Chapter 3
A Review on Antibiotics Consumption, Physico-Chemical Properties and Their Sources in Asian Soil

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3.1 Introduction

Antibiotics are the widely used antimicrobial drugs for prevention and treatment of bacterial infections by killing or inhibiting the growth of bacteria. A large variety of antibiotics are extensively used across the globe to treat human and animals. Antibiotics are used not only to treat individual animal with bacterial infections, but also to promote the growth of livestock. Consumption of antibiotics by livestock was reported to be 63,200 tons in 2010, which is more than the total human consumption worldwide (Van Boeckel et al. 2015). To meet the projected population of 8.5 billion in 2030, the consumption of antibiotics may rise by two-thirds and reach 105,600 tons (United Nations 2015). This increase may be due to the increase in the number of livestock production raised in large scale to meet the increasing demand (Van Boeckel et al. 2015).

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Antibiotic consumption increased by more than 30% between 2000 and 2010, from approximately 50 to 70 billion standard units. This is based on the data from 71 countries including most highly populated countries (Van Boeckel et al. 2015). Out of the total consumption, about 20% of antibiotics are used in hospitals and other healthcare clinics in most countries. Remaining 80% of antibiotics that are used in the community are either prescribed by healthcare providers or purchased directly by consumers over the counter without prescription (Kotwani and Holloway 2011). There is a probability that more than half of this usage by the community may end up in the wastewater treatment plants and finally to the surrounding environment thereby leading to antibiotic resistance in the ambient environment.

It is estimated that India alone consumed 12.9 billion antibiotic pills in 2010 followed by China (10 billion) and the USA (6.8 billion). Antibiotic usage in India alone has risen by 62%, from 8 billion pills in 2001 to 12.9 billion in 2010. Globally, antibiotics usage increased by 30% in the first decade of twenty-first century.

Antibiotics used by the human and animals are reaching the environment through excreta. Human excreta in the form of wastewater are treated in wastewater treatment plants (WWTPs), but 100% removal of antibiotics is simply not possible in conventional WWTPs. Some percentage of antibiotics gets partitioned in the sludge. So the sludge and final effluent from WWTPs contain antibiotics. The sludge is used as manure and the effluent is discharged into natural resources. Liquid manure from the livestock farming is also used for soil enrichment. These acts as the routes for the entry of antibiotics in different environmental matrices. Hence, it is important to understand the behavior of these compounds and their fate in the environment. This chapter aims to review the physico-chemical properties of antibiotics, their consumption pattern across the globe, and potential sources in soil.

3.2 Antibiotics: How Does It Work?

Effects of antibiotics include killing the bacteria by blocking the critical physiological processes in bacteria and prevent further proliferation, thereby helping the body's natural immune system to fight against the bacterial infection. Antibiotics work differently for different types of bacteria. Antibiotics like amoxicillin and gentamicin targets an extensive range of bacteria and hence are called broad-spectrum antibiotics. Antibiotics like penicillin affect only a few strains of bacteria and are hence categorized as narrow-spectrum antibiotics. There are wide range of antibiotics working in different manner against the bacteria. For example, as shown in Fig. 3.1, penicillin a β-lactam destroys bacterial cell walls, while other antibiotics can affect the way the bacterial cell work.

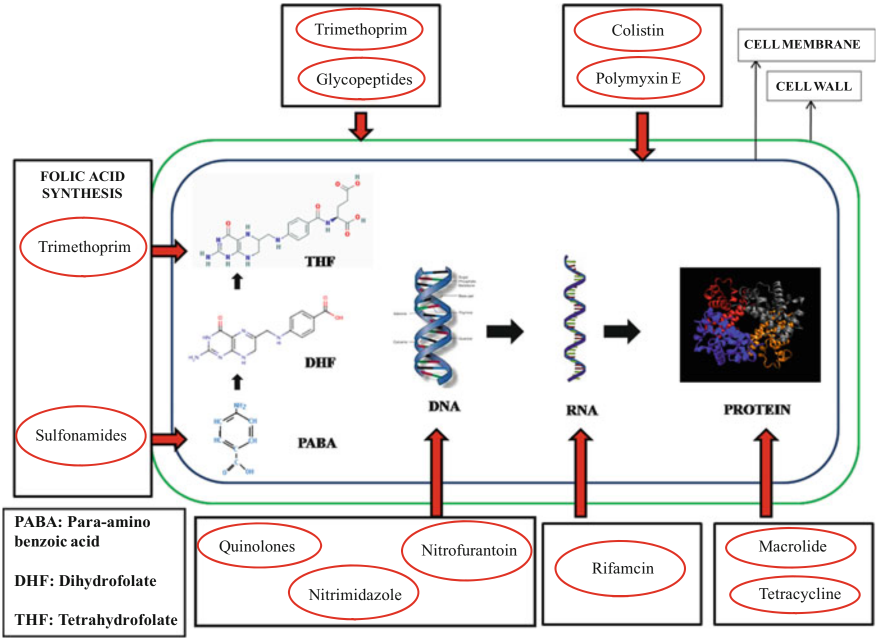


Fig. 3.1 Hypothetical schematic representation showing the mode of action of different antibiotics against bacteria

3.3 Consumption of Antibiotics

Consumption of antibiotics is broadly divided into three categories viz., (a) combating microbial infections, (b) agricultural usage, and (c) livestock infections and production. Consumption pattern of these categories around the world are described below.

3.3.1 Combating Microbial Infections

During 2000 and 2010, the rate of consumption of antibiotics has increased by 30%. Nearly three-fourth of this increase was contributed by Russia, India, South Africa and China. With 12.9×10^9 units, India consumed the maximum number of antibiotics in 2010, followed by China and the USA. Antibiotic consumption was found to be seasonally varying in most countries. Two last-resort classes of antibiotic drugs with increasing consumption rate were carbapenems (45%) and polymyxins (13%) (Haley and Morrill 2015).

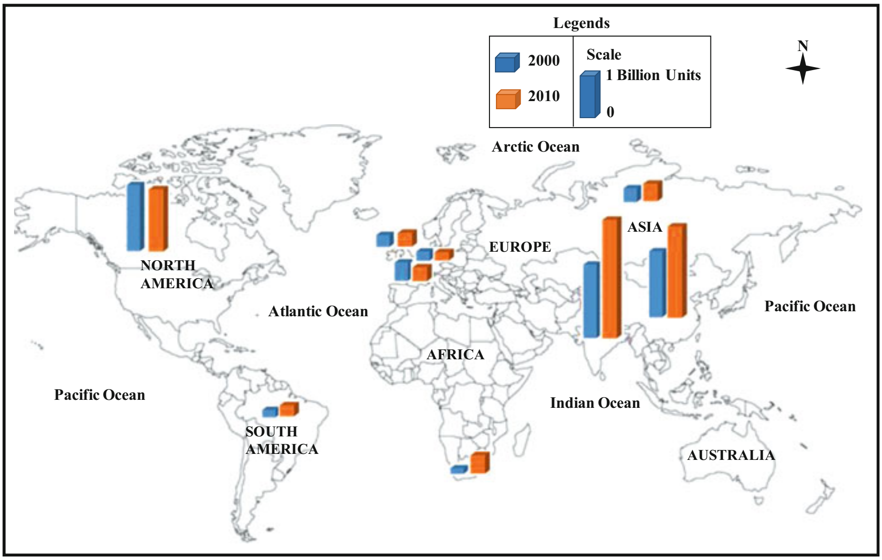


Fig. 3.2 Consumption of antibiotics by different countries across the globe during 2000 and 2010 (data courtesy-Van Boeckel et al. 2015)

Penicillins and cephalosporins accounted for more than 60% of the global consumption in 2010. These old antibiotics are still used for treating infections and their use increased by 40% during the last decade. Fluoroquinolones and macrolides consumption also increased by 30%. But there is not much increase in the consumption of tetracycline, trimethoprim and narrow spectrum of penicillin from 2000 to 2010 (Van Boeckel et al. 2015).

From Fig. 3.2 it is evident that high income countries like France, Germany and the USA realized the threat caused by the antibiotics and they have decreased their consumption since 2000 (Van Boeckel et al. 2015). But in developing nations like China, India and South Africa, antibiotic consumption has drastically increased from 2000 to 2010. In South Africa, the consumption has doubled. Variation in the consumption of antibiotics followed seasonal pattern. There was a sharp increase in antibiotic consumption during winter when compared to summer associated with the increased rate of diseases during winter.

3.3.2 Livestock and Agricultural Usage

As the population increases, the demand for animal food also increases. Antibiotics are therefore extensively used to promote the growth of poultry and aquaculture farms. It was estimated that 63,200 tons of antibiotics were consumed by livestock in the year 2010 (Van Boeckel et al. 2015) which accounts for more than 60% of the estimated 100,000 tons of antibiotics produced annually across the globe (Bbosa and Mwebaza 2013). With this projected increase, the global antibiotic consumption in livestock production may rise up to 105,600 tons by 2030. Sixty-six percent of this increase was due to the raise in the number of animals and the remaining 34% was due to the shift from extensive to intensive farming (Van Boeckel et al. 2015). The analysis of consumption pattern of antibiotics in 2010 showed that China consumed the major part of the total consumption of antibiotics in livestock followed by the USA, Brazil, Germany and India. This is because the developed countries like Germany reduced their consumption after understanding the threat caused by antibiotic resistance. With projected rise in population by 13% in 2030, the rate of consumption of antibiotics is also expected to double in developing nations like India, China and South Africa (Van Boeckel et al. 2015).

3.4 Physico-Chemical Characteristics of Antibiotics

Physico-chemical properties of the listed group of antibiotics have been given in Table 3.1.

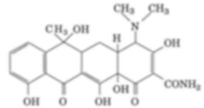
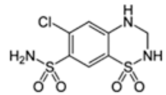
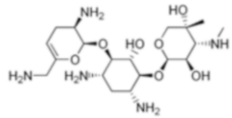
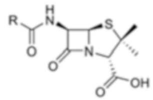
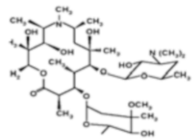
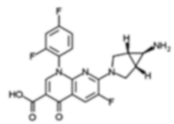
3.4.1 Tetracycline and Sulfonamides

Amphoteric antibiotics such as tetracycline and sulfonamides have p*K*a values 3 and 2 respectively. Though tetracycline is sparingly soluble in water, the solubility of the corresponding hydrochloride is much higher. On the other hand, sulfonamides are insoluble in water and undergoes protonation at pH 2–3 and deprotonation at pH 5–11 (Gao et al. 2012a, b). Depending on the dissociation constant (K_d) value of tetracycline (range: 417–1026 mL/g) and sulfonamides (range: 0.9–18.1 mL/g), it has been reported that tetracycline has a higher tendency to migrate in soil than that of sulfonamides (Hu et al. 2010a, b).

3.4.2 Fluoroquinolones

Fluoroquinolones, the representative quinolone derivatives with fluorine at the sixth position, are used as antibacterial agents with a broad range of therapeutic activity (Tokura et al. 1996). The quinolones are amphoteric and with a few exceptions, generally exhibiting poor water solubility at slightly acidic or alkaline condition (pH 6–8). Although the impact on therapeutic efficacy is not clear, they appear to act as weak bases and are much less effective in acidic than in nonacidic condition. The quinolone nucleus contains a carboxylic acid group at position 3 and an exocyclic oxygen at position 4 (hence the term 4-quinolones), which is the active

Table 3.1 Physico-chemical properties and structure of antibiotics

Class	Molar mass (g/mol)	Water solubility (mg/L)	Log Kow	pKa	Henry's constant (Pal/mol)	Structure
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	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	332.4–615.6	10–500	−8.1 to −0.8	6.9–8.5	8.5×10^{-12}–4.1×10^{-18}	
ß-Lactam	334.4–470.3	22–10,100	0.9–2.9	2.7	2.5×10^{-19}–1.2×10^{-12}	
Macrolides	687.9–916.1	0.45–15	1.6–3.1	7.7–8.9	7.8×10^{-36}–2.0×10^{-26}	
Fluoroquinolones	229.5–417.6	3.2–17,790	−1.0 to 1.6	8.6	5.2×10^{-17}–3.2×10^{-8}	

DNA-gyrase binding site. It exhibits its antibacterial activity by preventing the unwinding and duplication of the DNA.

3.4.3 Macrolides

Macrolides are a group of antibiotics that can work on a broad range of bacteria primarily by inhibiting the protein synthesis in bacteria. It has the inability to stay activated in highly alkaline or acidic condition; it can stay activated only in pH ranging from 4 to 10. The presence of one more deoxy sugar attached to the lactone ring enhances the possibility of macrolides to undergo a varied number of chemical reactions. The macrolides typically have a large lactone ring in their structure and are much more effective against Gram-positive than Gram-negative bacteria. They contain a dimethyl amino group which makes them basic. They are sparingly soluble in water but dissolves in polar organic solvents.

3.4.4 Aminoglycoside

Aminoglycoside antibiotics consist of an aminocyclitol group, with amino sugars attached to the aminocyclitol ring in glycosidic linkage. The basic nature and high water solubility characters of the antibiotics come from the amino groups and the hydroxyl groups on the sugar, respectively. Removal of the hydroxyl group from the amino sugars (e.g., tobramycin) increases the lipid solubility thereby increasing the activity as it can get absorbed in the lipid layer of the human body. One major drawback of aminoglycoside drug is its p*K*a value ranging from 8 to 10 which limits the movement of this drug in human body.

3.4.5 β-Lactam

These antibiotics are characterized by the four-membered β-lactam ring which is the active component in the drug and acts on bacteria by inhibiting the cell wall synthesis.

3.5 Sources of Antibiotics in Asian Soil

Antibiotics that are consumed by human beings and animals are not completely absorbed or metabolized; therefore, they are released to the environment through their excreta. Conventional WWTPs does not completely remove these kind of compounds. In some areas, treated water is used for irrigating land wheras sludge from the treatment plant is used as manure. Manure from the livestock farms are also used as fertilizer. So eventually, 30–50% of the used antibiotics reach different environmental matrices like surface water, groundwater and soil. Some studies also demonstrated the risk associated with the consumption of fresh vegetables grown in soil which is amended with antibiotic laden manure (Kumar et al. 2005). It is therefore very important to know the sources, environmental concentrations and risks associated with the presence of antibiotics in soil as soil can act as a sink for organic compounds. Antibiotics may enter into the soil from different pathways:

(i) Sludge from WWTPs used as manure
(ii) Livestock excreta used as manure
(iii) Treated water used for irrigation
(iv) Surface runoff from solid waste municipal dumpsite
(v) Application of antibiotics in aquaculture farms

(i) Sludge from WWTPs **used as manure**

For a long period of time, sewage sludge was used as fertilizer because of high nitrogen and phosphorous content. But later it was found that sewage sludge contains heavy metals, pharmaceutical and personal care products, phthalates, dioxins, polycyclic aromatic hydrocarbons, flame retardants and other endocrine disrupters. Wastewater to be treated in the plant includes industrial effluents, storm water runoff, washings from agricultural fields and domestic wastewater. Wastewater from the WWTPs may enter the farmlands and might pose adverse impact on health of both human and animals via exposure through the food chain. Levels of antibiotics in sludge from different studies from China have been given in Table 3.2. In sludge, oxytetracycline was found to be dominant.

(ii) Livestock excreta used as manure

Antibiotics are used in livestock farms to suppress parasites, to treat diseases caused by bacteria, and to promote growth of livestock production (Kim and Carlson 2007). The percent of absorption and metabolism of antibiotics in animal body is

Table 3.2 Antibiotics in the sludge from wastewater treatment plant used as manure

Compounds	Sludge(μg/g)	Country	Reference
Tetracycline			
Tetracycline	2174.46	Sheyang, China(NE)	An et al. (2015)
Oxytetracycline	7369.67	Sheyang, China(NE)	An et al. (2015)
Chlortetracycline	3843.79	Sheyang, China(NE)	An et al. (2015)
Doxycycline	2104.27	Sheyang, China(NE)	An et al. (2015)
Sulfonamides			
Sulfamethoxazole	665	Sheyang, China(NE)	An et al. (2015)
Sulfadiazine	50.32	Sheyang, China(NE)	An et al. (2015)
Sulfamerazine	37.21	Sheyang, China(NE)	An et al. (2015)
Sulfadimidine	27.14	Sheyang, China(NE)	An et al. (2015)

Table 3.3 Antibiotics from livestock excreta used as manure

Compounds	Livestock manure (mg/g)	Country	Reference
Tetracycline			
Tetracycline	56.95	Sheyang, China(NE)	An et al. (2015)
	43.5	North China	Hu et al. (2010a, b)
	3.5	Beijing	Li et al. (2015)
Oxytetracycline	47.25	Sheyang, China(NE)	An et al. (2015)
	183.5	North China	Hu et al. (2010a, b)
	23.271	Beijing	Li et al. (2015)
Chlortetracycline	143.97	Sheyang, China(NE)	An et al. (2015)
	26.8	North China	Hu et al. (2010a, b)
	26.218	Beijing	Li et al. (2015)
Doxycycline	6.5	Sheyang, China(NE)	An et al. (2015)
Fluoroquinolones			
Enrofloxacin	8.684	Beijing	Li et al. (2015)
Ciprofloxacin	4.3	North China	Hu et al. (2010a, b)
	9.342	Beijing	Li et al. (2015)
Norfloxacin	4.187	Beijing	Li et al. (2015)
Ofloxacin	15.7	North China	Hu et al. (2010a, b)
Perfloxacin	24.7	North China	Hu et al. (2010a, b)
Lomefloxacin	0.038	Beijing	Li et al. (2015)
Macrolide			
Roxithromycin	0.067	Beijing	Li et al. (2015)
Lincomycin	3.8	North China	Hu et al. (2010a, b)
Sulfonamides			
Sulfamethoxazole	18.5	Sheyang, China(NE)	An et al. (2015)
	5.7	North China	Hu et al. (2010a, b)
	0.102	Beijing	Li et al. (2015)
Sulfadiazine	4.98	Sheyang, China(NE)	An et al. (2015)
	0.022	Beijing	Li et al. (2015)
Sulfamerazine	4.59	Sheyang, China(NE)	An et al. (2015)
Sulfadimidine	1.95	Sheyang, China(NE)	An et al. (2015)
Sulfamethazine	0.061	Beijing	Li et al. (2015)
Sulfadoxin	32.7	North China	Hu et al. (2010a, b)
Sulfachloropyridazine	2.76	North China	Hu et al. (2010a, b)

less. Approximately 30–90% of the antibiotics used are being excreted through urine and feces and subsequently released into the surrounding environment (Heberer 2002; Bound and Voulvoulis 2004; Kwon et al. 2011). Different studies across the globe reporting the level of antibiotics in livestock have been given in Table 3.3. When comparing the antibiotic concentration in sludge and livestock manure, the latter showed higher values. For example, tetracycline content in sludge and in livestock manure were 2.17 mg/kg and 56.95 mg/kg, respectively (Jing An et al. 2015). So it is evident that antibiotics used for veterinary purposes may affect the human health via food chain.

(iii) Treated water used for irrigation

Recycling of treated water for irrigation is an old practice. Regulation of treated water for irrigation is limited to very few parameters even in the USA. Most of the antibiotic compounds are not metabolized in the body and unused drugs are directly disposed off into the sewage collection system (Kummerer and Henninger 2003). Various processes in the WWTPs do not completely remove the antibiotics and therefore get discharged into the environment (Kummerer and Henninger 2003). Antibiotics are considered as pseudo-persistent contaminants. Antibiotics do not degrade easily hence with the increasing consumption, the concentration of these pseudo-persistent contaminants are increasing in the environment (Shi et al. 2012). The antibiotics concentration in wastewater from different studies have been given in Table 3.4. Azithromycin, clarithromycin, ciprofloxacin, erythromycin, norfloxacin, ofloxacin, sulfamethoxazole, and trimethoprim are the antibiotics normally detected in WWTP effluents (Fatta-Kassinos et al. 2011; Li and Zhang 2011; Sim et al. 2011; Ghosh and Mandal 2010; Watkinson et al. 2007). Some studies have detected antibiotics, such as erythromycin, sulfamethoxazole, trimethoprim and tetracycline in

Table 3.4 Wastewater containing antibiotics used for irrigation

Compounds	Wastewater (ng/l)	Country	Reference
Tetracycline			
Tetracycline	560	New York	Batt et al. (2006)
	48,000	Wisconsin, USA	Karthikeyan et al. (2006)
Oxytetracycline	47,000	Wisconsin, USA	Karthikeyan et al. (2006)
Fluoroquinolones			
Enrofloxacin	250	Wisconsin, USA	Karthikeyan et al. (2006)
Ciprofloxacin	10	USA	He et al. (2015)
	970	New York	Batt et al. (2006)
	310	Wisconsin, USA	Karthikeyan et al. (2006)
Norfloxacin	250	Wisconsin, USA	Karthikeyan et al. (2006)
Ofloxacin	9	USA	He et al. (2015)
Macrolide			
Erithromycin	3900	Wisconsin, USA	Karthikeyan et al. (2006)
Roxithromycin	1500	Wisconsin, USA	Karthikeyan et al. (2006)
Salfonamides			
Sulfamethoxazol	156	South Africa	Rahzia et al. (2012)
	1340	New York	Batt et al. (2006)
	310	Wisconsin, USA	Karthikeyan et al. (2006)
Sulfamethazine	50	China	Sun et al. (2014)
	300	Wisconsin, USA	Karthikeyan et al. (2006)

wastewater irrigated soils (Chen et al. 2011; Kinney et al. 2006). Variability in distribution of antibiotics concentration depending on the land usage pattern shows that the presence of antibiotics depends on varied soil characteristics like microbial diversity, moisture content and soil temperature.

(iv) Surface runoff from solid waste dumpsite
After expiry date, all the unused antibiotics are improperly dumped into solid waste disposal sites in developing nations. In most of the developing countries, the animal waste from slaughtering houses, its excreta, the unused medicines are collected by municipality and finally reaches solid waste dumpsite. During rainy season, all these wastes are washed away and the surface runoff can ultimately end up in the surface water. Leachate containing such leftover antibiotics in the solid waste stream of the municipal dumpsites can penetrate into the groundwater. In some countries, organic solid waste is converted into manure by composting. The amount of removal of the antibiotics by composting is unknown. The final product from composting is generally used as manure in agriculture. So this is a possible source for entry of antibiotics in soil.

(v) Application of antibiotics in aquaculture farms
Antibiotics such as tetracycline and oxolinic acid are extensively used in aquaculture farms (Table 3.5). The amount and type of antibiotics used for aquaculture varies with local and government regulations and farming practices. So the overall consumption pattern of antibiotics in aquaculture differs from one country to another. It has been found that antibiotic usage in Norway for aquaculture is 1 g per metric ton while in Vietnam it is 700 g per metric ton (Defoirdt et al. 2011). Unlike prophylactic use of antibiotics metaphylactic usage is commonly practiced for aquacultural purposes. In metaphylactic usage, the entire population is exposed to the medicine even if it is not required by some part of the population.

3.6 Occurrence of Antibiotics in Asian Soil

From the sources discussed previously in this chapter, it is evident that antibiotics can end up in the soil, and finally via plant uptake, such chemicals may enter the food chain. Despite such existing sources, limited data is available on the level of antibiotics in Asian soil. Antibiotic levels in soil in China and Korea among Asian countries have been given in Table 3.5. All the tetracycline compounds showed highest range in Shenyang region, China. Agriculture, animal husbandry, and agricultural product processing units were dominant in north-eastern part of Shenyang city. Sulfonamide compounds also showed very high concentration in Shenyang city. Sulfonamides and tetracycline are the two antibiotics most commonly used to promote growth in livestock production. So it is evident that the high concentration of these two compounds in Shenyang city is due to the use of these

Table 3.5 Occurrence of antibiotics in Asian soil

Compounds	Soil (μg/kg)	Country	References
Tetracycline			
Tetracycline	976.17	Shenyang, China	An et al. (2015)
	20.9–105	Northern China	Hu et al. (2010a, b)
	20.83–177.64	Korea	Awad et al. (2014)
	22	Beijing, China	Li et al. (2015)
Oxytetracycline	2.5–50 (μg/g)	Denmark	Rabùlle and Spliid (2000)
	124–2683	Northern China	Hu et al. (2010a, b)
	1398.47	Shenyang, China	An et al. (2015)
	0.09–0.71	Korea	Awad et al. (2014)
	423	Beijing, China	Li et al. (2015)
Chlortetracycline	1590.16	Shenyang, China	An et al. (2015)
	33.1–1079	Northern China	Hu et al. (2010a, b)
	0.07–0.85	Korea	Awad et al. (2014)
	120	Beijing, China	Li et al. (2015)
Doxycycline	870.45	Shenyang, China	An et al. (2015)
Fluoroquinolones			
Enrofloxacin	2–200 (μg/g)		Nowara et al. (1997)
	389	Beijing, China	Li et al. (2015)
Ciprofloxacin	250	Shenyang, China	An et al. (2015)
	10.3–30.1	Northern China	Hu et al. (2010a, b)
	253	Beijing, China	Li et al. (2015)
Norfloxacin	69	Beijing, China	Li et al. (2015)
Ofloxacin	0.6–1.6	Northern China	Hu et al. (2010a, b)
Perfloxacin	ND	Northern China	Hu et al. (2010a, b)
Lomefloxacin	10	Beijing, China	Li et al. (2015)
Macrolide			
Erythromycin	ND	Beijing, China	Li et al. (2015)
Roxithromycin	5.7	Beijing, China	Li et al.(2015)
Lincomycin	1.1–11.7	Northern China	Hu et al. (2010a, b)
Salfonamides			
Sulfamethoxazole	671.52	Shenyang, China	An et al. (2015)
	0.1–0.9	Northern China	Hu et al. (2010a, b)
	0.5–1.1	Korea	Awad et al. (2014)
	1.2	Beijing, China	Li et al. (2015)
Sulfadiazine	760.09	Shenyang, China	An et al. (2015)
	0.6	Beijing, China	Li et al. (2015)
Sulfamerazine	311.26	Shenyang, China	An et al. (2015)
Sulfadimidine	11.45	Shenyang, China	An et al. (2015)
Sulfamethazine	0.2–25 (μg/g)		
	ND–1.11	Korea	Awad et al. (2014)
Sulfathiazole	0.04–0.38	Korea	Awad et al. (2014)

two antibiotics in livestock production. As compared to China, the antibiotic concentration in Korean soil is less. This may be because, since 2005, South Korea is gradually decreasing the use of antibiotic growth promoters in livestock production.

3.7 Conclusion

Like several other organic pollutants, anitibiotics also reach soil mostly after partially treated or untreated antibiotics present in wastewater stream. Studies across the globe have reported the uptake of antibiotics by plants. The pathway of these pollutants generally depends on its physio-chemical properties. Studies have shown the development of antibiotic resistance genes in soil, plants, and humans. Further studies are required to find the fate of these pollutants in the environment and the associated risk due to the occurrence of these antibiotics in the environment.

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