Chapter 5
Antibiotics Pollution in the Paddy Soil Environment

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5.1 Introduction

Antibiotics are without a doubt one of the great discoveries and a turning point in human history. They have revolutionized medicine in several aspects and are widely used in human medicine for therapeutic treatment of infectious diseases and in veterinary medicine to treat and prevent infections, which, otherwise, could lead to chronic infections or even death. They are also commonly used to treat plant infections and for promoting growth in animal farming (Cabello 2006). Growth promoters have been banned in Europe since 2006 (EC Regulation No. 1831/2003), however, some agricultural practices still use large amounts of antibiotics (Woolhouse et al. 2015). The use of antibiotics is increasing in both developed and developing countries which results in an accumulation in soils, water, and biota around the world (Xu et al. 2015). It is estimated that approximately 63,200 tons of antibiotics were used in livestock in 2010 worldwide which is more than the amount of antibiotics used by humans, and it is expected that by 2030, this number will rise up to 105,600 tons due to the increase of human population (Van Boeckel et al.

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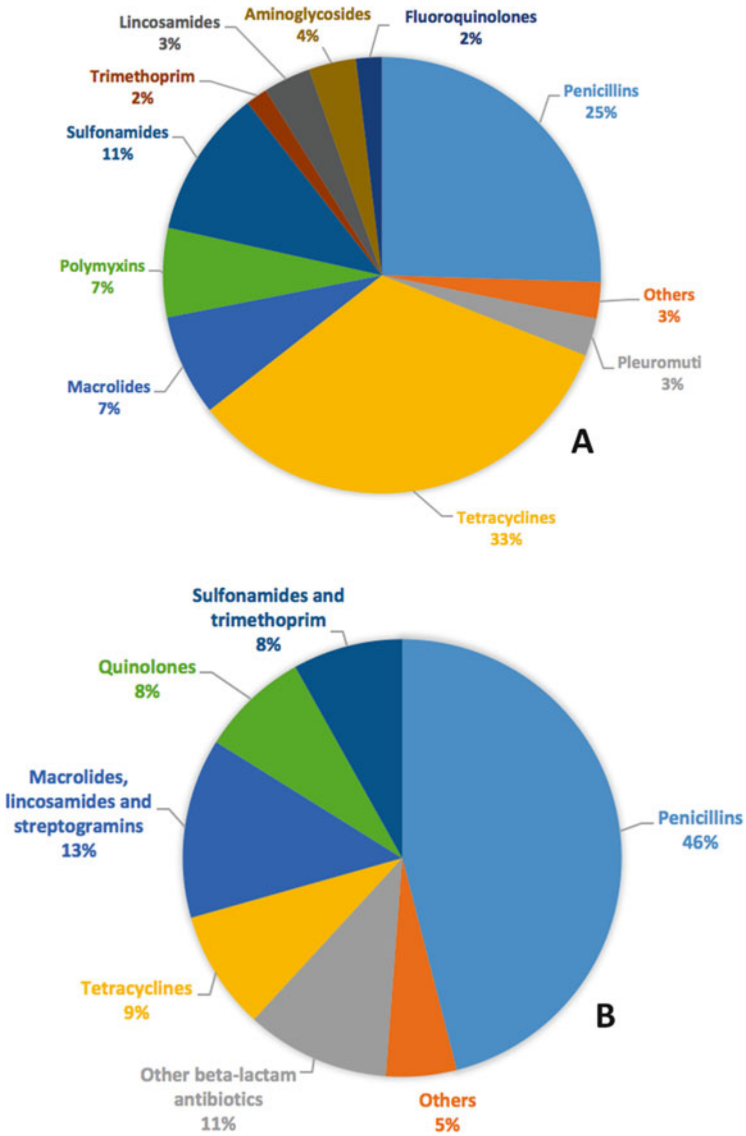

Fig. 5.1 (**a**) Consumption of different classes of antibiotics by humans expressed as percentages of daily doses per 1000 habitants per day in 30 European countries in 2015. (**b**) Consumption of different classes of antibiotics by food-producing animals expressed as percentages of the total sale in mg per population correction unit in 29 countries in Europe in 2014

2015). Data from 2014 and 2015 (Fig. 5.1) revealed that penicillins, followed by macrolides, lincosamides, and streptogramins, are the most consumed antibiotics by humans, whereas tetracyclines followed by penicillins and sulfonamides are the most consumed by food-producing animals in Europe (ECDC 2014, 2015). The intensive use of antibiotics both for farming and clinical proposes has led to an environmental pollution which may have serious repercussions in human and animal health. Antibiotics make a selective pressure on microorganisms selecting only the resistant ones. Therefore, the residues from farms and hospital settings may be a source of both antibiotics and resistance genes. The emergence of antibiotic pollution in the environment is not only considered a serious problem because of the influence on microbial communities but also because it represents an ecological risk. The antibiotic pollution is causing potential toxic effects on plants, animals, and eventually humans that go from molecular level to organism level and even to ecosystem level (Gothwal and Shashidhar 2015). The type of pollutant is variable: antibiotics can be from natural or synthetic origin, being the first ones more easily biodegraded than the synthetic ones in natural environments. For instance, macrolides, β-lactams, and aminoglycosides are quite degradable in soils environment, while tetracyclines, sulfonamides, and quinolones are more resistant to degradation (Silva et al. 2017). Nevertheless, different antibiotics have different degradation rates. Despite their biodegradability, antibiotics continue to be considered pollutants, since their degradation depends on their physicochemical properties, the climatic conditions, and the soil properties (Doretto and Rath 2013). Further, the principal sources of contamination, hospitals and farms, are continually producing residues and releasing them into the environment which, despite the antibiotic degradation, makes it very complicated to eradicate this sort of pollutant from the environment.

5.2 Antibiotic Environmental Pollution

Veterinary medicine is responsible for a great part of antibiotic soil pollution. Most of the antibiotics administrated to farm animals are excreted to environment via manure which is usually an important ingredient in organic and sustainable farming systems. Between 30 and 90% of these antibiotics are still biologically active when they reach the soils since they cannot be totally metabolized nor absorbed by the animals (Bound and Voulvoulis 2004). The concentration of several antibiotics present in manure has been quantified. For instance, macrolides concentration was in ranges of 0.07–0.14, 1.05–2.1, and 0.62–1.24 mg/kg for cattle, pig, and poultry manures, respectively; and concentrations of sulfonamides and tetracyclines in manure were 0.49, 8.44, and 1.39 mg/kg and 1.65, 16.56, and 15.62 mg/kg, respectively (Kim et al. 2011). The most common antibiotics found in swine and beef manure are oxytetracycline, chlortetracycline, sulfamethazine, monensin, tylosin, virginiamycin, penicillin, and nicarbazine and their concentrations ranges from 0.5 to 215 mg/L of manure slurry (Kumar et al. 2005). Martínez-Carballo et al. (2007) investigated the prevalence of antibiotics in manure samples of pig, chicken, and turkey, as well as soils fertilized with manure in Austria. The recoveries of samples were between 61 and 105%. From pig manure, it was detected a concentration of 46 mg/kg of chlortetracycline, 29 mg/kg of oxytetracycline, and 23 mg/kg of tetracycline. As for the chicken and turkey manure, resistance to sulfadiazine was detected in a maximum concentration of 20 and 91 mg/kg, respectively. When applied to farmlands, antibiotics contained in manure reach the upper soil layer and they may accumulate in the soil, may be washed away into surface waters, or may filter to groundwater (Boxall et al. 2003). A large occurrence of antibiotics in wastewater treatment plants, such as ciprofloxacin and ofloxacin, has been reported. The inefficient ability of wastewater treatment plants to eliminate antibiotics makes these facilities one of the main sources of antibiotic contamination in rivers and streams. Also, wastewater treatment plants are considered an important point source of potential evolution and spreading of antibiotic resistance into the environment. Zhou et al. (2013) investigated the occurrence of 11 classes of 50 antibiotics in a wastewater treatment plant. The results showed the existence of 20 different antibiotics in the influents and 17 in the effluents being sulfamethoxazole, norfloxacin, ofloxacin, erythromycin, and trimethoprim the most frequently detected. Also, 21 antibiotics were detected at concentrations up to 5800 ng/g in the sewage sludge, with tetracycline, oxytetracycline, norfloxacin, and ofloxacin as the most abundant. This poses a serious risk to human and animal health as rivers are a source of water for human and animal, either directly or indirectly (Rodriguez-Mozaz et al. 2015). Also, the wastewater from the treatment plants is often used for crop fields irrigation. Although antibiotics represent a source of environmental contamination, their action on bacterial communities also represents a contribution to the increase of antibiotic resistance genes.

5.2.1 Effect of Antibiotics on Bacterial Communities and Dissemination of ARG in the Environment

Antibiotic-resistant genes can also be considered a form of pollution. This pollutant is directly related to the antibiotic pollution since it may facilitate the development and spread of antibiotic resistance though the environment. Antibiotic-resistant genes and bacteria have always been part of the natural environment since resistance is an important process of evolutionary conservation (Gothwal and Shashidhar 2015). However, some antibiotic resistance genes (ARGs) are naturally associated with some bacterial strains; this characteristic is known as intrinsic resistance. This type of resistance occurs when the bacteria have features that provide antibiotic resistance and the presence of these features is independent of previous antibiotic exposure or gene transfer between bacteria (Wright 2010). The intrinsic resistance can be caused by inactivating enzymes, reduced antibiotic uptake, and lack of the target. The resistance that is not innate is called acquired resistance. The arise of this type of resistance follows the use of antibiotics for therapy and agricultural purposes (Lin et al. 2015). The mechanisms that are at the basis of acquired resistance are mutations in bacterial genome and horizontal gene transfer. In general, a single mutation is not enough to create a high resistance to a certain antibiotic. However, it is sufficient to provide a low resistance which enables the bacteria to survive and acquire additional mutations or genetic information. The mutations confer resistance to bacteria by modifying the proteins present in the outer membrane of bacteria preventing the entry of the antibiotic, modifying or eliminating the binding site where the antibiotic would bind, and regulating efflux pumps and enzymes which expel and inactivate the antibiotic, respectively (Tenover 2006). Nevertheless, horizontal gene transfer (HGT) is accepted as the mechanism responsible for the widespread of antibiotic resistance genes. HGT occurs through phage (1) transduction which consists in the enclosing of the host DNA into a bacteriophage which is the vector for the injection of DNA into the recipient cell; (2) transformation which involves uptake and incorporation of naked DNA; and (3) conjugation which is the most common mechanism of transference occurring in bacteria and requires the cell contact to transfer the DNA. Plasmids, integrons, and transposons are elements that are responsible for the transference of resistance between microorganisms (Dzidic and Bedekovic 2003).

Antibiotics present in the environment, either in high, low, or sub-inhibitory concentrations, exert a selective pressure on bacteria leading to a gradual increase in the prevalence of resistance. When this happens with clinical-related bacteria, we may be facing a serious health public problem. Nevertheless, other factors may contribute to the selective pressure and the increase of antibiotic resistance in the environment such as heavy metals and natural compounds produced by microorganisms themselves. Dissemination of antibiotic resistance through the environment may also occur due to the application of manure to agricultural fields when manure already contains antibiotic-resistant bacteria and ARG. Manure from pigs has a greater content in ARG and antibiotic-resistant bacteria than manure from other livestock animals which is associated with the amounts of antibiotics used in these animals (Enne et al. 2007). In a study conducted in Germany, 16 different manures originated from pig facilities were investigated and it was found a high abundance of the ARG *sul*1 and *sul*2 correlated with high antibiotic use in the farms (Heuer et al. 2011). Schwaiger et al. (2009) investigated the pig manure from 120 farms and found higher concentrations of the ARG *tet*M and *tet*O when tetracycline was detectable in manure. Also, they found highest abundance of these genes in the largest facility which houses 2000 pigs and where amoxicillin and tetracycline were routinely used. Wild animal may also act as reservoirs and disseminators of ARG, even when there is no apparent contact with antibiotics, in particular wild birds which have the potential for long-distance dissemination. These animals inhabit and can travel to a wide range of environments that can be either close to human activities or remote places, disseminating the resistance along the way (Allen et al. 2010). In a study conducted by Gonçalves et al. (2013), the antimicrobial resistance was studied in samples obtained from wild specimens of Iberian lynx. Forty-five isolates were obtained and presented high percentages of resistance to tetracycline and erythromycin, as well as the ARG *tet*M, *tet*L, *erm*(B), *aac*(6′)-Ie-*aph*(2″)-Ia, *ant* (6)-Ia, and *aph*(3′)-IIIa. Silva et al. (2018) investigated the prevalence of vancomycin-resistant enterococci, which is associated with nosocomial infections, in wild red-legged partridges. Six isolates were recovered and showed erythromycin and tetracycline resistance and harbored the ARG *erm*(B) and *tet*(M). The dissemination of ARG can also occur due to the wastewater treatment plants effluents which have considerable amounts of antibiotics and ARG which have not been eliminated in full during the treatment process ending up in wastewater streams (Xu et al. 2015). One of the big concerns and yet not fully understood nor characterized of antibiotics spread is the plants uptake of these pollutants, particularly crops.

5.3 Antibiotics Uptake by Plants

Antibiotics can be taken up by crops, aquatic plants, and vegetables through manure application and wastewater irrigation (Fig. 5.2). Their presence in food plants imposes a risk to human and animal health and defies the standards of food safety. In the last 50 years, several studies have been carried out regarding the antibiotics uptake by plants and their consequences. The studies were made either in a controlled environment with culture of plants in antibiotic medium or in the natural environment with manure application. However, it was verified that the results differ with the different environments (Sarmah et al. 2006). In one of the first studies made, it was used wastes containing tylosin and oxytetracycline to fertilize tomatoes and the results revealed absence of antibiotics in the tomatoes (Bewick 1979). Nevertheless, in more recent studies, it was found bioaccumulation of antibiotics in carrot

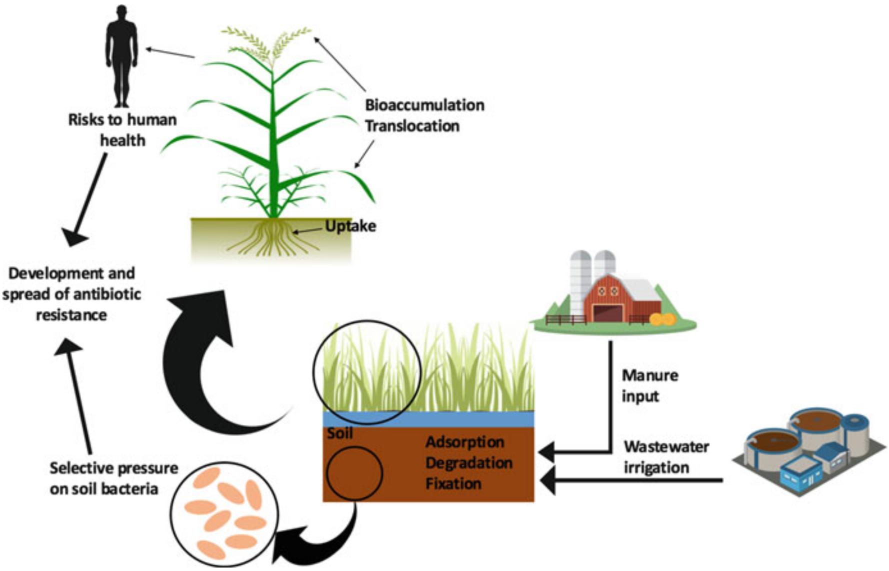

Fig. 5.2 Transport route of antibiotics in environment since agricultural farms (by manure application in soils) and wastewater treatment plants (by soil irrigation) to plants, humans, and microbial communities

and barley grown in soil spiked with ciprofloxacin (Eggen et al. 2011). Other studies conducted aiming if plants grown in soils fertilized with manure containing antibiotics uptake those antibiotics revealed that onions (*Allium cepa*), corn (*Z. mays*), and cabbage (*Brassica oleracea*, var. capitata) absorbed chlortetracycline from loamy sand and sandy loam soils (Kumar et al. 2005). Another study with the same purpose showed that lettuce, corn, and potatoes take up antibiotics when grown in soil fertilized with livestock manure containing sulfamethazine (Dolliver et al. 2007). Nitrofurans are commonly used antibiotics and have been found in soils. These compounds have a high mutagenic and carcinogenic capacity which is a concern for human and animal health. A recent study has revealed that spring onions uptake and accumulate these compounds from contaminated soil into their root bulbs (Wang et al. 2017). One of the most consumed crops are root vegetables such as potatoes, carrots, and onions; however, these crops may be more vulnerable to antibiotic contamination since they are in direct contact with soil. The bioaccumulation of antibiotic in the several plant constituents is in this sequence: leaf > stem > root (Hu et al. 2010). The same study concluded that the winter season is more favorable for bioaccumulation. They also determined the accumulation of oxytetracycline, tetracycline, and chlortetracycline in coriander leaves which were 78–330, 1.9–5.6, and 92–481 mg/kg, respectively; the accumulation of 1.7–3.6, 1.1, and 5–20 mg/kg of ofloxacin, pefloxacin, and lincomycin, respectively, in celery leaves; and 0.2–0.6, 0.1–0.5, 8–30, and 0.9–2.7 mg/kg of sulfadoxine, sulfachloropyridazine, chloramphenicol, and sulfamethoxazole, respectively, in radish leaves. Wastewater is used for crop irrigation and may also be a source of antibiotic contamination. Chinese white cabbage, water spinach, Chinese radish, corn, and rice were investigated for the presence of antibiotics after irrigation with domestic wastewater or fishpond water. The antibiotics were absorbed by the plants roots and then transported to stems, leaves, and fruits. It was found that quinolones, followed by chloramphenicol and tetracyclines, had the highest accumulation (Pan et al. 2014). Antibiotics also affect the germination, growth, and development of plants. Tetracyclines have reduced the production of pinto beans; however, nutrient uptake in wheat and corn was promoted by this antibiotic. Six antibiotics were used to investigate their phytotoxic effect on plants. Sulfamethoxazole, sulfamethazine, and trimethoprim were found to inhibit the plant growth in soil (Liu et al. 2009). The chloroplastic and mitochondrial protein synthesis in plants is affected by several antibiotics such as macrolides, tetracyclines, and fluoroquinolones. Tetracyclines also inhibit plant growth and may cause chromosomal aberrations. ß-lactam antibiotics may also affect the plastid division in lower plants (Kasten and Reski 1997; Opriş et al. 2013).

The antibiotics translocated from soil and water to crops may cause allergic and toxic reactions in animals and humans, especially children. Also, the presence of two or more antibiotics in crops and their interaction after ingestion may cause toxicity or even death. Plant foods contaminated with antibiotic may also contribute to antibiotic resistance in humans and animals. For instance, tetracycline can be a promoter in trigging horizontal gene transfer between different bacteria (Shoemaker et al. 2001).

5.4 Antibiotic Pollution in Paddy Soil

Manure has been widely used in soils as a fertilizer since it contributes to the nutrient input to maintain production in soils. However, long-term manure application may lead to antibiotic accumulation. Sewage sludge, which is a product of wastewater treatment processes, is commonly used for agricultural proposes due to its content in organic matter. This method is extensively used in the USA (about 60% of sewage sludge produced is applied to agricultural fields), Portugal, the UK, Iceland, and Spain (Liu et al. 2017). Nevertheless, the sludge of treatment plants serving domestic and industrial areas may contain antibiotics and ARG. Both of these methods, as well as the use of surface water and groundwater, are used for paddy soils management which represents a concern to human and animal health since paddy soils represent a large portion of global cropland, especially in Asia where the rice production accounts for over 90% of global rice production (Cosslett and Cosslett 2018). Several studies have been made regarding the application of manure containing antibiotics on paddy soils, as well as the antibiotic concentrations detected in paddy soils (Table 5.1). The presence of six antibiotics commonly used in livestock, namely, of oxytetracycline, tetracycline, chlortetracycline, sulfamethoxazole, sulfadiazine, and sulfamethizole, and eight antibiotic-resistant genes (*tet*A, *tet*G, *tet*M, *tet*O, *tet*Q, *tet*W, *sul*I, and *sul*II) was investigated in paddy soils of South China subjected to long-term applications of manure (Tang et al. 2015). Oxytetracycline, tetracycline, and chlortetracycline were detected in high concentrations in all soil samples treated with manure and their concentration decreased with increasing depth. Among the genes investigated, the *tet*A, *tet*G, *sul*I, and *sulI*I genes had high relative abundances with average values. Sulfonamides were not detected in this study possibly due to their moderate degradation rates. However, Awad et al. (2015) report the presence of sulfonamides and their corresponding ARGs in paddy soils, and more, the sulfonamides were detected in higher concentrations than tetracyclines. Ok et al. (2011) studied the influence of a manure composting facility near a paddy field on the presence of antibiotics in the paddy soil and detected low concentrations of antibiotics in the rice paddy soil which was located at the bottom of the water stream. Another study conducted in South China aimed to characterize ARGs in paddy soils (Xiao et al. 2016). From the 25 ARG studied, 16 were detected in the paddy soils. Also, multidrug resistance genes were the most dominant type in the samples. Kim et al. (2017) investigated the prevalence of bacteria resistant to sulfamethoxazole, sulfamethazine, and sulfathiazole and the correspondent ARG in both long-term fertilized and natural paddy soils in Korea. The results showed a high frequency of antibiotic-resistant bacteria harboring the sulfonamide-resistant genes *sul*I and *sul*II in both natural and fertilized soils. The manure was also analyzed and it was concluded that the concentrations range from 40 to 95%, particularly in manure from pig farms. The effects of tetracycline, sulfamonomethoxine, ciprofloxacin, and their combination on the bacteria of paddy soils with rotation system were studied by Lin et al. (2016). They concluded that antibiotic effects on the soil microbiome depended on antibiotic type and

Table 5.1 Antibiotic concentration (μg/kg) detected in paddy soils

	TC	OTC	CTC	SMT	SMX	STZ	NFX	ERY	CAP	TYL	Reference
Paddy soil	5.0–21.9	–	–	1.3–4.2	–	–	20.5–66.7	20.5–66.7	3.2–22/3	–	Pan et al. (2014)
	6.97–29.7	11.66–41.27	23.84–344.74	–	–	–	–	–	–	–	Tang et al. (2015)
	0.5–0.93	–	1.5–6	2–17.68	1.8–10.24	1.9–8.34	–	–	–	84.47–222.84	Awad et al. (2015)
	0.82–2.94	–	1.68–3.77	20.3–28.38	0.77–5.43	3.32–38.82	–	–	–	–	Ok et al. (2011)

TC tetracycline, *OTC* oxytetracycline, *CTC* chlortetracycline, *SMT* sulfamethazine, *SMX* sulfamethoxazole, *STZ* sulfathiazole exposure time. The effect of tetracycline on soil microbiome was acute but short, whereas sulfamonomethoxine and ciprofloxacin were responsible for delayed antibiotic effect. The combination of antibiotics has the same effect as tetracycline. A few studies have also investigated the effect of antibiotics on plant growth and their uptake by plants growing in paddy soils. In a study conducted by Xu et al. (2016), it investigated the effect of oxytetracycline pollution on rice growth. The main effect was detected at the seedling stage, and the effect on the underground part of the plant was greater than the aboveground part. Negative effects on biomass of the plant's root were identified when the concentration of oxytetracycline on paddy soil was higher than 30 mg/kg. The antibiotic accumulated in the several parts of the plant follows the order: root > leaf > stem > grain; however, the rice roots showed a low capacity to uptake oxytetracycline from the soil. Hawker et al. (2013) studied the uptake capacity of rice growing in paddy soils with oxytetracycline, chlortetracycline, and norfloxacin at initial soil/water concentrations of 10, 20, and 30 μg/g. The concentrations of antibiotics detected in the plants were directly proportional to the concentrations in the soils. Nevertheless, the time the plant takes to uptake the maximum concentration varies between compounds. Regarding plant growth tests, it was shown that among several antibiotics including trimethoprim, tylosin, tetracycline, and chlortetracycline, only sulfonamides (sulfamethoxazole and sulfamethazine) affected strongly the rice growth in paddy soil. There was no significant inhibition of the other antibiotics on rice growth (Liu et al. 2009).

5.5 Conclusions

Antibiotics and antibiotic resistance genes (ARG) are now considered pollutants due to their increase in the environment and their nefarious effects on human, animal, and environmental health. The spread on antibiotics and ARG on the environment is mainly due to certain human activities and application of manure and wastewater from wastewater treatment plants serving hospitals and municipalities on agricultural fields. This may lead to the spread of resistant bacteria and the emergence of new multidrug-resistant bacteria. Also, the soils and water antibiotic contamination may have negative effects on crops growth and development. Some antibiotics are uptaken by plant foods which after consumed may increase even more the antibiotic resistance and/or cause toxicity. The presence of antibiotics and ARG in rice paddy soils is a great concern since these crops are extensively consumed worldwide and several studies have proven that the uptake of antibiotics by rice occurs. Therefore, to remedy this situation, the minimization and mitigation are the best solutions. A better use of antibiotics and lower-dose prescribing may lead to a decrease in the occurrence of drug wastage. Also, since antibiotics are highly excreted, lower doses of antibiotics may help reduce the entry of antibiotics into the environment.

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