Chapter 4
Antibiotics and Antibiotic Resistance Genes (ARGs) in Soil: Occurrence, Fate, and Effects

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4.1 Introduction

The era of anthropogenic antibiotics began after the discovery of penicillin in 1928 by Alexander Fleming (Diggins 1999). Natural soil is the reservoir of autochthonous soil microorganisms which biosynthesize antimicrobial secondary metabolites (Martinez-Fleites et al. 2006; Raaijmakers et al. 1997). Nevertheless, since the first introduction of antibiotics, new chemical entities of antimicrobials have been discovered and were synthesized on an industrial scale (Kumar and Gayen 2011). Antibiosis is a natural chemical regulation mechanism among organisms, especially

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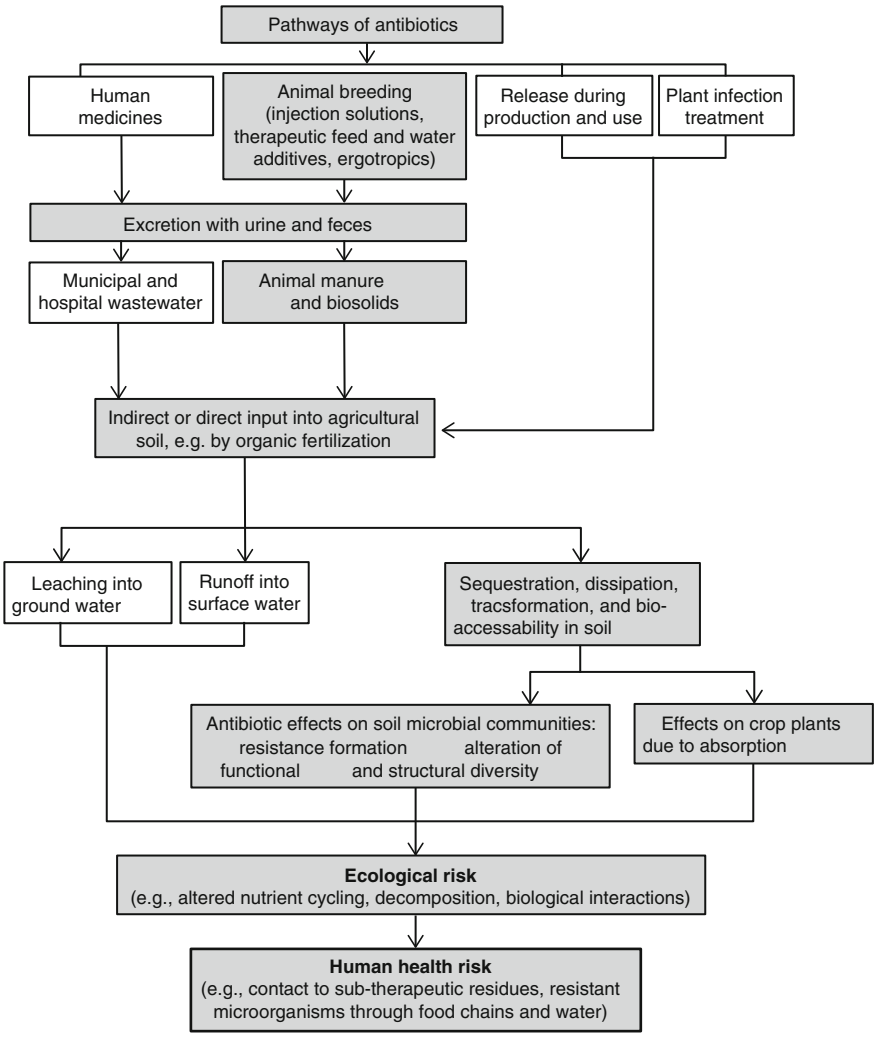

Fig. 4.1 Pathways of antibiotics (Adapted from Du and Liu 2012)

microorganisms. Hence, antibiotics also biosynthesize in soils (Gottlieb 1976). Today, to treat and control many bacterial infections, synthetic and naturally antibiotics have been widely used in veterinary and human medicines, but misuse or overuse of antibiotics contributes to the emergence and spread of antibiotic resistance genes (ARGs) in the environmental compartments (Tang et al. 2015). Antibiotic resistance genes (ARGs) are emerging environmental contaminants and may pose a threat to public health (Chen and Zhang 2013). There are some typical pathways of antibiotics by which they are introduced into the environment: (1) inadvertent release during production and use, (2) their application against plant diseases, (3) sewage sludge with antibiotic residues of human medicine, and (4) medicated animals' manure which received therapeutic feed/water additives, injection solutions, or ergotropics (see below; Fig. 4.1; adapted from Du and Liu

2012). As a result, antibiotics have been detected in different environmental compartments such as groundwater of farms and in aquatic and soil environments (Martinez 2009). Forty different tetracycline-resistance (*tet*) genes with three specific mechanisms (i.e., target modification with ribosomal protection protein, antibiotic efflux pumps, and antibiotic inactivation) have been characterized to date (Roberts 2005). Four sulfonamide-resistance (*sul*) gene types, including *sul1*, *sul*2, *sul*3, and *sul*A, have also been studied (Pei et al. 2006). In both animals and humans, a significant amount of antibiotics (up to 75 %) can be excreted in an unaltered state (Elmund et al. 1971) which could pose threat to soil environment in general and particularly to humans. So this chapter covers the antibiotics and ARGs' general information, their fate in soil environment, pollution caused by the ARGs, and their impact on human health.

4.2 Physical Properties of Antibiotics

The compounds which are synthesized through secondary metabolism of living organisms are known as antibiotics, with exceptions for semi- or completely synthetic substances. Antibiotics are heterogeneous compounds with different fields of usage such as antiinfectives, antimycotics, and anthelmintics, have different structural classes (tetracyclines, nucleosides), and reveal different molecular structures and diverse physical and chemical properties (Garrod and O'Grady 1968). Depending on the pH of the medium, most antibiotics tend to ionize; pk_a values are related with the diverse functional groups of the compounds. Some important antibiotic compounds' physicochemical properties ranges are listed in Table 4.1. However, a brief description of physicochemical properties of selected antibiotics is given below:

4.2.1 Tetracyclines

Tetracyclines (TCs) are polyketides, and structure is like that of a naphthacene ring (Fig. 4.2). The TCs have three pk_a values and are amphoteric. They exhibit stability in acids, but not in bases, and form salts in both media (Podojil et al. 1984). Most TCs are sparingly soluble in water, while the solubility of the corresponding hydrochlorides is much higher. The TCs strongly absorb light and, thus, are susceptible to photodegradation (Chen et al. 2008).

4.2.2 Sulfonamides

Sulfonamides (SAs) are relatively insoluble in water and characterized by two pk_a values (Fig. 4.3). SAs indicate protonation of the amino group at a pH of 2–3 and deprotonation of the $R_1SO_2\ NHR_2$ moiety at a pH of 5–11 (Ingerslev and Halling-

Table 4.1 Physical properties of antibiotics (Osol and Remington 1980)

Compound class	Molar mass (g/mol)	Water solubility (mil/l)	log K_{ow}	pk_a	Henry's constant (Pa l/mol)
Tetracyclines chlortetracycline, oxytetracycline, tetracycline	444.5–527.6	230–52,000	−1.3 to 0.05	3.3/7.7/9.3	1.7×10^{-23} –4.8×10^{-22}
Sulfonamides sulfanilamide, sulfadiazine, sulfadimidine, sulfadimethoxine, sulfapyridine, sulfamethoxazole	172.2–300.3	7.5–1500	−0.1 to 1.7	2–3/4.5–10.6	1.3×10^{-12} –1.8×10^{-8}
Aminoglycosides kanamycin, neomycin, streptomycin	332.4–615.6	10–500[a]	−8.1 to −0.8	6.9–8.5	8.5×10^{-12} –4.1×10^{-8}
β-Lactams penicillins: ampicillin, meropenem, penicillin G; cephalosporins: ceftiofur, cefotiam	334.4–470.3	22–10,100	0.9 to 2.9	2.7	2.5×10^{-19} –1.2×10^{-12}
Macrolides erythromycin, oleandomycin, tylosin	687.9–916.1	0.45–15	1.6 to 3.1	7.7–8.9	7.8×10^{-36} –2.0×10^{-26}
Flouroquinolones ciprofloxacin, enrofloxacin, flumequin, sarafloxacin, oxolinic acid	229.5–417.6	3.2–17,790	−1.0 to 1.6	8.6	5.2×10^{-17} –3.2×10^{-8}
Imidazoles fenbendazole, metronidazole, oxfendazole	171.5–315.3	6.3–407	−0.02 to 3.9	2.4	2.3×10^{-13} –2.7×10^{-10}
Polypeptides avermectin, bacitracin, ivermactin, virginiamycin	499.6–1038	Not completely	−1.0 to 3.2		Negligible–2.8×10^{-23}
Polyethers monensin, salinomycin	670.9–751.0	2.2×10^{-6} –3.1×10^{-3}	5.4 to 8.5	6.4	2.1×10^{-18} –1.5×10^{-18}
Glycopeptides vancomycin	1450.7	>1000	Not soluble in octanol	5.0	Negligible
Quinoxaline derivatives olaquindox	263.3	1.0×10^{-6}	−2.2	10	1.1×10^{-18}

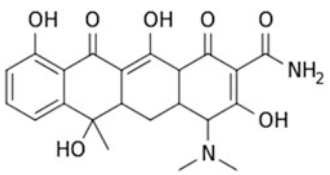

Fig. 4.2 The four rings of the basic tetracycline structure

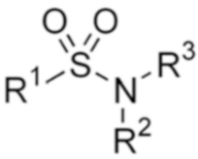

Fig. 4.3 The structure of the sulfonamide group

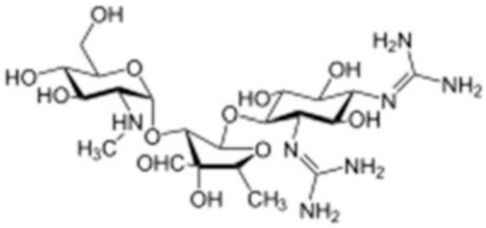

Fig. 4.4 The structure of the aminoglycosides group

Sørensen 2000). In general, the atmospheric SAs behave as weak acids and form salts in strongly acidic or basic solutions.

4.2.3 Aminoglycosides

Aminoglycosides like antibiotics are basic and strongly polar cationic compounds (Fig. 4.4). Their molecular structure is comprised of two or more amino sugars that are glycosidically bound to aminocyclitol. They are susceptible to photodegradation, mostly hydrophilic, and water soluble.

4.2.4 Fluoroquinolones

Fluoroquinolones (FQs) showed large chemical stability and are known as quinolones (Fig. 4.5). They are degraded by UV light, insensitive to hydrolysis and increased temperature. Their antibiotic potency depends mostly on the aromatic fluorine substituent at the C-6 position (Sukul and Spiteller 2007).

4.3 Natural Antibiotics Occurrence in Soil

New pharmaceuticals were discovered due to secondary metabolites of natural resources and often served as blueprints for the development of synthetic antibiotics (Sarmah et al. 2006). Soil microbial communities and plant roots serve as the reservoir of natural antimicrobial production (Gottlieb 1976; Mavrodi et al. 2012; Raaijmakers and Mazzola 2012), often comprising fungal, pseudomonad, and actinomycete species (Butler and Buss 2006; Raaijmakers et al. 2002). It has been reported that the production of antibiotic in natural microbial communities

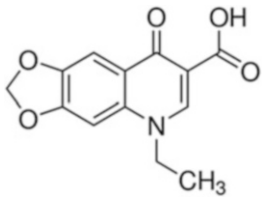

Fig. 4.5 Quinolone antibiotic

is suggested to promote microbial fitness, defense, signaling, gene regulation, and competiveness (Mavrodi et al. 2012). Hence, antibiotics are considered as a part of the disease regulation in soil. The detection and quantification of natural antimicrobials, in nutrient-poor soil, are often prohibited by fast degradation, strong sorption to the soil matrix, and concentrations near the detection limit (Mavrodi et al. 2012; Thomashow et al. 1997). However, the natural broad-spectrum antibiotic phenazine-1-carboxylic acid was successfully quantified at concentrations up to 1.6 $\mu g/g^{-1}$ root fresh weight in nutrient-rich rhizosphere soil of wheat plants (Mavrodi et al. 2012). Rhizosphere samples of plants exhibited natural antibiotic concentrations in the range 0.02–5.0 $\mu g/g^{-1}$ (Mavrodi et al. 2012; Thiele-Bruhn 2003). The antibiotic resistance evolution in natural microbial communities is thought due to the exposure to autochthonous antimicrobial compounds. Such exposure might also alter the response to synthetic antibiotics from anthropogenic sources (Aminov and Mackie 2007). Soil microbial communities are probably composed of more and less antibiotic-susceptible strains, suggesting also coadaptations to some synthetic antimicrobials.

4.4 Anthropogenic Antibiotics Occurrence in Soil

Anthropogenic synthesized antibiotics contamination of terrestrial soil and aquatic environments is a widespread problem, which begins through hospital waste and with the excretion by the animals (Boxall et al. 2004; Kümmerer 2008a). Most of antibiotics have been designed to be readily excreted after medication with rather short half-lives, for example, 0.1–26 h for SA antibiotics and 1.5–16 h for FQ antibiotics (Picó and Andreu 2007). Of the applied drug, 44 % SDZ (SA) was excreted unchanged as parent compound, with acetyl conjugates (26 %) and hydroxylated compounds (19 %) as major metabolites (Lamshöft et al. 2010). Of the applied DIF (FQ), approximately 96 % were excreted as parent compound, with sarafloxacin as the major metabolite (Lamshöft et al. 2010). The concentrations of SA in contaminated manure typically ranged from 1 to 10 mg kg^{-1}, occasionally up to 235 mg kg^{-1} fresh weight (Hamscher and Mohring 2012; Kumar et al. 2005). Monitoring of manure samples from Austria exhibited SAs, tetracyclines, and FQ concentrations up to 91 mg kg^{-1}, 46 mg kg^{-1}, and 8 mg kg^{-1}, respectively (Martínez-Carballo et al. 2007). Feedlot pig manure from China contained tetracycline and FQ concentrations up to 60 mg kg^{-1} and 47 mg kg^{-1}, respectively (Zhao et al. 2010). Consequently, agriculture soils are enriched with large quantities of antibiotic compounds with contaminated animal manure. Under long-term conventional farming practice, a tetracycline concentration of 200 µg kg^{-1} was extractable from soil (Hamscher

et al. 2003). Farmland soils of southern China had FQ and SA concentrations of even 1537 μg kg^{-1} and 321 μg kg^{-1}, respectively (Li and Zhang 2011). SDZ concentrations up to 90 μg kg^{-1} were reported in the soil of wheat-planted and manure-fertilized agricultural landscapes (Grote et al. 2007). Antibiotic concentration in field soil increased due to mixtures of different antibiotics such as SAs, FQs, and tetracyclines, as indicated in the northern Marmara region of Turkey (Karcı and Balcıoğlu 2009). However, due to low extraction efficiencies of many compounds, antibiotic concentrations in soil are probably underestimated.

4.5 Antibiotics Fate in the Soil Environment

When the antibiotics are added to the soil solid phase, they are liable to microbial transformation. Since the 1940s, there are some compounds like sulfonamides which have been extensively used in the animal husbandry and pig production (Kümmerer 2008b; Zhou et al. 2012). The changes occur because of the abovementioned biotransformation results in the retransformation of metabolites into the parent compound similarly as in fertilizers (Giang et al. 2015; Jechalke et al. 2014). For many antibiotics, mineralization accounts for less than 2 % of the added compounds (Forster et al. 2009; Junge et al. 2012). Because of poor light penetration, the photodegenration in the soils as an alternative pathway of pharmaceutical degradation is limited (Ozaki et al. 2011). Final pathways to be considered are potential transfers of the antibiotics from soil into the atmosphere, hydrosphere, and biosphere (Fig. 4.6). Low vapor pressure is responsible for the fate of the

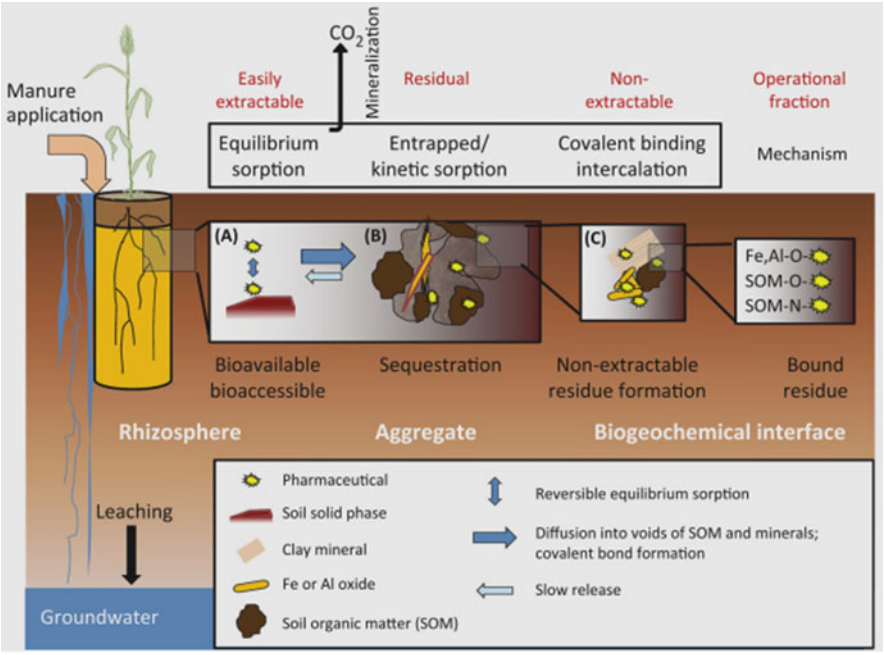

Fig. 4.6 Antibiotics fate in soil and its compartments (Adapted from Jechalke et al. 2014)

pharmaceuticals in soil and here volatilization is not relevant. All antibiotics may disperse because of the surface runoff and particle-facilitated transport in the environment (Burch et al. 2014; Joy et al. 2013, 2014). The vertical percolation or leaching that occurs in the groundwater is restricted to a few antibiotics such as sulfanomides, which mainly occurs in preferential flow path. So that is the reason that the largest fraction of most antibiotics applied to soils with manure is usually returned in the surface soil (Ostermann et al. 2013; Srinivasan and Sarmah 2014). For the removal of antibiotics from the soil, the plant uptake by several pharmaceuticals is done (Felizeter et al. 2012; Sabourin et al. 2012), but there concentrations are commonly so small in the plant tissues that there plant uptake might not represent a major pathway (Engelhardt et al. 2015; Fang et al. 2014; Rosendahl et al. 2012). Sorption and desorption reactions are responsible for the interaction of the veterinary antibiotics with the soil solid phase. Biotransformation, biological effects, their mobility, and uptake by plants are controlled by the sorption and desorption processes. Sorption is not only a function of polarity and water solubility for most antibiotics, and its effect on the chemical specifications and charge of the compounds is particularly controlled by the pH value (e.g., Schaffer et al. 2012; Yang et al. 2012). The history of fertilization and other solutes can also affect sorption. Sorption of a Sulfonamide antibiotic (sulfamethoxazole) was reduced in soils fertilized and irrigated with untreated wastewater for 14–100 years, most likely as a result of a saturation of high-affinity sorption sites, sorption competition with other solutes, and changes of soil organic matter properties, whereas sorption of ciprofloxacin was not affected (Dalkmann et al. 2014).

Resulting in hysteresis and a subsequent kinetic sorption and desorption with slow release rates, the primary sorption reaction of antibiotics is often governed by the reversible equilibrium process (Doretto and Rath 2013; Kasteel et al. 2010). Only fractions of the non-extractible antibiotic residues are formed in parallel to the reversible processes of equilibrium sorption and sequestration. Rigid moieties in soil organic matter (SOM) (Pignatello and Xing 1995), nomopores within oxides, and clay interlayers (Nowara et al. 1997) are stopped to be released into the soil due to the formation of the voids due to the physical diffusion and also from enzymatically catalyzed formation of covalent bonds due to this formation of non-extractible residues, e.g., Bialk et al. (2007) and Gulkowska et al. (2013).

4.6 Antibiotic Resistance Genes (ARGs) in the Soil Environment

Antibiotic-resistant bacteria enrichment in soil environment is considered as one of the most serious threats to public health in the twenty-first century. Resistance genes enter the food system via amendment of soils with manure from antibiotic-treated animals, which are considered a reservoir of such genes (Gillings 2013). Application of pig manure is the cause of sulfonamide-resistance genes dispersal to

soil bacteria. Further, it has been found that dairy cow manure amendment enhanced the proliferation of genes encoding β-lactamases and resident antibiotic-resistant bacteria in soil even though the cows from which the manure was derived had not been treated with antibiotics.

Manure amendment and resistance exhibit a correlation which has been proved by a number of studies in previous few decades. For example, the prevalence of sulfonamide-resistant isolates was increased in a field soil after 2 years of slurry application of antibiotic-containing manure, compared to preapplication soil (Byrne-Bailey et al. 2009). In further microcosm experiments, the accumulation of resistance genes by the agricultural practice of repeated manure amendment was shown (Heuer et al. 2011). Sulfonamide 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).

However, there are fewer reports available on the long-term effects of antibiotics pollution with antibiotics and resistant bacteria. A recent study by Tang et al. (2015) revealed the accumulation of antibiotic resistance genes in paddy soils from four field experiments in south of China over decades of increasing use of antibiotics.

4.7 Environmental and Public Health Effects of Antibiotic Resistance Genes Pollution

Antibiotic resistance genes' pollution could increase the human pathogens by obtaining resistance. When the human microbia containing the residues is released in the environment in which the bacteria-enriched resistance elements are present, then the determinants by human-linked bacteria increase the possibility of acquiring novel resistance. So that is why it is stressed that residuals from hospitals in which human commensal and infective bacteria and also antibiotics are released should be minimized at all costs to avoid interchange of genetic material (Sirés and Brillas 2012). As stated by Baquero et al., the possibility of the variation of genetics and the novel mechanisms resistance's possible emergence that are reintroduced in the human environment is because of the other types of microbiota in different ecosystems (from soil sediments of groundwater to animal microbiota) coming in contact with the human microbiota (Baquero et al. 2008). The physiology of natural microbial populations and their dynamics is challenged by the spread of resistance genes that currently exist in the human- or animal-associated microbial which are found without the antibiotic pollution in different environments, as indicated by several reports. Bacteria that is found in humans and animals has the genes on several occasions. The above fact has not been focused or studied in detail, but it is said that the environmental populations are responsible for the spread of those genes. Now the question arises here that in the recipient organisms these antibiotic resistance genes may produce relevant changes or not. The case has been proven by some studies. For instance, resistance to either glycopeptides or beta-lactam antibiotics strongly modifies the structure of the peptidoglycan in Gram-positive

bacteria (Mainardi et al. 2008; Martinez et al. 2009), and it has been described that antibiotic resistance of small colony variants of *S. aureus* is associated with the rewiring of bacterial metabolism (Heinemann et al. 2005). For the bacterial metabolism, there is an indication that acquisition could have incalculable consequences. This could also lead to the evolution of the environmental biosphere. Up till now, the studies that have been made so far in which the antibiotic resistance has an effect of antibiotic pollution are different regarding the antibiotic genes that come with pollution. Firstly, this results in the outburst of the resistant bacteria that exist in the humans or animals. When the antibiotic exposure is ceased, the microbial community outcome is largely settled. If a gene transfer unit that already contains antibiotic resistance genes in the environment also exists as contaminants, then their diffusion will be favored by the occurrence of the antibiotics, and when the discharge of the antibiotics is reduced or ceased, then the modification of the antibiotic resistance will be lower.

4.8 Conclusion

This chapter provides a comprehensive overview of antibiotics and ARGs in soil, potentially providing knowledge for managing antibiotic resistance emanating from agricultural activities. Although there are numerous recent studies on antibiotics and antibioticresistance genes, many questions still need to be addressed more systematically. Information on the effects of reductions in antibiotic use on the overall level of resistance is needed in order to evaluate management options. Along the article, we review the impact that pollution by antibiotics or by antibiotic resistance genes may have for both human health and the evolution of environmental microbial populations.

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