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Antibiotic Use in Animal Production: Environmental Concerns

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Introduction

Antibiotic[1] use in animal production has led to improved feed use efficiency and increased growth rates. In turn, these resulted in reduced food production costs and reduced excrement of manure nutrients which may cause pollution problems.

On the other hand, antibiotic use leads to antibiotic resistance and a possible reduction in effectiveness of treatment options for both animals and humans. This publication addresses these issues.

Disease-causing **microorganisms**[2], including **bacteria**, are the most diverse and numerous organisms on earth. Diverse in their habitat, environmental adaptation, and mechanisms of reproduction, they have short generations with high multiplication rates. Such characteristics help develop antibiotic resistance. Resistance has developed to antibiotics used for human treatment but very limited evidence is shown for development of antibiotic resistance because of its use in animal production.

[1]Definitions for these terms in bold are given in the Definition of Terms section at the end of the publication.
[2]The term "microorganism" is used loosely in this publication to refer to microscopic, often single-celled organisms causing major animal and human diseases.

Antibiotics Mode of Action

Antibiotics inhibit or kill susceptible bacteria in four broad ways:

- disruption of microbial cell wall synthesis;
- inhibition of DNA replication;
- inhibition of protein synthesis; and
- inhibition of cell division, development, and differentiation.

Resistance develops when a susceptible bacterium develops an alternative path for its cell functions and processes that are no longer inhibited by the antibiotic.

The most common source of antibiotic resistance for microorganisms is genetic modification. The vast majority of drug-resistant organisms emerge as a result of single- or multiple-gene mutations. Resistance to an antibiotic can develop when an organism acquires a foreign gene from another microorganism or picks a free or "naked" gene source from the environment by a process called transformation.

Resistance mechanisms are often specific to a particular antibiotic and bacterial species, and a specific resistance mechanism may be limited to a specific environment. However, the discovery of similar genes and mechanisms across unrelated bacteria in some cases suggests that such resistance genes have been transferred between bacteria.

Antibiotic Use in Livestock Production

Antibiotics are used for **therapeutic** purposes to prevent or control the development of disease in humans and animals alike. Therapeutic antibiotic use is often at a higher dose than **"subtherapeutic"** purpose and is generally administered in water or by injection. In livestock production, antibiotics are also used at subtherapeutic level to promote growth and increase feed efficiency. Subtherapeutic antibiotic use in animals is administered as an additive to the feed or through an implant. The use of antibiotics in feed is a regulated activity under the *Code of Federal Regulations, Title 21, Part 558*.

For use in the U.S., antibiotics for animal production must be approved by the Food and Drug Administration after rigorous evaluation for safety against major risk factors with respect to the animal, the consumer, and the environment. Antibiotics are assessed for:

- efficacy (the ability to achieve the claimed outcomes by the manufacturer),
- target animal safety,
- environmental safety,
- human occupational safety, and
- human food safety.

The use of approved antibiotics is regulated and instructions must be followed to avoid unintended consequences. The drug manufacturer, the regulatory agency, the veterinarian, the producer, and the producer's employees involved in administering the feed additive have collective responsibility for controlling unintended public health impacts of antibiotic use in food-producing animals.

Antibiotics Approved for Animal Production, Mode of Action and Quantity Used

Antibiotics for Therapeutic Purpose

Antibiotics are used therapeutically to control an infectious disease or treat a sick animal, preferably as part of an integrated disease management approach that incorporates other management components such as minimizing external sources of infection on to the farm and other biosecurity measures. Therapeutic antibiotic use is restrictively specific as to the type, quantity, strength, frequency, length of use, route of administration, and **withdrawal times** (therapeutic regimen) as dictated by the manufacturer's label or by additional label instructions from a veterinarian.

Antibiotics for Subtherapeutic Purpose

The use of subtherapeutic antibiotics is an important component of modern livestock production. Antibiotics are added to feed in regulated small amounts for maintaining health, promoting growth, and increasing feed efficiency.

Subtherapeutic use must adhere to manufacturer's label instructions. These instructions help prevent adverse effects on the animals, avoid illegal levels of tissue residue, and allow appropriate withdrawal of the antibiotic for the recommended time before the animal product enters the food chain. The presence of an antibiotic residue in animal products above the regulatory standard violates the *Code of Federal Regulations, Title 21*, and the animal product can be condemned in accordance with the federal *Food, Drug & Cosmetic Act*.

Regular intake of antibiotics as feed additives can reduce disease risk and increase nutrient use efficiency by reducing production of urea, methane, and ammonia in the intestine. The improved efficiency gained through antibiotic use decreases the amount of feed and land necessary to raise the animals and decreases manure production per animal *(Table 1)*.

Commonly Used Antibiotics in the Production of Food Animals

A partial list of antibiotics used in the production of swine, beef and cow-calf, and poultry is shown in *Tables 2, 3,* and *4.* The list shows the name of the antibiotic, use level, treatment objectives, and the required withdrawal time. A complete list of FDA-approved animal drug products can also be found in the FDA Green Book available at *http://www.fda.gov/cvm/Green_Book/elecgbook.html*.

Antibiotic feed additive use is not common in milking dairies. The FDA will not accept drug residue in milk or sale of milk from sick animals. Milk is checked by the milk plant and by offices such as the office of dairy services at the state's department of agriculture. Tests can detect a drug in milk from treated animals even when this milk has been diluted in the tank by milk from many cows.

Milk for human consumption must meet minimum safety standards for somatic cell count (about 100,000), bacteria counts, and have no antibiotic or chemical residues. The FDA's *Pasteurized Milk Ordinance* requires Grade "A" milk delivered to dairy plants to be screened for antibiotic residues prior to processing.

Screening is performed on milk samples obtained from milk tank trucks arriving from farms at milk assembly points. At the same time, producer samples from individual farms on the load are tested, using the same protocol when necessary.

Table 1. Physiological, nutritional, and metabolic effects ascribed to antibiotic feed additives in livestock (+ shows an increase in response, - shows a decrease in response).

Physiological Effects		*Nutritional Effects*		*Metabolic Effects*	
Growth and metabolism of harmful gut bacteria	-	Energy retention	+	Ammonia production	-
Efficiency of nutrient absorption by modifying the gut wall	+	Gut energy loss	-	Toxic amine production	-
Gut absorptive capacity	+	Nitrogen retention	+	Alpha-toxin production	-
Fecal moisture	-	Limiting amino acid supply	+	Fatty acid oxidation	-
Mucosal cell turnover	-	Vitamin absorption	+	Fecal fat excretion	-
Stress	-	Vitamin synthesis	-	Liver protein synthesis	+
Feed intake	±	Trace element absorption	+	Gut alkaline phosphatase	+
		Fatty acid absorption	+	Gut urease	-
		Glucose absorption	+	Methane	-
		Calcium absorption	+	Toxic amine production	-
		Plasma nutrients	+		

Table 2. FDA-approved commonly used antibiotics for therapeutic and subtherapeutic purposes in swine production.

Drug	*Drug Use Level in Feed (g/ton) and Treatment Objective*	*Withdrawal Time (days)*
Apramycin	150 (Disease control)	28
Arsanilic acid	45-90 (Feed efficiency and growth)	5
Bacitracin methylene disalicyate	10-30 (Feed efficiency and growth)	None
	250 (Disease control)	None
Bacitracin zinc	10-15 (Feed efficiency and growth)	None
	20-40 (Feed efficiency)	None
Bambermycins	2 (Feed efficiency and growth)	None
	2-4 (Growth)	None
Carbadox	10-25 (Feed efficiency)	42
	50 (Disease control)	42
Chlortetracycline	10-50 (Feed efficiency and growth)	None
	>50 (Disease control)	None
Lincomycin	20 (Feed efficiency and growth)	None
	40-200 (Disease control)	None
Oxytetracycline	10-50 (Feed efficiency and growth)	5
	22 (Disease control)	5
Penicillin	10-50 (Feed efficiency and growth)	None
Roxarsone	23-34 (Feed efficiency and growth)	5
	182 (Disease control)	5
Tiamulin hydrogen fumerate	10-11 (Feed efficiency and growth)	None
	35-200 (Disease control)	2-7
Tilmicosin	181-363 (Disease control)	7
Tylosin	10-20 Finisher (Feed efficiency and growth)	None
	20-40 Grower (Feed efficiency and growth)	None
	20-110 Starter (Feed efficiency and growth)	None
	10-100 (Disease control)	None
Virginiamycin	6-10 (Feed efficiency and growth)	None
	>25 (Disease control)	

Table 3. FDA-approved commonly used antibiotics for therapeutic and subtherapeutic purpose in beef and cow-calf[1] production.

Drug	*Drug Use Level in Feed (mg per head per day) and Treatment Objective*	*Withdrawal Time (days)*
Bacitracin zinc	35-70 (Feed efficiency and growth)	None
Bambermycins	1-5 (Feed efficiency and growth) 2-45 (Pasture, slaughter, feeder cattle growth)	None None
Chlortetracycline	350 (Disease control)	2
Laidlomycin	5-10 (Feed efficiency and growth)	None
Lasalocid	10-30 (Feed efficiency and growth)	None
Monensin	5-30 (Feed efficiency, growth, and disease control) 25-400 (Intensive feeding and weight gain)	None None
Oxytetracycline	75 (Feed efficiency and growth) 75 (Disease control) 0.1-5 mg per lb of body weight (Disease control)	None None 0-5
Tylosin	8-10 (Disease control)	None
Virginiamycin	10-25 (Feed efficiency, growth, and disease control)	None

[1]Foraging pasture constitutes the major proportion of a cow-calf ration as compared to purchased feeds. Hence antibiotics are formulated on a per-head basis.

Table 4. FDA-approved commonly used antibiotics for therapeutic and subtherapeutic use in poultry production

Drug	*Drug Use Level in Feed (g/ton) and Treatment Objectives*	*Withdrawal Time (days)*
Arsanilic acid	75-120 (Feed efficiency, growth, and pigmentation)	5
Avilamycin	5-10	None
Bacitracin	4-50 (Feed efficiency and growth)	None
Bambermycins	1-20 (Feed efficiency and growth)	None
Chlortetracycline	10-100 (Feed efficiency, growth, and disease control)	None
Lincomycin	2-4 (Feed efficiency and growth)	None
Oxytetracycline	5-50 (Feed efficiency, growth, and disease control)	0-3
Penicillin	2-50 (Feed efficiency and growth)	None
Roxarsone	23-46 (Feed efficiency, growth, and pigmentation)	None
Spiramycin (Banned in EU[1])	5-20	None
Avoparcin (Banned in EU)	7.5-15	None
Tylosin (Banned in EU)	4-50 (Feed efficiency and growth)	None
Virginiamycin (Banned in EU)	5-20 (Feed efficiency and growth)	None

[1]EU = European Union.

A tank truck sample that tests positive will not be used for human consumption. Moreover, the presence of antibiotics in milk interferes with the manufacture of several dairy products such as delaying starter activity for cheese, butter, and yogurt. Antibiotics also decrease the acid and flavor production associated with butter manufacturing, in addition to reduced curdling of milk.

Human and Environmental Health Concern

Antibiotic Toxicity

To ensure consumer safety from antibiotic residues in food animals, the drug sponsor conducts a number of studies assessing the effect of the product on systemic toxicity, repeat dose toxicity, reproductive toxicity, developmental toxicity, genotoxicity, carcinogenicity, and human intestinal flora. The FDA reviews the methodology and results to set acceptable daily intake (ADI) and maximum residue limits (MRL) and associated withdrawal time to allow the drug residue to deplete below calculated MRL and ADI levels. Withdrawal time is product-specific. A similar product could have different withdrawal times depending on the difference in formulation of the product for a specific purpose.

Toxicology studies determine the dose at which no adverse effect is observed. This dose is used to calculate: 1) the amount of drug residue that can be consumed by an adult daily for a lifetime, without appreciable risk to human health; and 2) the maximum residue limits of a drug in a treated animal. Producers are required to follow label instructions and withdrawal times (*Tables 2, 3,* and *4*) to keep drug residue in animal products from reaching consumers.

According to a recent review by Lee and group, the measured level of antibiotic concentrations in the environment, including concentrations found in animal manure and lagoon effluent, are lower than the level believed to cause observable adverse effect on routinely tested organisms. However, this general observation should be understood in line with the limited research information and limited field sample analysis potential. There are also some reported effects on non-target organisms under extreme conditions, which include an observed negative effect of antibiotics on microorganisms involved in normal soil processes such as nitrification and organic matter decomposition.

Plant uptake of antibiotics from manure-applied plots has been reported, although observed levels are extremely low and not of concern to humans and animals feeding on these plants and plant products. Uptake of sulfamethazine (an antibiotic) by corn, lettuce, and potatoes has been documented with concentrations in plant tissue ranging from 0.1 to 1.2 ppm dry weight. Sulfamethazine concentration in plant tissue increased, with concentration in the applied manure. However, the total accumulation of sulfamethazine in the plant tissue after 45 days of active growth was less than 0.1 percent of the total applied to soil in manure.

Antibiotic toxicity to humans is unlikely to be a concern from antibiotics that may appear in animal products or food crops receiving manure. Current FDA approval processes have a proven history of protecting human health from antibiotic residue in animal products. Currently, toxicity to humans via soil or water pathways appears very unlikely. However, additional research may be needed to determine toxicity of antibiotics to helpful microorganisms in manure and the soil.

Microbial Resistance to Antibiotics

The use of antibiotics may eliminate susceptible microorganisms, leaving resistant ones behind. Such resistant bacteria can cause an infection both in humans and animals and may not respond to regular antibiotic treatments. The emergence of such antibiotic-resistant bacteria is a serious concern. People or animals infected with resistant bacteria may be sick for a longer time than with an infection caused by bacteria that is easily treatable with common antibiotics.

The FDA has published guidelines for an evidence-based approach to prevent **antimicrobial** resistance in humans that may result from the use of antibiotics in animals. This regulatory tool, known as *Guidance #152*, is a checklist of points to consider when weighing the potential human impact of a new animal drug. An electronic copy of *Guidance #152* is available at *http://www.fda.gov/cdrh/oivd/guidance/152.pdf*.

The National Antibiotics Resistance Monitoring System (NARMS) monitors resistance to antimicrobial drugs used in humans and food animals. Established in 1996, NARMS is a collaborative effort of the FDA, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA) facilitating a nationwide system to track the change in susceptibility of microorganisms to a wide range of antibiotics important in human and animal medicine. Each year, samples are taken and tested to determine changes over time in the resistance of certain gut bacteria to selected antimicrobial drugs.

For example, approximately 30,000 samples of *Salmonella* isolates were tested from 1997 to 2003 and about 1 percent were found to be resistant. See the following link for details: *http://www.fda.gov/cvm/NARMSSB-07White.htm*. There is an increasing trend in resistance for the isolates from human sources, but no clear trend for isolates taken from food animals except for a slight increase of Ceftiofur resistance in *Salmonella* among

cattle. The antibiotic drugs tested are selected based on their importance in human and animal medicine *(Table 5)*. Antibiotics of significant importance in human medicine may be banned for use in animal production or restricted to the therapeutic use under the prescription or supervision of a veterinarian. For example, in July 2008, the FDA issued a prohibitive order limiting **extra-label use** of Cephalosporins in food-producing animals, to limit the development of microbial resistance to this class of drugs based on evidence gathered by NARMS.

There is genuine concern that using antibiotics in large-scale animal production may contribute to more instances of antibiotic resistance. However, the consensus of reports from the FDA and other sources that looked objectively into this issue found no conclusive evidence of food-animal antibiotic use leading to resistance development in humans.

The FDA has acted and initiated the necessary measures when there was a confirmed link in resistant development to the use of a certain antibiotic in food animal production and will likely continue to do so in the future. However, constant assessment of this potential risk will need to continue in the future.

Economic Impact of Antibiotics in Animal Production

Using antibiotics increases an animal's daily weight gain and reduces costs and feed inputs per unit of animal product. Antibiotic use also improves feed efficiency by reducing maintenance costs of the animal and providing protection at critical growth stages. Antibiotics also reduce mortality. The increased production efficiency from using antibiotics is expected to:

- reduce the number of animals needed to produce a given amount of animal product such as beef;
- reduce the level of inputs such as gasoline, fertilizer, and insecticide used to produce feed; and
- reduce the amount of manure produced per unit of animal production.

Therefore, gained efficiency in animal production from using antibiotics should benefit the environment and food supply. However, economic and environmental benefits from antibiotic use in animal production must be weighed against the risk for the development of resistance.

Management Options to Mitigate Antibiotic Resistance

Minimizing antibiotic resistance risk, means using antibiotics appropriately and judiciously. The American Veterinary Medical Associations (AVMA) and the FDA Center for Veterinary Medicine have developed guidelines on the judicious use of antibiotics in order to optimize resource use efficiency and to minimize the development of antibiotic resistance. See this link for details: *http://www.avma.org/issues/default.asp#antimicrobials*.

1. Prevent disease by providing integrated and sound management systems:
   - providing best-practice sanitation and hygiene;
   - providing high-quality feed and protection from the elements to reduce stress;
   - implementing biosecurity measures;
   - performing regular health exams;
   - using vaccines; and
   - controlling parasites.
2. Accurate and timely diagnosis of sick animals ensures proper and timely treatment methods.
3. If you must use antibiotics, work with a veterinarian to select the treatment option and to prepare a written treatment protocol. Use proper dose, route, treatment, and withdrawal time.
4. Treat the appropriate animals and the fewest number of animals possible.

Table 5. Ranking of antibiotics for monitoring the emergence of resistance in the U.S.

Critically Important or High Concern	*Highly Important or Medium Concern*	*Important or Low Concern*
Broad spectrum Cephalosporins	Aminoglycosides	Narrow and expanded spectrum Cephalosporins
Fluoroquinolones	Amoxicillin	Monobactams
Macrolides	Ampicillin	Quinolones
Lincosamides	Glycopeptides	
	Streptogramins	
	Tetracyclines	

5. Establish written protocols when using antibiotics.
6. Keep records of animal or group identification, drug used, date treated, dosage used, route and location for administration, who administered the product, and any other useful information.
7. Work with a veterinarian to determine the most effective therapy, and maintain a working relationship commonly referred to as "valid veterinarian-client-patient-relationship." This means the veterinarian knows the operation, the management of the operation, the livestock, and is involved in any diagnosis, treatment, and follow-up.
8. Use antibiotics and other medications as ordered. It is the law.
9. Train people who treat livestock on your farm operation.
10. Minimize environmental contamination.

Manure storage and treatment options may provide additional means for reducing antibiotic risk in manure. According to a study from Colorado, manure type and treatment time determine the level of break-up for three antibiotics (Chlortetracyline, Tylosin, and Monensin) from manure before field application.

High-intensity management at storage (amending, watering, and turning) reduced the half-life of the three antibiotics to 4 to 15 days while watering or turning alone reduced the half-life to 8 to 30 days. Thus, a 40-day composting period would reduce concentrations by approximately 94 percent for the intensively managed compost system (assumes 10-day half-life) and by 75 percent for the less intensive composting management (20-day half-life). Additional reductions will occur during stockpiling or storage. More research is needed on treatment or management options and their value for reducing antibiotic concentration.

Impact of Eliminating Antibiotics: Case Studies

The recent subtherapeutic antibiotic ban in Europe provides the opportunity to observe the consequences of antibiotic withdrawal. In Europe, the ban of subtherapeutic use of antibiotics has been reported by some to result in deterioration in animal health, including increased diarrhea, weight loss, and mortality due to *Escherichia coli* and *Lawsonia intracellularis* in early post-weaning pigs, and clostridial **necrotic enteritis** in broilers. Furthermore, as a result of these infections, there is an increase in usage of therapeutic antibiotics, including that of tetracycline, aminoglycosides, trimethoprim/sulphonamide, macrolides, and lincosamides, all of which are of direct importance in human medicine. In Sweden, the ban of subtherapeutic antibiotics caused the age-to-30 kg body weight to increase by two days in pigs and increased the problems of necrotic enteritis in broilers. The ban did not affect egg production in layers, growth rate in turkeys, or productivity in specialized beef production. The Swedish Animal Health Service concluded poultry, calves, and pigs can be reared without continuous use of growth promoters, if the benefits of other production practices such as hygiene are maximized.

The ban on antibiotic feed additives in Europe reduced the incidence of resistance in indicator bacteria in raw food products of animal origin. While the carriage of certain resistant pathogens among healthy individuals has diminished, there has been no apparent positive impact on the level of antibiotic resistance in human patients or in hospitals. Moreover, the incidence of food-borne disease continued to rise in Europe for some bacteria such as *Salmonella*, highlighting the complexity of any potential relationship between antibiotic use in livestock and antibiotic-resistant disease in humans.

Conclusions

Using antibiotics to increase feed efficiency or for therapeutic purposes will contribute to the emergence of resistant microorganisms. At this time, there's limited evidence that this resistance impacts human health. However, this risk cannot be ignored. Current regulation of antibiotic use for animal health, field monitoring of resistance, and research will be essential to understand and minimize these risks.

Important points to take away from this publication are the following:

- All antibiotics should be used judiciously.
- Microorganisms are constantly mutating or exchanging DNA with each other and with the environment, which could result in the development of resistance for existing antibiotics. Resistance development is a natural process as much as it is induced by the presence of antibiotics in the environment.
- Regulations are in place to reserve some broad spectrum antibiotics of critical importance for human treatment.
- The use of antibiotics increases selection pressure for microbial resistance. However, the issue is complex and a link of increased microbial resistance in human illnesses to a single factor such as the use of antibiotics in livestock production has not been verified.

- Strict regulations are in place to limit the transfer of antibiotic residue to consumers through animal products of treated animals, as well as to prevent antibiotic toxicity concerns from food products of treated animals.
- Antibiotics are detected in manures, soils, and water but at concentrations below levels that cause toxic effects on non-target organisms including humans. However, these concentrations may increase the development of antibiotic resistance.
- Reduced antibiotic resistance development in animal agriculture currently focuses on use of best-management practices in the use of antibiotics as developed by the AMVA and FDA.
- Recent efforts to ban subtherapeutic use of antibiotics in animal agriculture in Europe have not clearly reduced antibiotic-resistant disease in humans to date, and may result in decreased productivity and other negative environmental consequences.

Definition of Terms

Antimicrobial: a broad class of natural, synthetic, or semi-synthetic products that kill or inhibit the growth of bacteria or other microorganisms. Antimicrobials include antibiotics and these terms are often used synonymously.

Antibiotics: a substance that is naturally produced by a microorganism that can kill or inhibit the growth of other microorganisms at a very low concentration.

Bacteria: single-cell organisms that may cause disease in animals and humans and are treated by antibiotics. Other disease-causing organisms, such as viruses, are not treated by antibiotics.

Extra-label use of antibiotic: the actual or intended use of a drug in a manner not in accordance with the approved labeling. The provision for such use establishes certain conditions under which veterinarians are permitted to use approved animal or human drugs in an extra-label manner in animals. (This includes what is commonly known as **subtherapeutic use**.)

Microorganisms (for the purposes of this guide): single-celled organisms causing major animal and human diseases.

Necrotic enteritis is a disease caused by *Clostridium perfringens*. Signs include droopiness, lack of appetite, diarrhea, ruffled feathers, and mortality in the flock, sometimes occurring quite suddenly. The disease is common at a young age and rarely occurs after 30 days of age.

Subtherapeutic use: the use of antibiotics below a disease treatment or control threshold for the purpose of improved feed efficiency or weight gain. "Subtherapeutic" is a term mainly adopted by organizations and individuals questioning the use of antibiotics for purposes other than the treatment of diseased animals or to prevent the development of a disease.

Therapeutic use: the use of antibiotics for the treatment of infectious diseases. Therapeutic antibiotics are given at a higher dose than subtherapeutics and are generally administered in water or by injection.

Withdrawal (withholding) time: The time from when an animal was last given a drug to when it is considered safe for human consumption (marketing of the animal product).

References

Casewell, M., C. Friis, E. Marco, P. McMullin, and I. Phillips. 2003. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *Journal of antimicrobial chemotherapy* 52:159-161.

U.S. Food and Drug Administration Center for Veterinary Medicine Web site: *http://www.fda.gov/cvm/*

Irwin, K., D.R. Smith, G.M. Ebako, S. Ensley, D. Dee Griffin, A. Wohlers. 2003 *Guidelines for the prudent use of antibiotics in food animals.* University of Nebraska–Lincoln.

Lee, L. S., N. Carmosini, S.A. Sassman, H.M. Dion, and M.S. Sepúlveda. 2007. Agricultural contributions of antimicrobials and hormones on soil and water quality. *Advances in Agronomy* 93:1-68

Prescott, J.F., J.D. Baggot, R.D. Walker. 2000. *Antimicrobial therapy in veterinary medicine.* Iowa State University Press. Ames.

Tollefson, L., D. Morris, C. Boland, and J. Kay. 2006. Licensing approval of antimicrobials for use in animals. Pgs 361-374 in Aarestrup, F.M. (ed.) *Antimicrobial resistance of animal origin.* ASM Press. Washington D.C.

USDA-APHIS. 2007. Antimicrobial Resistance Issues in Animal agriculture. Center for Epidemiology and Animal Health. *http://www.aphis.usda.gov/vs/ceah/cei/taf/emerginganimalhealthissues_files/antiresist2007update.pdf*

Wierup, M. 1997. Ten years without antibiotic growth promoters — results from Sweden with special reference to production results, alternative disease preventative methods, and the usage of antibacterial drugs. *The Medical Impact of the Use of Antimicrobials in Food Animals. October 13-17, 1997;* Berlin, Germany. Geneva: World Health Organization.

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