

Prioritizing Environmental Risks of Veterinary Antibiotics Based on the Use and the Potential to Reach Environment

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Veterinary antibiotics have been widely used to increase feed efficiency, to prevent disease, and to promote growth as well as to control disease. The antibiotics administered can be excreted through the urine and feces. One of the major routes of veterinary antibiotics entering soil and water environment is via the application of animal manure to agricultural land as an organic fertilizer source. Since little is known about impacts of antibiotics on the environment, this study was conducted to prioritize the veterinary antibiotics based on the consumption and potential to reach the environment. Among 83 veterinary antibiotics consumed in Korea, ten antibiotics were used at the greater dose than 25 Mg in 2004. Potential to reach the environment was determined according to excretion rate after administered to animals and sorption affinity to soil solids after applied to agricultural land. Seventeen antibiotic active ingredients (AIs) were classified as 'High' priority in terms of the potential to reach the environment. An overall priority score was determined by combining priority score based on consumption with the degree of potential environment exposure. Twenty veterinary antibiotic AIs were classified as 'Very high' or 'High' priority requiring detailed assessment. The antibiotic AIs were identified four aminoglycosides, two macrolides, two penicillins, five sulfonamides, three tetracyclines, two quinolones, and two miscellaneous. Eight veterinary antibiotic AIs including amoxicillin, carbadox, chlortetracycline, neomycin, oxytetracycline, sulfamethazine, sulfathiazole, and tylosin were identified to have a greater priority of environmental risk in Korea.

Key words: Consumption, Excretion rate, Prioritization, Sorption affinity, Veterinary antibiotics

Introduction

Antibiotics have been administered to livestock in order to control disease when illness is present. In addition to these therapeutic uses, antibiotics are routinely given to healthy livestock by adding to feed or water to increase feed efficiency, to prevent disease, and to promote growth. Dewey et al. (1999) reported that 88% of 712 swine farms in the United States used antibiotics in feeds and most of the antibiotics (92%) were fed at a set interval, especially for young growing swine. The antibiotic treatment at nontherapeutic levels is considered to increase body weight by suppression of intestinal bacteria (Mitscher, 1978), inhibition of subclinical infections, reduction in harmful microbial metabolites, and/or enhanced nutrient uptake by reducing microbial use (Gaskins et al., 2002). Net gain by feeding antibiotics

to swine is estimated to be \$45.5 million per year (Mathews Jr., 2001). About 1,400 Mg of veterinary antibiotics in total is used in the Republic of Korea every year (National Veterinary Research & Quarantine Service, 2005).

Generally, oral antibiotics are slowly absorbed by animals, and a mixture of the parent compounds of antibiotics and their metabolites can be excreted via the urine and feces (Halling-Sorensen et al., 1998; Montforts et al., 1999; Tolls, 2001; Winckler and Grafe, 2001; Boxall et al., 2002; Halling-Sorensen et al., 2002; Aga et al., 2003; Vaclavik et al., 2004). Antibiotics can be persistent in animal manure and soil although they are gradually decomposed by physical, chemical, and biological reactions. For example, the half-life of chlortetracycline in manure was reported more than 30 days (Gavalchin and Katz, 1994; Montforts et al., 1999). The decomposition rate of antibiotics may be affected by the antibiotic properties and environmental conditions. The major antibiotic properties include water solubility,

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photosensitivity, biodegradation, acid base dissociation constant (pK_a), and sorption behavior. The environmental conditions include temperature, redox conditions, pH, and bacterial activity. The residual chlortetracycline in soil after 30 days was 44% at 30°C, 88% at 20°C, and nearly 100% at 4°C (Gavalchin and Katz, 1994). The half life of chlortetracycline in field soils was 25-34 days (Halling-Sorensen et al., 2005) and 21-24 days (Carlson and Mabury, 2006). About 40% of the tylosin remained in soil after 30 days at 4°C (Gavalchin and Katz, 1994). The half life of tylosin was 49-67 days in field soils (Halling-Sorensen et al., 2005). Antibiotics can accumulate in soil with the continuous application of animal manure to agricultural land. Such accumulations may adversely affect soil ecosystems. Soil microbes that are resistant to tylosin and tetracyclines have been reported in soils amended with animal manures (Halling-Sorensen et al., 2002; Onan and LaPara, 2003; Sengelov et al., 2003; Halling-Sorensen et al., 2005). Since animal manure have been used as a good organic fertilizer source, the application of animal manure to agricultural land is known to be one of the major routes of veterinary antibiotics entering soil and water environment.

Antibiotics entering soil have the potential to contaminate surface waters through overland flow (runoff) or via drainflow, and to groundwater by leaching (Halling-Sorensen et al., 1998; Boxall et al., 2004; Kay et al., 2004; Burkhardt et al., 2005; Kreuzig et al., 2005; Kay et al., 2005a; Kay et al., 2005b). For example, Kay et al. (2004) reported that peak concentrations of sulfachloropyridazine and oxytetracycline in drainflow from a 1.55 ha field were 613 and 36 $\mu\text{g L}^{-1}$, respectively, although mass losses of the antibiotics were less than 0.5%. They suggested that preferential flow via desiccation cracks and worm channels to the tile drains was one of the most important routes. In runoff water from 5 × 2 m plots, sulfachloropyridazine and oxytetracycline were detected at 703 and 71 $\mu\text{g L}^{-1}$, and their mass losses were 0.42% and 0.07%, respectively (Kay et al., 2005b). One or more antibiotics were found in about 50% of 139 stream water samples obtained from across the United States (Kolpin et al., 2002). Ingerslev et al. (2001) reported that tylosin and oxytetracycline were considered moderately persistent in surface water systems, whereas olaquinox was more biodegradable. Ash et al. (2002) studied 16 rivers in the United States and found that more than 40% of bacteria were resistant to antibiotics.

Little study has been conducted to examine the type and amount of veterinary antibiotics in the soil and aquatic environments in Korea, but this does not guarantee free of any antibiotic in the environment. Among cattle, swine, and chicken slaughtered in 2006 in Korea, 121,936 livestock products were inspected of the residual antibiotics and 309 (0.25%) of them had higher levels than the critical standards in the livestock products (National Veterinary Research & Quarantine Service, 2007). Antibiotics resistant microbes have been reported from animal wastes and water samples of the River Sumjin (Park et al., 2003; National Veterinary Research & Quarantine Service, 2005). Therefore, it is necessary to monitor veterinary antibiotics in water environment and initially identify candidate antibiotics with relatively high potential to reach the aquatic environment prior to detailed assessment. Kim et al. (2006) suggested additional risk assessments for ten antibiotic substances among 126 human use antibiotics based on the production amount of 2003 and metabolism in human body.

The objective of the study was to prioritize environmental risks of veterinary antibiotics based on their usage in the Republic of Korea and the potential to reach soil and aquatic environments.

Materials and Methods

Veterinary antibiotics administered to livestock may enter soil and aquatic environments after metabolism in treated animals. Potential of the antibiotics to reach the environment can be assessed in three stages; application, excretion, and behavior in soil. Possible pathways of the antibiotics into the aquatic environment are shown in Fig. 1.

The prioritization was determined based on the use in Korea (stage 1) and potential to reach the environment (stage 2 and 3). It is reasonable that veterinary antibiotics used in a greater amount might have a higher potential to reach soil and aquatic environments. The usage data for veterinary antibiotics sold in Korea were obtained from the annual report of National Veterinary Research & Quarantine Service (2005). In 2004, 1,368 Mg of 83 veterinary antibiotic active ingredients (AIs) were used in the Republic of Korea (Table 1). Tetracyclines were most commonly used (51% of the total use amount), followed by penicillins (13%), sulfonamides (12%), aminoglycosides (4.6%), macrolides (3.6%), quinolone

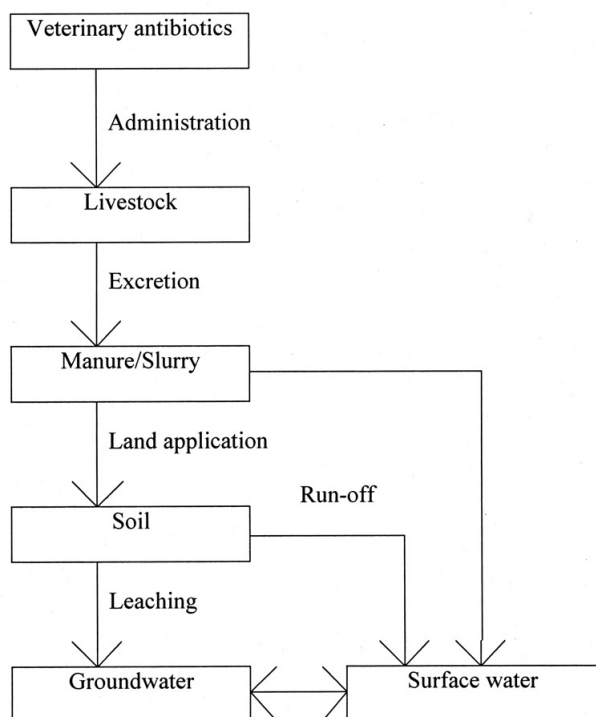


Fig. 1. Possible pathways of the veterinary antibiotics into the aquatic environment.

Table 1. Consumption of veterinary antibiotics in Korea in 2004.

Chemical group	Number of active ingredients	Consumption [†] kg	Proportion %
Tetracyclines	4	698,632	51.1
Penicillins	5	169,166	13.3
Sulfonamides	17	162,241	11.9
Aminoglycosides	8	62,829	4.6
Macrolide	8	48,587	3.6
Quinolone	11	44,509	3.3
Polypeptide	5	31,796	2.3
Chloramphenicols	3	20,351	1.5
Lincosamides	2	11,981	0.9
Cephaloporins	4	1,865	0.1
Miscellaneous	16	116,078	8.5
Total	83	1,368,011	100.0

[†] National Veterinary Research & Quarantine Service (2005).

(3.3%), polypeptide (2.3%), and chloramphenicols (1.5%), that is different from the use pattern in the United States (tetracyclines 29%, polypeptide 11%, macrolides 7.1%, sulfonamides 6.9%, and penicillins 2.7%) (Mellon et al., 2001) and the United Kingdom (tetracyclines 46%, sulfonamides 20%, β -lactams 14%, macrolides 13%, and aminoglycosides 4.6%) (Capleton et al., 2006). Most of the antibiotics (56%) were used for swine in Korea.

Veterinary antibiotic AIs used in 2004 were classified based on the consumption; 'High' for greater than 25 Mg per year, 'Medium' for between 3 and 25 Mg annually, and 'Low' for less than 3 Mg per year. In comparison, Capleton et al. (2006) classified veterinary antibiotic AIs used greater than 10 Mg annually as 'High' and those less than 1 Mg per year as 'Low'. It needs to be noted that about 460 Mg AI of therapeutic antimicrobials is used in the United Kingdom per year compared to about 1,400 Mg in Korea.

Potential to reach the environment was assessed according to metabolism of the antibiotics in livestock (or excreted antibiotics relative to administered dose) and behavior in soil after amended to agricultural land. It is reasonable that veterinary antibiotics less metabolized within the treated animal body can have a relatively high potential to reach the environment. The degree of metabolism in livestock varies depending on chemical group, as well as within the chemical group. For instance, tetracyclines, penicillins, and macrolides are generally metabolized less than 20% by animals, while greater than 70% for sulfonamides (Hirsch et al., 1999; Boxall et al., 2004). Therefore, tetracyclines, penicillins, and macrolides have a relatively high potential to be found in animal excreta and in turn soil and aquatic environments compared with sulfonamides. Some aminoglycosides are metabolized less than 20%, while greater than 80% for some aminoglycosides. In addition to metabolism in livestock, sorption to soil is also an important factor determining the potential to enter aquatic environment. It is not surprising that less retained antibiotics by soil solids have a greater potential to reach groundwater and then surface water compared with highly sorbed antibiotics. 'High' priority was allocated to antibiotics with excretion rate of greater than 70% or with distribution coefficient of less than 10. Unfortunately, sufficient data and information were not available for all the veterinary antibiotics at this time. In order to compensate for data deficiency, priority for the potential to reach the environment determined by Boxall et al. (2003) and Capleton et al. (2006) were also referenced to categorize the veterinary antibiotic AIs used in Korea. They assessed the potential of veterinary antibiotic AIs to enter the environment based on three criteria; the target treatment group, the route of administration, and metabolism of compounds, which was focused on application and excretion of veterinary antibiotics.

In order to determine an overall priority, the priority

based on consumption was combined with the priority of the potential to reach the environment. Antibiotic AIs with 'High' for both use and the potential were assigned to 'Very high' category, and 'High' category for AIs with 'High' for either use or the potential.

Results and Discussion

Among 83 veterinary antibiotic AIs used in 2004, 10 antibiotic AIs were classified as 'High' with use greater

than 25 Mg annually and 26 antibiotic AIs as 'Medium' (Table 2). 'High' AIs were chlortetracycline (398 Mg yr⁻¹), oxytetracycline (297 Mg yr⁻¹), amoxicillin (98 Mg yr⁻¹), sulfathiazole (96 Mg yr⁻¹), penicillin G (53 Mg yr⁻¹), neomycine (36 Mg yr⁻¹), carbadox (35 Mg yr⁻¹), tylosin (31 Mg yr⁻¹), salinomycin (30 Mg yr⁻¹), and sulfamethazine (27 Mg yr⁻¹), which were an aminoglycoside, a macrolide, two penicillins, two sulfonamides, two tetracyclines, and two miscellaneous. 'Medium' AIs include four aminoglycosides, a chloramphenicos, a

Table 2. Prioritization of veterinary antibiotics active ingredients based on consumption in Republic of Korea. Ordered according to priority and then alphabetically.

Priority	Veterinary antibiotic active ingredient	Chemical group	CAS [†] number	Consumption [‡] Mg yr ⁻¹
High (10)	Amoxicillin	Penicillin	26787-78-0	97.9
	Carbadox	-	6804-07-5	34.5
	Chlortetracycline	Tetracycline	57-62-5	397.8
	Neomycin	Aminoglycoside	1404-04-2	36.3
	Oxytetracycline	Tetracycline	79-57-2	296.5
	Penicillin G	Penicillin	6130-64-9	52.6
	Salinomycin	-	53003-10-4	30.3
	Sulfamethazine	Sulfonamide	57-68-1	26.9
	Sulfathiazole	Sulfonamide	72-14-0	96.4
	Tylosin	Macrolide	1401-69-0	31.4
	Ampicillin	Penicillin	69-53-4	18.0
	Apramycin	Aminoglycoside	37321-09-8	3.8
	Avilamycin	-	11051-71-1	3.6
	Bacitracin	Polypeptide	1405-87-4	15.6
	Ciprofloxacin	Quinolone	85721-33-1	7.5
	Colistin sulfate	Polypeptide	1264-72-8	7.6
	Dihydrostreptomycin	Aminoglycoside	128-46-1	8.7
	Doxycycline	Tetracycline	564-25-0	3.1
	Medium (26)	Enrofloxacin	Quinolone	93106-60-6
Erythromycin		Macrolide	114-07-8	12.6
Florfenicol		Chloramphenicos	73231-34-2	19.4
Kanamycin sulfate		Aminoglycoside	29701-07-3	3.6
Lasalocid		-	-	4.0
Lincomycin		Lincosamide	154-21-2	11.5
Monensin		-	17090-79-8	16.9
Nicarbazine		-	330-95-0	3.4
Norfloxacin		Quinolone	70458-96-7	4.4
Oxolinic acid		Quinolone	14698-29-4	3.3
Streptomycin sulfate		Aminoglycoside	3810-74-0	5.0
Sulfadiazine		Sulfonamide	68-35-7	5.0
Sulfadimethoxine		Sulfonamide	122-11-2	3.5
Sulfamethoxazole		Sulfonamide	723-46-6	14.8
Sulfaquinoxaline		Sulfonamide	59-40-5	6.0
Tiamulin		-	55297-95-5	12.9
Trimethoprim		Sulfonamide	738-70-5	7.6
Virginiamycin		Polypeptide	21411-53-0	4.8

[†] CAS, Chemical Abstracts Service

[‡] National Veterinary Research & Quarantine Service (2005).

lincosamide, a macrolide, a penicillin, three polypeptides, four quinolones, five sulfonamides, a tetracycline, and five miscellaneous. Kim et al. (2006) reported that top ten 'human' use antibiotics based on production amount in Korea were amoxicillin (158 Mg yr⁻¹), cefaclor (83 Mg yr⁻¹), roxithromycin (45 Mg yr⁻¹), cephradine (35 Mg yr⁻¹), cefatrizine (28 Mg yr⁻¹), cefadroxil (25 Mg yr⁻¹), aztreonam (23 Mg yr⁻¹), ceftazidime (22 Mg yr⁻¹), rifampicin (13 Mg yr⁻¹), and ribostamycin (10 Mg yr⁻¹). It is interesting that considerable amount of amoxicillin has been used for both human and livestock in Korea.

The priority for the potential to reach the environment was determined for the 36 antibiotic AIs classified as 'High' and 'Medium' consumption by assuming less potential for antibiotics with little consumption. Excretion rate and distribution coefficient of the antibiotics are presented in Table 3, but not all the 36 antibiotics due to

limited data. For additional information, priority for the potential determined by Boxall et al. (2003) and Capleton et al. (2006) was also presented in Table 3. Note that they did not consider the fate and behavior of veterinary antibiotics in soil as mentioned in 'Materials and Methods' section. About 80% of animal wastes are applied to agricultural land in a form of compost or slurry in Korea (Lee, 2006). Seventeen antibiotic AIs were classified as 'High' and eight antibiotic AIs as 'Medium' or 'Low.' The reason why many antibiotics were assigned to 'High' was due to a conservative perspective because of incomplete and limited information about the excretion rate and behavior in soil of veterinary antibiotics.

Overall, eight antibiotics AIs were classified as of 'Very high' priority category requiring further detailed assessment, 12 AIs as 'High' category, and 16 AIs as 'Medium' priority (Table 4). Capleton et al. (2006)

Table 3. Prioritization of veterinary antibiotics active ingredients according to potential to reach the environment. Ordered according to priority and then alphabetically.

Priority	Veterinary antibiotic active ingredient	Excretion rate [†]	Priority by other study [‡]	Distribution coefficient [§]
		%		L kg ⁻¹
	Amoxicillin	80-90 ^a	H	
	Apramycin		H	
	Carbadox	70-90 ^b		
	Chlortetracycline	>70 ^a	H	
	Dihydrostreptomycin	>60 ^c	H	
	Doxycycline	>70 ^a		
High (17)	Enrofloxacin		H	260-5,610 ^a
	Erythromycin	>60 ^a		
	Neomycin	>80 ^d	H	
	Oxolinic acid		H	70-116 ^a
	Oxytetracycline	>80 ^a	H	420-1,030 ^b
	Streptomycin sulfate	>60 ^c		
	Sulfadiazine		H	2-3 ^b
	Sulfadimethoxine			2-10 ^b
	Sulfamethazine		L	1-3 ^a
	Sulfathiazole			3-5 ^b
	Tylosin		H	8-128 ^a
Medium or Low (8)	Ampicillin	30-60 ^a		
	Avilamycin		L	
	Ciprofloxacin			430 ^a
	Florfenicol	<20 ^f	H	
	Lincomycin	28-38 ^g	M	
	Penicillin G	50-70 ^a	U	
	Sulfamethoxazole	<15 ^a		
	Trimethoprim	<60 ^a	H	76 ^b

[†] Excretion rate, excreted antibiotics relative to administrated dose; key: a, Hirsch et al. (1999); b, von Wittenau (1969); c, Pratt and Fekaty (1986); d, Breen et al. (1972); e, Huber (1966); f, Plumb (2002); g, Hornish et al. (1987).

[‡] Boxall et al. (2003) and Capleton et al. (2006): H, high; M, medium; L, low; U, unknown.

[§] Key: a, Tolls (2001); b, Thiele Bruhn (2003).

Table 4. Prioritization of veterinary antibiotics active ingredients based on both consumption and potential to reach the environment. Ordered according to priority and then alphabetically.

Priority	Veterinary antibiotic active ingredient
Very High(8)	Amoxicillin, carbadox, chlortetracycline, neomycin, oxytetracycline, sulfamethazine, sulfathiazole, tylosin
High(12)	Apramycin, dihydrostreptomycin, doxycycline, enrofloxacin, erythromycin, oxolinic acid, penicillin G, salinomycin, streptomycin sulfate, sulfadiazine, sulfadimethoxine, sulfamethoxazole
Medium(16)	Ampicillin, avilamycin, bacitracin, ciprofloxacin, colistin, florfenicol, kanamycin, lasalocid, lincomycin, monensin, nicarbazine, norfloxacin, sulfaquinoxaline, tiamulin, trimethoprim, virginiamycin

prioritized 83 veterinary antibiotics approved for use in the United Kingdom and assigned 13 antibiotics to 'High' priority, 19 to 'Medium', 5 to 'Low', and 46 to 'Very low' category. Among the 13 antibiotics in 'High' priority, seven AIs were not consumed in Korea and only amoxicillin was assigned to 'Very high' priority in this study. It is interesting that Kim et al. (2006) also suggested amoxicillin for additional risk assessment among 126 human use antibiotics in Korea.

It should be noted that more information is necessary to accurately prioritize the potential risk of veterinary antibiotics because a little is known about the potential to reach the environment. Consequently, veterinary antibiotics assigned to 'High' priority in this study should not be considered as a great source of exposure to the environment. Rather, they represent a relatively high priority of environmental risk.

It is reasonable that the toxicological properties of the veterinary antibiotics need to be considered in addition to consumption and the potential to reach environment. Capleton et al. (2006) assessed toxicity profile according to the acceptable daily intake, a range of toxicological endpoints considered of particular relevance, potential for bioaccumulation, and presence of biologically active metabolites. Among eight antibiotic AIs in 'Very high' priority, amoxicillin, chlortetracycline, and sulfamethazine were assigned as 'High' toxicity, dihydrostreptomycin, oxytetracycline, and tylosin as 'Medium', and neomycin as 'Low' category.

In summary, eight veterinary antibiotic AIs including amoxicillin, carbadox, chlortetracycline, neomycin, oxytetracycline, sulfamethazine, sulfathiazole, and tylosin were identified to have a greater priority of environmental risk out of 83 veterinary antibiotics consumed in Korea.

Conclusion

An overall priority of veterinary antibiotics was

determined according to their consumption and the potential to reach the environment. In 2004, about 1,400 Mg of 83 antibiotic AIs were consumed in the Republic of Korea. Ten antibiotics were used at the greater dose than 25 Mg in 2004. Among 36 antibiotic AIs used greater than 3 Mg per year, 17 AIs were classified as 'High' potential to reach the environment based on the excretion rate from treated animals and degree of sorption to soil solids after applying to agricultural land. Based on both the use and the potential to reach the environment, eight veterinary antibiotic AIs with 'Very high' priority of environmental risk included amoxicillin, carbadox, chlortetracycline, neomycin, oxytetracycline, sulfamethazine, sulfathiazole, and tylosin.

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사용량과 잠재적 환경 유출 가능성을 기준으로 한 축산용 항생제의 우선순위 결정

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가축 질병의 예방 및 치료뿐만 아니라 사료 이용효율 증대와 생산 촉진을 위하여 축산용 항생제가 쓰여져 왔으며, 이 항생제는 가축분뇨를 통해 배출되어 농경지에 유입될 가능성이 있다. 나아가 용탈과 표면 유거를 거쳐 수계에 도달할 수 있으나, 모든 항생제의 환경 유출 가능성을 검토하는 데에는 많은 시간과 노동력, 예산이 필요하다. 본 연구는 축산용 항생제의 사용량과 잠재적 환경 유출 가능성을 기준으로 우선 순위를 결정하고자 수행되었다. 2004년에 우리 나라에서 판매된 항생제는 83종으로 약 1,400 톤에 달하였으며, 이 가운데 25 톤 이상 사용된 항생제는 10종이었다. 3 톤 이상 쓰인 36 종의 항생제를 대상으로, 가축의 배출율과 토양 흡착 정도를 가지고 잠재적 환경 유출 가능성을 판단하여 17 종을 선발하였다. 축산용 항생제의 사용량과 잠재적 환경 유출 가능성을 종합하여 검토한 결과, amoxicillin과 carbadox, chlortetracycline, neomycin, oxytetracycline, sulfamethazine, sulfathiazole, tylosin 등 8종이 상대적으로 환경으로의 유출 가능성이 높아 금후 정밀한 평가가 요구되었다. 비록 항생제의 가축분뇨로의 배출율과 토양내 동태에 대한 정보가 제한적일지라도, 본 연구에서는 한국에서 쓰이고 있는 축산용 항생제의 사용량과 알려진 항생제의 배출율과 토양 흡착 정도를 바탕으로 환경으로의 유출 가능성이 큰 항생제를 결정하였다.