inhibitory effect of OTC on activated sludge bacteria occurs at significantly lower concentrations ($EC50 = 0.14$ mg L^{-1}) (Halling-Sørensen 2001) compared with soil bacteria ($EC50 = 50$ mg kg^{-1} dry soil) (Vaclavik et al. 2004). The growth inhibition of soil bacterial isolates has been observed in agar diffusion disk tests for CTC and SDZ, whereas in microcosms with soil spiked with these antibiotics no effects have been observed up to the highest tested concentrations of 50 mg kg^{-1}, either on respiratory activity or on bacterial population structure (Zielezny et al. 2006).

Numerous studies have documented changes of in soil microbial community structure as a result of exposure to antibiotics in the environment. Most often, molecular fingerprinting techniques reveal changes in band patterns or in intensities of signals representing different microbial species (Hammesfahr et al. 2008; Reichel et al. 2013; Zielezny et al. 2006). The long environmental residence times of FQ_S in soil matrices affect the composition and activity of soil microbial communities, which was demonstrated for CIP at 200 μg kg^{-1} by Girardi et al. (2011). Schmitt at al. reported that the contamination of soil with SCP resulted in small changes in the community level physiological profile (CLPP) accompanied by increased pollution induced community tolerance (PICT) against further additions of the sulfonamide. A decrease in the microbial diversity indexes at 100 μg L^{-1} of TC was observed in a batch reactor experiment (Zhang et al. 2013a). The microbial community structure of wheat rhizosphere soil exposed to different concentrations of OTC was highly affected. It was shown that exposure to OTC inhibited the growth of *Bacillus* and therefore results in a decline in soil enzyme activity in the wheat rhizosphere (Yang et al. 2009). In contrast, Berglund et al. observed no effect on bacterial diversity after continuous exposure to a mixture of 12 antibiotics in experimental wetlands (Berglund et al. 2014). Similarly, no significant differences were observed in constructed wetlands in terms of bacterial abundance, richness or diversity, among different treatments (without a pharmaceutical addition or with TC or with ENR at concentrations of 100 μg L^{-1}) or throughout the duration of the experiment. However, a significant effect of both time and treatments was noted on bacterial community structure by Fernandes et al. (2015). A high level of diversity is considered to be an important feature of ecosystem integrity, as it implies functional redundancy, acting as a genetic and functional reservoir that increases community resilience to disturbance (Bissett et al. 2007). Therefore, a loss of community diversity has been used to indicate a decline in ecosystem function (Allison and Martiny 2008). It has been shown that changes in microbial community structure can affect the ecological functions of soil ecosystems, e.g. biomass production and N-transformation processes (Kotzerke et al. 2008). Nevertheless, other studies have revealed that community shift is not necessarily mirrored by altered soil functioning, but is masked by functional redundancy sustained by a structurally changed microbial community (Fernandes et al. 2015; Hammesfahr et al. 2008).

Additionally, the ratios of bacteria/fungi and Gram positive/Gram negative bacteria, the two indicators most often used to describe changes in microbial community structure, were studied. An increased fungi/bacteria ratio was reported after the application of manure containing SDZ (at a concentration of 10–100 mg kg^{-1}) in soil, due to both a reduction in bacterial biomass and a stimulated growth of fungi (Hammesfahr et al. 2008). Other antibacterials, such as SPY, OTC (Thiele-Bruhn and Beck 2005) and SMX (Demoling et al. 2009), also increased fungi/bacteria ratios. A shift towards Gram positive bacteria and fungi was observed after the application of slurry from SDZ and DFX medicated pigs (Reichel et al. 2013). It is noteworthy that antimicrobial agents may also act on non-target organisms; OTC and PEN, when combined together, reduced the lengths of active hyphae of fungi in forest soils (Colinas et al. 1994).

Bacteria form one of the most important groups of organisms in soil and are essential for the decomposition of organic matter, and geochemical cycles such as the carbon, nitrogen, sulfur and phosphorus cycles. Knowledge of the effects of antibiotics on the ecological functions of soil is still limited. Three reports have described the influence of SDZ on soil nitrification/denitrification processes (Kotzerke et al. 2008; Ollivier et al. 2010; Schauss et al. 2009). SDZ affects the abundance and diversity of nitrifying bacteria and leads to a decrease in ammonia-oxidizing bacteria and an increase in ammonia-oxidizing archaea (Ollivier et al. 2010; Schauss et al. 2009). Apart from the nitrification process, Kotzerke et al. also studied the effects of SDZ on denitrification processes in soil. With SDZ at 10–-100 mg kg^{-1}, the denitrification rate in the soil samples was significantly reduced (Kotzerke et al. 2008).

The antibiotic effects on microbial activities and enzymes in soil have also been reported. The influence of various antibiotics, such as CIP, SDZ (Kotzerke et al. 2008; Zielezny et al. 2006), TYL (Demoling and Bååth 2008; Muller et al. 2002), CTC and SCP (Vaclavik et al. 2004) on the soil respiration rate and soil biomass production has been reported. OT effects on soil microbial respiration have been determined in soil with or without the addition of manure. In all cases, an NOEC of 10 mg kg^{-1} was obtained (Boleas et al. 2005). In contrast, Hund-Rinke et al. (2004) did not find any influence of TC on soil respiratory activity with concentrations up to 50 mg kg^{-1} soil. The inhibition of alkaline phosphatase after exposure to 10–-30 mg kg^{-1} OTC in soil was observed, while the other three soil enzymes tested (acidic phosphatase, dehydrogenase, and urease) were not affected (Yang et al. 2009). Thiele-Bruhn and Beck reported that dehydrogenase activity and basal respiration in soil were not significantly affected by either SPY or OTC, regardless of the doses of antibiotics. The lack of any observed effect could be, according to the authors, explained by shifts in the microbial community structure that compensated for effects on single species. In other studies, Thiele-Bruhn tested nine pharmaceutical antibiotics for their effects on the reduction of microbial iron(III) in six different topsoils. The derived effective doses (ED [μmol kg^{-1} soil]) for the different antibiotics increased in the following order: CTC (53) <SDM (58) < OTC (170) < SDZ (190) < SMD (270) = TC (270) < SPY (430), although no effect was found for SFL and FBZ at doses of up to 5.8 and 3.3 mmol kg^{-1}, respectively. Both the inherent chemical properties of antibiotics and environmental parameters could influence the actual effects of antibiotics on the soil microbial community. The effects of antibiotics are influenced by their actual concentrations in soil that could come into direct contact with microbes (bioavailable concentration). The actual concentration in the soil and aqueous phase is a function of time, stability or the persistence of the antibiotic, soil properties (such as soil pH, soil organic matter, and soil minerals), and microbial activity (Thiele-Bruhn 2003). A number of studies have shown that sorption may lead to the reduction (Hund-Rinke et al. 2004; Kotzerke et al. 2008; Thiele-Bruhn 2005) of antibiotic effects on microbial communities. Determined effective concentrations (EC50) in soil solution derived from sorption experiments are considerably smaller and range from 0.004 μmol L^{-1} (CTC) to 120 μmol L^{-1} (SPY) (Thiele-Bruhn 2005).

The consequences of the observed changes in community structure influence the function of the soil and it is expected that such disturbances might have significant and long-term effects on ecosystem homeostasis. However, long-term studies frequently detect a recovery of the community biomass and a growth of certain microbes that were initially inhibited. Demoling et al. (2009) employed PLFA and pollution-induced community tolerance (PICT) analysis to evaluate the effects of SMX on soil microbes, which demonstrated an initial decrease in bacterial growth rates and a gradual amplification of more tolerant species, as reflected by an increase in PICT. Similarly, in Kotzerke et al. (2008), microbial activity recovered at day 32 when a high concentration of SDZ was added.

4.2 Resistance of Bacteria

The application on land of manure from antibiotic-treated animals has been reported to frequently increase not only the levels of antibiotics, but also the abundance of resistant bacteria and antibiotic resistance genes (ARGs) in soils (Ghosh and LaPara 2007; Martínez 2008; Białk-Bielińska et al. 2014). Resistance genes, as well as resistant bacteria in the environment are increasingly seen as an ecological problem and, furthermore, are considered to be new contaminants which might pose a potential worldwide human health risk (Zhu et al. 2013). The diversity and abundance of various ARGs has been detected in soil with the application of swine manure in different countries (Heuer et al. 2011; Huang et al. 2013; Wu et al. 2010a, b).

The development of resistance is believed to be promoted by continuing exposure to sublethal concentrations of antibiotics (Thiele-Bruhn 2003). SA_S concentrations as low as 0.1 mg kg^{-1} of soil could have a selective effect on resistant populations in soil (Heuer et al. 2008). The extent of the increase in resistance in soil following manure fertilization is related to the intensity of manure fertilization (Karci and Balcioğlu 2009; Sengeløv et al. 2003). A study of agricultural soil from The Netherlands has shown the accumulation of antibiotic resistance genes over six decades of increasing use of antibiotics (Knapp et al. 2010). Nine classes of *tet* genes are dominant in arable soil after 6 years of the application of fresh or composted manure (Peng et al. 2015). Fang et al. (2014) reported that bacterial community tolerance to CTC and SDZ in manure-amended soil increased significantly with the frequency of antibiotic treatment. Following three sequential applications of manure containing antibiotics, the accumulation of numbers of copies of sulI and sulII significantly increased compared to the treatment with antibiotic-free manure or unfertilized control soil (Heuer et al. 2011). Changes in community tolerance after exposure to a certain pollutant can be measured by PICT analysis. PICT changes under antibiotic treatment not only reflect shifts in microbial community structure, but also imply the amplification of antibiotic resistance within a community (Ding and He 2010). Several studies found substantial PICT increases after soil was treated with $\mathrm{SA_S}$, e.g., SDZ (Brandt et al. 2009), SMX (Demoling et al. 2009) or SCP (Schmitt et al. 2005) and TYL (Demoling and Bååth 2008).

The resistance of microorganisms is not only provoked by the input of antibiotics into the environment and their selective pressure. It appears to be more important that resistant microorganisms co-occur with manure introduced into soils. However, it was demonstrated that manure-derived bacteria could not thrive in soil environments, and gradually decreased after manure treatment (Hammesfahr et al. 2008; Heuer et al. 2008), which was attributed to differences in environmental conditions between the soil and animal gut. It is known that the survival times of culturable fecal bacteria in soil are only in the range of weeks to months (Chee-Sanford et al. 2009). Since bacteria from manure are not sufficiently adapted to soil environments, horizontal gene transfer from manure to indigenous soil bacteria might be important for the dissemination of resistance in soil (Chee-Sanford et al. 2009; Gillings and Stokes 2012; Götz and Smalla 1997; Heuer et al. 2011). Most ARG cassettes are found on integrons frequently located on plasmids and transposons, which might be transferred from manure bacteria to soil bacteria (Binh et al. 2008; Allen et al. 2010; Heuer et al. 2011). Plasmids belonging to the groups Inc-P1, IncQ, IncW, and IncN, which play an important role in disseminating antibiotic resistance genes, have been identified in both manure and farm soil samples (Binh et al. 2008; Heuer et al. 2011; Smalla et al. 2000). Also, an increased activity of integrases and transposases, enzymes related to transposition processes, has been observed. Resistance genes located on broad host range plasmids make transfer between distantly related species more possible (Heuer et al. 2011; Zhu et al. 2013). Additionally, LowGC-type plasmids have been observed to be highly abundant in manure and manured soil. Some antibiotic resistant bacteria in soil and manure are phylogenetically close to human pathogens (for example, Acinetobacter spp.-identified as a potential host for LowGC plasmids), making genetic exchange more likely (Byrne-Bailey et al. 2009). Moreover, it has been shown that broad host range resistance plasmids belonging to the IncP-1ε group are frequently captured from manure and manure treated soil into E. coli recipients (Heuer and Smalla 2012).

Microbes containing the ARGs from manure or soil are possibly subject to dispersal via leaching to subsurface soils and groundwaters (Pruden et al. 2012). Sulfite-reducing TC resistant clostridia have been detected in manure, manure fertilized soils and groundwater (Huysman et al. 1993). It was reported that, in contrast to the decreasing concentration of antibiotics, four ribosomal protection protein genes (tetM tetO tetQ tetW) increased with soil depths and the gene copies normalized to 16S rRNA even reached 10^{-4} or 10^{-3} in the deepest 40–60 cm layer (Tang et al. 2015). The emergence and spread of ARGs in different depths of soil may also be closely associated with mobile genetic elements (Binh et al. 2008; Heuer and Smalla 2012; Zhang et al. 2011). Huang et al. (2013) reported that the resistance determinants can migrate to deeper soil layers and could possibly contaminate the groundwater by vertical transport. On the other hand, it has been documented in manure amended plots that the abundance of ARGs in surface soils is orders of magnitude higher than in subsoils (Joy et al. 2014). Moreover, Fahrenfeld et al. (2014) reported that no evidence existed for the surface or subsurface transport of ARGs in soil due to manure application using a field-scale mass balance approach.

There is little information on how quickly a reduction in antibiotic use will result in decreased resistance. According to Tamminen et al. (2011), once established by the selective pressure of antibiotics, resistance genes persist even after the selective pressure is removed. The prevalence of SA resistance genes (*sulI* and *sulII*) was observed in bacterial isolates from agricultural soils in the United Kingdom after 2 years of the application of manure containing antibiotics, compared to non-amended soil (Byrne-Bailey et al. 2009). Hong et al. (2013) reported an increased abundance of *tet* genes in soil after pig manure application, and these levels remained elevated for up to 16 months. A reduction in resistance levels was reported in the literature; however, it was only in the range of percentages, and resistance genes persisted for many years in the absence of the corresponding antibiotic compounds (Johnsen et al. 2009). Acquired antibiotic resistance genes and mobile genetic elements often impose a cost on the host cell, which reduces that host's fitness in the absence of antibiotics. It is also possible that the cost of acquired resistance genes in the absence of selective pressure is further reduced at the population level by heterogeneous permissiveness for horizontal gene transfer. Resistance genes persist in a permissive subpopulation that increases in relative abundance in cases of antibiotic selection (Heuer et al. 2011).

The survival of microorganisms in the presence of antibiotics is not only due to acquired resistance. Soils represent habitats and sources of indigenous antibiotic-producing microorganisms (Thiele-Bruhn 2003). Natural antibiotics produced by bacteria and fungi occur in the environment and control the dynamics of microbial populations. Such antibiotics synthesized in situ are found especially in the soil rhizosphere, with concentrations of up to 5 μg g^{-1} (Thiele-Bruhn 2003). Among numerous other soil organisms, 30–50% of actinomycetes isolated from soil are able to synthesize antibiotics (Allen et al. 2010). Antibiotic producers contain resistance genes within a biosynthetic gene cluster to avoid autoinhibition (Cundliffe 1989). Many investigations have revealed that numerous soil microorganisms have a natural tolerance towards antibiotics. Out of 36 strains of microorganisms from uncontaminated soil and water, only seven were susceptible to 21 diverse antibiotics (Thiele-Bruhn 2003). In particular, pseudomonas are often intrinsically resistant to antibiotics (Halling-Sørensen et al. 2003a, b). Therefore, it is not surprising to detect a set of diverse ARGs in both untreated soils and control pristine soils; and these ARGs represent nearly all the classical resistance mechanisms including antibiotic efflux, target protection, and antibiotic inactivation (Walsh 2000). Moreover, it has been shown that resident soil antibiotic resistance bacteria are also found to significantly increase following the application of manure from cows without a history of antibiotic treatment (Udikovic-Kolic et al. 2014). The substrates from manure may permit the growth of microbial populations carrying *tet* and *sul* genes (Heuer et al. 2011). The addition of nitrogen fertilizer may strongly influence the content of ARGs in soil (Forsberg et al. 2012). Other factors that might indirectly enhance the spread of antibiotic resistance are metals which accumulate in soil owing to manure application. Cu, for instance, has been shown to co-select for antibiotic resistance in microbial soil communities under field conditions (Berg et al. 2010). However, it has been shown that resistance in pristine soils differs quantitatively and qualitatively from soils under agricultural influence. For example, in soil samples from the Rocky Mountain National Park the TC resistance genes tetB, tetC, tetW, and tetO are not detected by real-time PCR, while these genes are abundant in soil samples from other sites in Colorado affected by agricultural or urban activities (Jiaa et al. 2014).

Soil is considered to be the largest environmental reservoir, comprising as much as 30% of the known ARGs in public repositories (Nesme et al. 2014). High-throughput functional metagenomic analysis has found that soil bacteria harbor resistance gene cassettes against all major classes of antibiotics with high levels of similarity to genes from human pathogens (Forsberg et al. 2012). As the only ecosystem interacting constantly with all compartments of the biosphere, soil is prone to genetic exchange by means of horizontal gene transfer between ecologically distinct lineages found in other ecosystems (Nesme and Simonet 2015). The pollution of the environment by veterinary antibiotics and antibiotic resistant determinants likely increases the chance of human-associated bacteria and human pathogens acquiring resistances by mobile genetic elements such as broad host range plasmids, facilitating horizontal gene transfer between distantly related species (Heuer et al. 2011).

5 VPs vs. Plants

Manure, both solid and liquid, is normally distributed onto residential allotment gardens (small scale), as well as crop plantations (large scale). This manure can be composted before use to increase the bioavailability of nutrients, improve the physical and chemical properties of composts and suppress phytopathogens (Moral et al. 2009). A side effect is the degradation of pharmaceutical bulk [more than 99% of the antibiotic removal from manure during 40 days of composting (Ho et al. 2013)].

VPs can be found in water (ng L^{-1}), soils (level of ng kg^{-1} to μg kg^{-1}) and manure/biosolids (ng kg^{-1} to mg kg^{-1}) (Ding et al. 2011; Dorival-García et al. 2015; Ho et al. 2012; Kemper 2008; Solliec et al. 2016; Wei et al. 2016), and all of these can affect the crop plant. Studies focusing only on the impact of VP_S on plants are scarce. Most studies have investigated the intake of pharmaceuticals from reclaimed wastewater or sewage sludge as a fertilizer (Carter et al. 2015; Cortés et al. 2013; Fatta-Kassinos et al. 2011; Grassi et al. 2013; Miller et al. 2015; Shenker et al. 2011; Verlicchi and Zambello 2015; Wu et al. 2013). The plants which fall within the scope of this study are edible crops, e.g. carrot, radish, lettuce, cucumber and tomato, onion (Carter et al. 2014; Chuang et al. 2015; Herklotz et al. 2010; Holling et al. 2012; Kang et al. 2013; Kumar et al. 2005; Sabourin et al. 2012), and also soya and cereals (Hawker et al. 2013; Marsoni et al. 2014). Most of these can be consumed without the need for processing.

The interactions between plants and pharmaceuticals have been under investigation for several years, because of the use of phytoremediation in constructed wetlands (Carvalho et al. 2014). Phytoremediation is a technology that utilizes plants and the associated rhizosphere microorganisms to remove, transform or contain toxic chemicals located in soils, sediments, groundwater, surface water and even the atmosphere (Susarla et al. 2002). Several of the studied plants have been shown to be effective in the phytoremediation of veterinary and human pharmaceuticals (Carvalho et al. 2014). This process is not only connected with plant uptake, biodegradation and photodegradation, but it is also important in pharmaceutical elimination (Zhang et al. 2014a, b). The ratio of these three elimination methods varies between pharmaceuticals (Matamoros et al. 2012; Zhang et al. 2013a, b), but the exact values for VPs are as yet unknown.

5.1 *Uptake and Translocation*

Generally, water and small solutes ($Mr \leq 500$) 108 can enter the root through the epidermis (Trapp and Mc Farlane 1995); they can then be transported via the xylem/phloem to internal tissues, provided they are not stopped by barriers inside roots (Miller et al. 2015). The chemical character of neutral compounds, mainly the lipophilicity, positively affects the ability to cross plant cell membranes by passive processes (Sterling 1994). The surface potential of the cytoplasmic membrane is negative, thereby charged molecules will interact with it (Devillers 2009). This leads to the accumulation of compounds within plant root cells. Some pharmaceuticals are expected to be subject to ion trapping, but experimental studies have not been carried out (Miller et al. 2015). Ion exchange of negatively charged walls and cationic pharmaceuticals can decrease their pathway to underlying cells, but currently there is no information to prove this statement. Protein-mediated transport, observed in the case of some plants, is another possible means of pharmaceutical uptake. Many organic nitrogen transporters obtained in plants have low selectivity (Rentsch et al. 2007), which suggests they can mediate in the transport of those VPs which are neutral and structurally similar to the originally transported compounds. Quaternary ammonium compounds can be taken up by plants as well (Warren 2013), but actually no VPs have a quaternary ammonium character. Some of the assimilated molecules rich in nitrogen can have high masses, of several thousand Da, so uptake is not limited to the low mass-compounds. Given that some molecules cannot enter the deeper layers they will stop in the roots. This has been proven for trimethoprim and sulfonamides (Tanoue et al. 2012). Accumulation in roots is in contrast to the translocation of VPs in plants to leaves, seeds and fruits. More information can be found in the review by Miller et al. (2015).

Since some plant roots represent a destination place for many pollutants, their accumulation in plants can be expressed using the root concentration factor (RCF), i.e. the ratio of the concentration in roots to the concentration in the exposure medium (soil or soil pore water). For example, the RCF of OTC and NOR in soybean roots are 0.68–3.32 and 0.16–1.52 (Boonsaner and Hawker 2010). The uptake factor (UF, concentration of an analyte in plant material to its concentration in soil) is more general than the RCF and more reliable than the BCF (concentration of an analyte in plant material to its concentration in water used for irrigation). The UF for lettuce and carrot is in a range lower than 0.01–1.4 (but mostly lower than the detection limit) for popular antibiotics (Boxall et al. 2006a). The highest BCFs (ratio of the analyte concentration detected in the plant tissue to the spiked concentration in the growth medium) have been obtained for carbamazepine (100 L^{-1} kg), fluoxetine and phenytoin (anti-epileptic drugs) in hydroponic experiments, so not for pharmaceuticals used for animal treatment (Wu et al. 2015), but in soils irrigated by treated wastewater. The bioaccumulation factor (BAF) varies between 0 and 4.75 ($R = CV/CS$; CV, antibiotic residues in vegetables; CV, antibiotic residues in soil) for veterinary antibiotics in vegetables grown in northern China (Hu et al. 2010b).

It is certain that the main mechanism of VPs intake by plants is transpiration-i.e. a passive mechanism (Dodgen et al. 2015; Liu et al. 2013a). The key role in this process is played by the properties of the chemical compounds. In the case of pesticides, the vital role of uptake by plants is fulfilled by hydrophobicity (Inoue et al. 1998; Trapp 2000). The ionic form of compounds also plays a role, but has an opposite effect to the uptake-i.e. ionizable compounds have a limited uptake (Wu et al. 2013). VPs constitute a very wide range of chemical compounds; so, their interaction with plants is assumed to be structure-dependent. Assays of OTC, CLC and NOR uptake by rice show that maximum concentrations are compound-dependent linear functions of initial soil/water concentrations, and are not related to K_{ow} (Hawker et al. 2013), and this suggests that root intake is connected with the ionization state of these zwitterionic compounds. MQ_S with a large size (>500) have been reported in many studies to not be taken up by plants (Boxall et al. 2006a; Jones-Lepp et al. 2010; Kang et al. 2013; Kumar et al. 2005; Pan et al. 2014). The most probable reason for this is their excessive mass for passive intake and the lack of protein-mediated or energy-dependent activity (Miller et al. 2015). Molecular weight and log K_{ow} have been reported to play a direct role in the uptake of small pharmaceuticals by lettuce (Calderón-Preciado et al. 2012). Given that all VPs are ionized in normal natural conditions, it can be suggested that their uptake will be limited. In addition, ionizable compounds are normally sorbed by soil minerals. The transport of hydrophobic pharmaceuticals is limited and they remain in roots (Dodgen et al. 2015). It has also been reported that basic compounds have higher transport (to leaves) rates using transpiration than acidic or neutral species (Dodgen et al. 2015). Some studies have reported that the intake of small molecules is connected with translocation by water mass flow, and thus pharmaceuticals are concentrated in older leaves (Shenker et al. 2011). However, this is not a rule for all plants. In the case of OTC uptake into alfalfa plants, some energy-dependent processes play a key role (Kong et al. 2007). Moreover, the uptake of this VP is positively related with the pH of the soil solution, where OTC is mostly in a neutral form. All of this information leads to confusion in terms of the prediction of VPs uptake, when the structure of a compound is taken as the predominant factor.

In most cases, hydroponic experiments have been used to estimate the priority of compounds and plant uptake, but the results can be totally different using real soil, because of VPs sorption into organic matter (Wu et al. 2015). The bioconcentrations obtained for pharmaceuticals determined in soil experiments are several times smaller than those for hydroponic experiments, which indisputably confirms that the sorption and transformation of VPs in a real environment significantly decreases their uptake to plants. The high divergence of results from hydroponic and field studies is not a surprise. Natural soil is rich in organic matter, and the correlation between the sorption of pharmaceuticals and the percentage of organic matter is positive (Białk-Bielińska et al. 2012). In the case of carbamazepine, a human pharmaceutical, the plant intake is much lower in the case of organic-rich soil (Shenker et al. 2011). Given that the irrigation of crops with manure increases the organic content in soil, the presumption is that this decreases plant uptake. A study carried out in Canada suggests that the potential for micropollutant uptake into crops under normal farming conditions is low (Sabourin et al. 2012). This has also been proven in a greenhouse study of the uptake of TMP and SMX by cabbage-in a soil rich in organic matter a lack of uptake was observed (Holling et al. 2012). In field studies, real samples presented no (Jones-Lepp et al. 2010) to low uptake values in the order of nanograms per gram in plant tissues (Calderón-Preciado et al. 2011, 2012).

The distribution of antibiotics in a plants taken from China was, in sequence, leaf > stem > root for the edible plants radish, rape, celery, and coriander (Hu et al.

2010b). In contrast, the concentration of SMX and TMP is higher in the root than the leaf (Herklotz et al. 2010). The same has been reported for CIP and NR in tests with barley, carrot, wheat and other forage crop plants (Eggen et al. 2011). The uptake of DC by radish and pakchoi is undetectable, but radish accumulates more SMC and NOR than pakchoi (Wang et al. 2016). OTC, NOR and CTC were found in rice roots in pot tests, but translocation into upper tissues was not observed (Hawker et al. 2013). This agrees with the results of TC_S and NOR tests with rice and soybean plants (Boonsaner and Hawker 2012, 2010). Generally, information for VPs is scarce. More information can be found for human pharmaceuticals (Wu et al. 2013).

5.2 *Metabolism*

The metabolism of small compounds, e.g. pesticides in plants, is generally a multistep process, including oxidation, reduction, hydrolysis and conjugation (Hoagland et al. 2000). The issue of the metabolism of pharmaceuticals in plants has not been discussed. Individual papers are focused on single compounds, but mostly not veterinary pharmaceuticals. For example, Huber et al. (2012) investigated the metabolism of diclofenac in barley and horse radish, and reported similar activation to that found in mammalian cells in a phase I reaction resulting in the hydroxylated metabolite 4OH-diclofenac, which is conjugated subsequently in phase II to a glucopyranoside, a typical plant-specific metabolite. In the case of triclosan (a bacteriostatic agent used for human purposes), phase I of metabolism was not reported for a carrot, while several conjugates (saccharides, disaccharides, malonic acid, and sulfate) were detected (MacHerius et al. 2012). A study of paracetamol uptake by hydroponically growing Indian mustard (*Brassica juncea* L. Czern.) showed the presence of glutathionyl and a glycoside conjugate, which is similar to the mammalian detoxification pathway (Bartha et al. 2010). Moreover, the uptake of this human pharmaceutical was coupled with an oxidative stress response in the plants. The biotransformation of BNZ_S in reed (*Phragmites australis*) results in the formation of glucosyl-glucosides, acetylglucosides and xylosylglucosides (Podlipná et al. 2013), which are less toxic than native pharmaceuticals, and this can support the use of reed as a tool for phytoremediation.

The accumulation of OTC and NOR antibiotics by soybean results in little effect on the growth rate and maximum levels in plants are observed after 2 days exposure, followed by declining concentrations (Boonsaner and Hawker 2010). This is connected with a high level of degradation for the tested antibiotics in soil (half-life <10 h for both), but it can also be proof that these compounds are degraded in plant cells.

5.3 Toxicity

The toxicity of VPs toward plants is rarely investigated, but these reviews have already been presented, covering both plants' lives in water (e.g. *Lemna minor*) and soil (Bártíková et al. 2016; Carvalho et al. 2014). Most investigations have focused on plant growth and development (Eggen et al. 2011; Furtula et al. 2012; Hoagland 1996; Kołodziejska et al. 2013; Kong et al. 2007; Pomati et al. 2004), chlorophyll content (Opris et al. 2013; Robinson et al. 2005) and seed germination (Liu et al. 2009). Other effects, such as root activity, phosphorus assimilation reduction, root alterations, and reproduction rate changes are also the endpoints of pharmaceutical toxicity toward plants. The toxicity of pharmaceuticals toward crop plants varies significantly between compounds, plant species and test conditions (Carvalho et al. 2014; Chen et al. 2016). The phytotoxicity of VPs has been reported in in vitro assays rather than in soil conditions. Moreover, the concentrations used did not meet the conditions of the environment (Jjemba 2002).

The inhabitation of root elongation (germination) is one of the most important endpoints of the toxicity of veterinary antibiotics (Pan and Chu 2016b). The EC50 of TC, SMT, NOR, ERY and CAP were 14.4, 157, 49.4, 68.8, and 204 mg L^{-1}, respectively. A quantitative structure-activity relationship (QSAR) model showed that in this test kit the hydrophobicity was the most important factor of phytotoxicity. Some studies have reported that the uptake of a human pharmaceutical (carbamazepine) affects nutrient and hormone homeostases in zucchini (*Cucurbita pepo*) plants when a high concentration (up to 4 mg kg^{-1} of soil) is obtained in tests (Carter et al. 2015). Such effects have never been tested for veterinary antibiotics.

Migliore et al. (2003) investigated phytotoxicity and the uptake of ENR in crop plants-*Cucumis sativus, Lactuca sativa, Phaseolus vulgaris* and *Raphanus sativus*. The toxic effect was reported at the high concentration of ENR 5000 μg L^{-1}, while hormesis (increased growth) at the concentrations of 10 and 50 μg L^{-1} of ENR. Interestingly, plants containing ENR at high tissue concentrations can partially metabolize this to CIP, which is normal for animal metabolisms. In an assay of OFN and LIN (together with human pharmaceuticals) uptake and effect on *Eruca sativa L.* and *Zea mays L.* (corn) plants, the use of a low ng L^{-1} of target VPs showed no negative impact on root length or seed germination (Marsoni et al. 2014).

CIP and NR produced negative effects on the growth and development of carrots roots when grown in soil concentrations of 6–10 mg kg^{-1} dry weight (pot tests) (Eggen et al. 2011), which suggests a negative impact on their metabolism in high concentrations of VPs. The same has been stated for SMX, when radish and pakchoi cultivation was irrigated by manure spiked with VPs (Wang et al. 2016).

Seeds seem to be more sensitive to pharmaceuticals than older plants. Values for NOEC (No-Observed Effect Concentration), LOEC (Lowest-Observed Effect Concentration) and EC50 for CTC for cucumber seeds (root length as endpoint) were 0.1, 1 and 48 mg L^{-1} (water used for irrigation), while the same values for a cucumber plant were 100, 300, and >300 mg L^{-1}, respectively (Liu et al. 2009).

Higher toxicity was observed for PEI_S. The EC50 of SAL observed for a *Brassica rapa* was between 1.38 and 3.71 mg kg^{-1} of soil depending on which growth endpoint was tested. The other PEI_S, MON, has already been proven to have herbicidal properties (Hoagland 1996). Two SA_S, SDM and SMT (11.5 mg L^{-1} of nutrient solution), have been proven to affect the root apparatus of barley, while the photosynthetic tissues remained almost unaffected (Michelini et al. 2013). In addition, increased potassium release was noticed, most probably because of an impairment of membrane permeability. In contrast to antibiotics, antiparasitic and anthelmintic pharmaceuticals seem not to be toxic for plants (Kołodziejska et al. 2013; Moore and Kröger 2010; Wagil et al. 2015).

Despite the occurrence of plant uptake of VPs, this uptake usually represents a low percentage of the mass depleted from the systems. Phytoremediation also depends on the rhizospheric microbial communities, which in natural conditions are rich and have a meaningful role in the elimination of pharmaceuticals. Considering the concentration levels that pharmaceuticals normally present in environmental matrices, either in wastewaters or reclaimed water, it is not expected that phytotoxic effects will occur in phytoremediation designed systems (Carvalho et al. 2014). In the case of manure, where the VPs concentration can be higher, an effect lethal to plants is also unlikely. It should be added that pharmaceuticals in soils can affect not only plants and bacteria, but also earthworms (Pino et al. 2015). The effect of antibiotics on a rhizosphere (microorganism community near the roots) is under investigation and this effect seems to be unlike that in the bulk of soil (Jechalke et al. 2014).

The results of studies focused on the prediction models of pharmaceutical concentrations in the environment indicate that the contamination of TC_S in top soil may represent a major issue both for compliance with maximum residue levels in food (100–300 ng g^{-1}) and for the worst-case scenario claims made for organic products (Brambilla and Testa 2014). The most critical compounds are five antibiotics and two analgesic anti-inflammatories (Verlicchi and Zambello 2014). Considering the environmental levels (much lower than concentrations in tests) and the fate of antibiotics in soil (sorption, degradation and chelating with metals), a low level of toxicity from VPs toward plants on real fields is expected (Liu et al. 2009). Given the acceptable daily intake for popular antibiotics and the concentration found in edible plants, there is little evidence of an appreciable risk for human (Aryal and Reinhold 2011; Boxall et al. 2006a; Kang et al. 2013). This was also stated by Prosser and Sibley, who combined information about the lowest therapeutic dose (mg day^{-1}), and the no observable adverse effect level (mg^{-1} kg^{-1} day^{-1}), and calculated the safety factor and the acceptable daily intake of pharmaceuticals (Prosser and Sibley 2015).

6 Current Legislation and Regulation

The public health hazards related to the use of VPs in agriculture and aquaculture involve several problems such as the increased risk of developing allergies in individuals with hyper-sensitivity or the development of antibiotic-resistant bacteria, because of the transmission of antibiotic-resistant pathogenic bacteria through the food chain (Botsoglou and Fletouirs 2001; Dibner and Richards 2005; Institute of Medicine 1989; Motarjemi et al. 2014; Pruneda 1950; WHO 2000). Moreover, the globalization of the food supply requires the harmonization of polices and standards based on a common understanding of food safety among authorities in countries around the world. Given the reported use in the EU in 2004 and animal production data, the average VP_S consumption factor (VPCFa) for antibiotics was 141 mg kg^{-1} meat, and for BNZ_S 6 mg kg^{-1} meat (Kools et al. 2008). To protect consumers from adverse health effects caused by food-borne residues of VPs, many countries maintain strict controls on the authorization, labeling, and use of VPs in food-producing animals. The European Union (EU), Food and Agriculture Organization (FAO) and Food and Drug Administration (FDA) have established certain regulations to monitor the pharmaceutical residues in foods of animal origin (Botsoglou and Fletouirs 2001). Some compounds have been banned for food safety reasons; for other agents the FDA is implementing a voluntary plan with industry to phase out or discourage their use because antimicrobial resistance may not be completely preventable (US Food and Drug Administration 2013). This approach can also be observed in EU countries. In the Euro Zone, in order to reduce human exposure to antibiotic residues, the consumption of any antibiotic is prohibited for growth promotion purposes (The Commision of the European Communities 2005). However, the evaluation of the exposure to pharmaceutical residues has always been controversial, particularly in those geographical regions which do not follow restrictive regulations on the use of veterinary medicines.

As mentioned, VPs may be excreted directly to soils by pasture animals or they may be released into the soil environment when animal manure is applied to land. Some of these are used in fish farms and are introduced directly into the aquatic system (e.g. Beausse 2004; Carbonell et al. 2009; Kuster et al. 2004; Zhao et al. 2010). In some cases, VP_S products are administrated in such a way that user exposure is more likely, or more extensive than with human counterparts. Among examples of this are the vaccination of poultry and dipping of sheep for ectoparasitic conditions (Woodward 2008). Moreover, many human medicinal products contain the same active ingredients as their veterinary counterparts. These pharmaceuticals are released into municipal sewage systems, and it is well-known that, depending on their chemical structure, they can survive passage through sewage treatment plants. Many of them may also show a strong tendency to sorption in sewage sludge, which is used to some extent for agricultural purposes, so this is another way of their introduction into soil (Buchberger 2011). It has been established that approximately ten million dry tons of digested municipal sludge (known as biosolids) is produced each year in the EU (about 40% of it is used in agriculture), and seven million dry tons in the U.S. (about 50% for agricultural purposes) (Dodgen et al. 2014; Environmental Protection Agency (2010); European Commission 2002; Roccaro and Vagliasindi 2014). European legislation (European Commission 2004) permits its use when concentrations of metals in soil do not exceed the maximum permissible limits; however, the concentrations of VPs in the soil (sludge) are not regulated (Carbonell et al. 2009; Clarke and Cummins 2015; European Commission 2004; Roccaro and Vagliasindi 2014). Moreover, according to the Urban Wastewater Treatment Directive (UWWTD), the 28 European Union (EU-28) members are required to collect and treat their urban wastewater. The reuse of the sludge is also encouraged and its final disposal to surface waters has been banned (Kelessidis and Stasinakis 2012). Treated wastewater water reuse is also growing in the U.S. (by 15% a year) (Wade Miller 2006); in many cases it is used for agricultural and landscape irrigation. It is clear that the use of treated wastewater is more regulated than the use of manure, while both can be contaminated by pharmaceuticals.

Taking into account the presented information, the presence of many VP_S at concentrations of up to the low mg kg^{-1} level in agricultural soils is well-confirmed and obvious and might cause adverse effects on the ecosystem and human health (Białk-Bielińska et al. 2016; García-Santiago et al. 2016; Rodriguez-Ruiz et al. 2015; Tarazona et al. 2013; Tuhkanen et al. 2007). However, as mentioned, the concentration limits of VPs in the environment (also in the soil compartments) are still not regulated, even though growing concern in the U.S. and Europe has resulted in the prescription of environmental risk assessments of VP_S (European Medicines Agency 2004, 2008, 2009; The European Agency for the Evaluation of Medical Products 2000; World Health Organization 2001). For example, Montforts (1999) has provided detailed emission and distribution models as well as environmental risk assessment for VPs; and regulatory demands on data quality for the environmental risk assessment of pharmaceuticals have been presented by Küster et al. (2009), whereas relevant EU legislation and risk assessment strategies for the control of emerging contaminants (e.g. pharmaceuticals) resulting from the application of biosolids to agricultural lands have been elaborated by Clarke and Cummins (2015). A risk assessment of persistent pharmaceuticals in biosolids taking into account uncertainty, has been presented by García-Santiago et al. (2016). There is no EU legislation defining the permissible levels of antibiotic concentrations in soils. European Agency for the Evaluation of Medicinal Products sets a threshold value of 0.1 mg kg^{-1} for residues of VPs in soils (EMEA 1996); however, this threshold only applies to approving new substances (Martínez-Carballo et al. 2007). In addition, there is no regulation of VPs content in manure to regulate its use as a fertilizer of crop fields.

7 Conclusion and Summary

It is evident that VPs are observed in the agricultural environment because of the intensive use of veterinary medicines for animal production and the subsequent manure application onto crop fields. The concentrations found in manure (Table 2) are as high as mg kg^{-1}, while they are lower in soil (mostly μg kg^{-1} or ng kg^{-1}). What is a noticeable is that VPs occur in a thin layer situated on the surface (up to ~40 cm depth), which is rich in organic matter with sorption properties. The sorption process can be reversible, and provide long-term evidence of VPs in soil media. However, the sorption properties decrease the negative effect of VPs. This was confirmed in the research cited in this review.

Firstly, sorption can effectively prevent leaching to groundwater, which has been suggested to pose a risk to human health. A strong interaction with soil particles has been determined for TC_S and FQ_S, whereas relatively weak interactions are exhibited by e.g. SA_S and IMD_S (Białk-Bielińska et al. 2012; Song and Guo 2014). The leaching of antibiotics and antiparasitic pharmaceuticals into groundwater is observed in laboratory tests, while they are not determined in field screening. The most probable reason for this is that laboratory tests give overestimated data, because concentration levels used in sorption studies (mg kg^{-1}) are often significantly higher than those that would normally be present in the environment (ng kg^{-1}). While sorption is a concentration-dependent process, new tools for leaching need to be investigated [e.g. the concentration-dependent effective distribution coefficient (K_d^{eff}) (Srinivasan et al. 2014)]. Moreover, leaching models used seem to underestimate the leaching behavior of VPs, probably due to a lack of consideration of factors affecting leaching in the field [e.g. degradation process, temperature changes, bioavailability (Blackwell et al. 2009)].

Secondly, a number of studies have shown that sorption may lead to the reduction of antibiotic effects on soil microbes (Hund-Rinke et al. 2004; Kotzerke et al. 2008; Thiele-Bruhn 2005). Numerous studies have documented changes in soil microbial community structure as a result of exposure to antibiotics, while the results reported on wetlands disagree (Berglund et al. 2014). Experiments have proved that the ratios of bacteria/fungi and Gram positive/Gram negative bacteria can be changed when mg/kg of VPs in soil are applied. Long-term studies frequently detect a recovery of the microbe community biomass and growth that was initially inhibited (Demoling et al. 2009; Kotzerke et al. 2008). Land application of manure from antibiotic-treated animals is reported to frequently increase the abundance of resistant bacteria and antibiotic resistance genes in soils (Ghosh and LaPara 2007; Martínez 2008). Currently, the development of resistance is not believed to be promoted by continuing exposure to sublethal concentrations of antibiotics, but it appears to be more important that resistant microorganisms are introduced together with manure. The resistance of bacteria obtained in soil may also be due to naturally occurring antibiotics and resistance genes.

Thirdly, the sorption of VPs plays an important role in plant uptake. Information about the intake of VPs by plants is mostly limited to hydroponic conditions, while the bioconcentration obtained for pharmaceuticals determined in soil experiments is several times smaller. The analysis of real samples taken from farmland show the absence of VPs in plant tissues (Wu et al. 2015). Given that the irrigation of crops with manure increases the organic content in soil, the presumption is that this decreases plant uptake. Several studies have suggested that the potential for VPs uptake into crops under normal farming conditions is low (Calderón-Preciado et al. 2011, 2012; Holling et al. 2012; Jones-Lepp et al. 2010; Sabourin et al. 2012). MQ_S with a large size have been reported in many studies to not be taken up by crops (Boxall et al. 2006a; Jones-Lepp et al. 2010; Kang et al. 2013; Kumar et al. 2005; Pan et al. 2014). In the case of smaller VPs, the ionization state seems to limit the root uptake and further translocation in plant tissue. Moreover, it seems that plants have their own defenses against pharmaceuticals and their metabolism tends in the direction of conjugate production. The phytotoxicity of VPs has been reported in in vitro assays rather than in soil conditions. Plants living in constructed wetlands can exist for years without any visible changes caused by pharmaceuticals (Verlicchi and Zambello 2014).

To sum up, the application of manure on crop fields poses risks, but this is substantially limited by the sorption of VPs into soil particles and the natural occurring processes of biotic and abiotic degradation. The composting of manure before use in aerobic conditions significantly reduces the bulk of VPs, and currently this is the only way eliminate antibiotics in manure before use as fertilizer, as VPs cannot be eliminated in animal production. The application of manure is not a continuous process, but occurs periodically before crop seeding. The microorganisms living in soil are generally not impacted upon by VPs in the concentrations observed in soils. If a negative impact occurs, the bacterial community has the ability to resist antibiotics and reconstruct the population. The plant uptake of VPs is negligible and limited to the roots. In the summer period, the degradation of VPs is accelerated, and the half-life of some antibiotics in manure and soil is in a matter of days. The higher half-life of some VPs is connected with the fact that sorbed fractions of compounds are much less susceptible to both biotic and abiotic degradation. The process of fertilization via the application of manure is of agricultural interest due mainly to its organic matter concentrations and nutrient input, and is much safer than the irrigation of fields with treated wastewater or wastewater sludge. Wastewater products are rich not only in antibiotics, but also human pharmaceuticals, metals, alkyl-phenols, phthalates and other micropollutants. Moreover, the continuous process of irrigation and the consequential accumulation of the above compounds can pose risks for not only organisms living there, but also human health.

The current state of the art in VPs in manure and their agricultural use is much broader than in 2003, when Boxall and coworkers investigated the risk caused by veterinary medicines in the environment (Boxall et al. 2003). Up-to-date information concerning the presence of antibiotics and the related presence of veterinary compounds, degradation, uptake by plants, toxicity to microorganisms, leaching and connected issues is presented in this review. Tentatively, it can be stated that VPs in manure do not pose a risk for the agricultural environment. However, we have to bear in mind that VPs are a diverse group of substances, and each of them should be approached separately. For example, the SA_S show a potential for leaching and a longer life time in soil. The one concern is that most current information comes from experiments with short durations, high concentrations of target substances and conditions divergent to the environment (e.g. hydroponic experiments into uptake). Moreover, only rare reports have focused on degradation/transformation products, which are generally more labile and can affect the environment in a different manner to the native VPs. There is also a lack of experiments on mixtures of VPs and other pollutants.

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