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Antibiotics in agriculture – application, threats and legal regulations

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Abstract. The discovery of the first antibiotic has become one of the most important medical advances. Since this time, a period of intensive research into antimicrobial substances has begun, which are also used in veterinary medicine and agricultural production. In animal production, antibiotics have therapeutic, as well as prophylactic and metaphylactic applications aimed at preventing bacterial diseases. They were also used as growth stimulants, which positively influenced, among others, for weight gain and more efficient use of feed. This form of antibiotic use in animal production was legally banned in 2006 in all European Union countries. In the cultivation of plants, antibiotics are also used to combat plant pathogens. The use of antibiotic agents has many consequences, both positive and negative. The most important risk of antibiotics overusing is the spread of antibiotic resistant bacteria. Another effect is environmental pollution and the contamination of agricultural products. Due to these factors, the use of antibiotics in agriculture is regulated by appropriate legal regulations.

Keywords: antibiotics, animal farming, antibiotic resistance, environment pollution

INTRODUCTION

The discovery of the first-ever antibiotic in 1928 became a critical event influencing medicine development. „For the discovery of penicillin and its curative effect in various infectious diseases," Alexander Fleming, together with Ernest B. Chain and Howard W. Florey, were awarded the Nobel Prize in Physiology or Medicine in 1945 (Przeniosło-Siwczyńska, Kwiatek, 2013; Ubysz, Tobiasz, 2016). Since then, intensive research on antimicrobial substances with applications in medicine and veterinary medicine and animal breeding began. During World War II, the large-scale production of penicillin began for the first time, where it was used to treat war casualties. At the end of the war, veterinarians gained access to the antibiotic, which they successfully used to treat *mastitis* in cattle. This was a significant advance, as penicillin proved to be much more effective in treating *mastitis* than previously available therapies (Gustafson, Bowen, 1997). In 1946, it was discovered that the addition of streptomycin to chickens' diet could improve their growth (Moore et al., 1946). In subsequent years, similar effects were found for chlortetracycline. Researchers found that the addition of spent fermentation products of this antibiotic to feed improved weight gain in chickens and reduced the amount of feed needed to achieve market weight in poultry (Stokstad et al., 1949). Studies on feed additives for other livestock have confirmed similar effects also in cattle and pigs (Cunha, 1950; Loosli, Wallace, 1950). Soon after these discoveries, antibiotics were permanently introduced into livestock feed.

The use of antibiotics is regulated by both national and European Union (EU) legislation. Unfortunately, despite the regulations, farmers and ranchers use vast amounts of pharmaceuticals, associated with the risk of environmental pollution and the emergence of antibiotic-resistant bacteria. This paper brings together existing knowledge on the use of antimicrobials in agriculture, addresses legal regulations on their dosage, and discusses the most critical risks. Finally, the report aims to explain the consequences of excessive and/or inappropriate use of antibiotics in animal husbandry and plant cultivation.

DEFINITION AND MECHANISM OF ANTIBIOTICS ACTION

The term "antibiotic" (from Gr. *anti* – against, *biotikos* – able to live) was first used in 1942 by Selman Waksman.

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(Kozińska, Sitkiewicz, 2017), the term refers to substances that kill microorganisms (bactericidal action) or inhibit their reproduction (bacteriostatic action). Antibiotics are chemical compounds of mainly natural origin, produced by many groups of microorganisms (mainly bacteria and fungi) as well as lichens, algae, and plants (Zalewska et al., 2017). Synthetic and semi-synthetic compounds with antimicrobial activity are also defined as antibiotics (Truszczyński, Pejsak, 2013). These substances are characterised by a diverse mechanism of action on microorganisms. Due to the mode of action, we divide them into several groups: (1) inhibiting the synthesis of nucleic acids (bacterial DNA or RNA), (2) inhibiting the synthesis of bacterial proteins, (3) acting on the synthesis of murein (blocking the structure of the bacterial cell wall) and (4) disrupting the structure of the cell membrane (Markiewicz, Kwiatkowski, 2008; Truszczyński et al., 2013).

USE OF ANTIBIOTICS IN AGRICULTURE

In animal husbandry

Numerous antibiotics are commonly used in animal husbandry (Table 1). The first purpose is therapeutic use, which aims to control and treat bacterial infections. Antibiotics are administered to symptomatic animals, and the dose of the agent is adjusted according to their health status. Among livestock, individual treatment is used for dairy cows and calves. It should be noted that such treatment is ineffective when applied to animals kept in large flocks, e.g., over 30,000 poultry or 100 piglets (Schwarz et al., 2001).

Table 1. Examples of antibiotics used in animal husbandry (based on Lathers, 2001; Sarmah et al., 2006).

Name of the antibiotic	Using
Avilamycin	Feed supplement
Bacitracin	Feed supplement
Erythromycin	Feed supplement
Penicillin	Feed supplement; Veterinary medicine
Tetracycline	Veterinary medicine
Cephalosporin	Veterinary medicine
Sulfonamides	Veterinary medicine
Chloramphenicol	Veterinary medicine
Aminoglycosides	Veterinary medicine

In the case of large groups of animals, antimicrobials (AMRs) are administered to the whole flock when individual animals show signs of disease. This is known as metaphylaxis. Early treatment of the entire herd reduces the number of sick or dead animals and minimises antibiotics, resulting in lower treatment costs (Schwarz et al., 2001).

The prophylactic use of antibiotics is a means of preventing possible infections to which animals are exposed. In this case, agents are administered to individuals or the entire herd when there are no clinical signs of disease but when there is a high probability of infection. Antibiotics are also administered prophylactically at so-called critical moments for the animals, e.g., during mixing of animals from different herds, transport, or at the end of lactation of dairy cows (Schwarz, Chaslus-Dancla, 2001; Biernasiak et al., 2010).

Another way of using antibiotics in animal production was antibiotic growth promoters (AGPs). However, this use of antimicrobial substances in animal husbandry was banned by law in 2006. The effect of growth promoters was not only to increase weight gain (by 4–28%), but they also improved nutrient absorption, leading to more efficient feed conversion (by 0.8–7.6%). In addition, a reduction in methane and ammonia emissions and more efficient use of phosphorus were also reported. Furthermore, the application of AGPs decreased the number of sick animals and losses in animal husbandry (Grela, Semeniuk, 2006). The use of such agents prevented infections of the digestive system and formed the balance of the intestinal microflora (Majewski, Anusz, 2018).

In plant cultivation

Phytopathologists quickly recognised the potential of antibiotics to treat plant diseases, especially those caused by bacteria. In the 1950s, about 40 antibiotics of bacterial or fungal origin were tested against various plant infections. Negligible toxicity to plants and efficacy at low doses distinguished antibiotics from plant protection products available at that time (McManus et al., 2002). Antimicrobial substances are used as pesticides in cultivating vegetables, fruits, and ornamental plants (Gothwal, Shashidhar, 2015).

Streptomycin is the most commonly used antibiotic worldwide to control plant pathogens. It is used to eradicate fire blight, a disease caused by the bacterium *Erwinia amylovora*. This infection affects many plant species such as apple and pear trees. Another is oxytetracycline, where streptomycin resistance has developed (Taylor, Reeder, 2020). Oxytetracycline is not as effective since it only inhibits the growth of the pathogen, whereas streptomycin has a bactericidal effect (Stockwell, Duffy, 2012). In addition, there are reports of the use of other antibiotics in crop cultivation. For example, gentamicin is used in Mexico and Costa Rica, oxolinic acid in Israel, and kasugamycin in Japan and other Asian countries (Taylor, Reeder, 2020).

In crop production, the primary method of antibiotic application is spraying (Stockwell, Duffy, 2012; Taylor, Reeder, 2020). In many countries, including the United

States, the use of antibiotics to control fire blight is widespread. In European Union countries, streptomycin was used in exceptional situations and under strict control (Mikiciński et al., 2016). Nevertheless, it should be emphasised that the amount of antibiotics used in crop cultivation is relatively tiny compared to the amount used in medicine, veterinary medicine, and animal production (Koch et al., 2021). It is estimated that the amount of antimicrobials used in crop production does not exceed 0.5% of the total antibiotic consumption in agriculture (Taylor, Reeder, 2020).

In aquaculture

Aquaculture deals with farming aquatic organisms, both freshwater and seawater (Stec, 2015). It is considered the fastest-growing food production sector (Silva et al., 2021). In aquaculture, the use of antimicrobials is also based on classification as therapeutic, prophylactic, and metaphylactic (Okocha et al., 2018). However, it is undeniable to note that due to the intensification of production and the culture conditions (excessive density, risk of mechanical damage, insufficient water quality), aquatic organisms are exposed to several diseases (Stec, 2015). Due to such a situation, the prophylactic use of antibiotics in the aquatic environment is widespread (Cabello, 2006).

In aquaculture, antimicrobials at therapeutic concentrations are administered to individuals that share tanks or cages (Romero et al., 2012). Due to the nature of the aquafarming and the physiological structure of aquatic organisms, the most optimal form of drug application is oral administration. The medicinal product's dosage and the treatment duration are done according to the veterinarian's recommendation (Żelazny, Gomułka, 2015). The most common way of delivering antibiotics to fish is mixing the drug with specially prepared feed (Romero et al., 2012).

RISKS ASSOCIATED WITH THE USE OF ANTIBIOTICS IN AGRICULTURE

Antibiotics have been and continue to be used in agricultural production on a large scale. However, it is considered that most of the antibiotics produced worldwide are used in agricultural production (Zalewska et al., 2017). Currently, 70% of the annual production of antimicrobial substances finds its application in animal husbandry (Adamek et al., 2019). It is estimated that until 2006, most of the antibiotics used in this sector (90%) were used as growth promoters, while the remaining 10% had a therapeutic use in disease control (Popowska, 2017). Undoubtedly, the use of antimicrobials on such a large scale has several consequences.

Antibiotic resistance

Resistance, i.e., the ability of bacteria to survive in the presence of an antibiotic, is one of the most severe adverse effects of the excessive use of these substances in agriculture (Khachatourians, 1998; Mazińska, Hryniewicz, 2020). Already in the 1940s, only a dozen years after the discovery of penicillin, Alexander Fleming warned that the overuse of antibiotics could lead to the emergence of microorganisms that were not sensitive to these substances (Alekshun, Levy, 2007; Bartlett et al., 2013; Przeniosło-Siwczyńska et al., 2015; Ventola, 2015). The appearance of drug resistance has been observed following the introduction of each new class of antibiotics, and the threat of such a phenomenon is intensified by the slow process of developing new drugs (Landers et al., 2012). In addition, the World Health Organization (WHO) has classified this phenomenon as one of the most serious global threats to public health (Dzierżawski, Cybulski, 2012). The 2017 report identified multidrug-resistans microbial species as the highest priority for the acquisition and development of new antibiotics because current treatments are being exhausted (Table 2).

Resistance of microorganisms to antibiotic substances takes two forms, natural and acquired. The former is very common in bacteria and reflects their evolutionary adaptation to antibiotics naturally present in their environment (Salisbury et al., 2002). It is worth noting that the phenomenon of antibiotic resistance already existed 30,000 years ago. Indeed, scientists discovered antibiotic-resistant bacteria in permafrost. This research shows that antibiotic resistance is an ancient, naturally occurring phenomenon, which is widespread in nature (D'Costa et al., 2011). The second type, acquired resistance, develops among microorganisms initially susceptible to a given substance. If it arises due to a spontaneous mutation, this resistance is called primary resistance and can occur without contact with the antibiotic. This type of resistance is determined by genes encoded in the chromosome and cannot be transferred to microorganisms belonging to another species (Mazur, Klag, 2004). Secondary resistance arises from the interaction of an antibiotic with microorganisms and is determined by genes located outside the chromosome DNA, i.e., on plasmids, transposons, and integrons (Mazur, Klag 2004; Leja et al., 2019).

Bacteria acquire antibiotic resistance due to horizontal gene transfer, using three processes (Truszczyński et al., 2013). Conjugation involves the direct exchange of plasmids between bacterial cells. Transduction is the process of transferring resistance genes by the infecting bacteriophage, while during the transformation process, the uptake of free DNA containing resistance genes occurs (Potrykus, 2002; Salisbury et al., 2002; Dzierżawski, Cybulski, 2012). The transfer of resistance through horizontal gene trans-

Table 2. Examples of bacteria resistant to selected antibiotics (based on WHO, 2017).

Pathogen	Infection caused	Antibiotic
Mycobacterium tuberculosis	Tuberculosis	Rifampicin
Acinetobacter baumannii	Venilator-associated pneumonia Bloodstream and wound infection	Carbapenemes
Pseudomonas aeruginosa	Pneumonia in immunocopromised patient with lung diseases	Carbapenemes
Enterococcus faecium	Bloodstream and urinary tract infection in hospitals	Vancomycin
Staphylococcus aureus	The main factor of hospital-acquired infection Skin and soft tissue infections	Vancomycin Methicillin
Helicobacter pylori	Non-cardia gastric cancer	Clarithromycin
Campylobacter spp.	Foodborne disease Acute diarrohea	Fluoroquinolones
Salmonella spp.	Enteric fever (Typhoid)	Fluoroquinolones
Neisseria gonorrhoeae	Gonorrhoea	Fluoroquinolones Third-generation Cephalosporin
Streptococcus pneumoniae	Pneumonia in children under 5 years of age	Penicillin
Haemophilus influenzae	Bacterial meningitis in children under 5 years of age	Ampicillin
Enterobacteriaceae	Community – acquired urinary tract infections Hospital – acquired infections (urinary tract infections, bloodstream infections and ventilator – associate pneumonia)	Third-generation Cephalosporin
Shigella spp.	The main cause of morbidity and mortality in the world, especially in developing countries	Fluoroquinolones

fer occurs between microorganisms belonging to the same species. This process also affects microbial strains belonging to different species and families (Truszczyński, Pejsak, 2013; Read, Woods, 2014). The phenomenon of antibiotic resistance can only arise due to selection pressure, i.e., the presence of an antibiotic in the location of the microorganism (Popowska, 2017). Under such conditions, bacteria with acquired resistance have a selective advantage, and their numbers increase while the development of susceptible microorganisms is inhibited (Salisbury et al., 2002).

Several mechanisms responsible for the resistance of microorganisms to antibiotics are described in the literature. We distinguish processes involving (Markiewicz, Kwiatkowski, 2008):

– modifying the target site of the antibiotic in the cell;
– converting the active drug into an inactive form using enzymes produced by resistant cells;
– inhibiting transport of the antibiotic into the cell;
– developing an alternative pathway or enzyme to bypass the drug susceptibility step;
– increasing production of an enzyme that is inactivated by the antibiotic;
– increasing the concentration of a metabolite that is antagonistic to the antibiotic substance;
– reducing the demand for the product of a metabolic pathway that is inhibited by the drug;
– the ability to produce an efflux pump that actively eliminates the antibiotic from the cell;
– changes in regulatory systems not directly related to the mechanism of action of the antibiotic substance;
– decreasing the activity or level of an enzyme catalysing the conversion of a drug into its active form.

Studies have shown that antibiotics in animal husbandry lead to the development of resistant bacteria in the animal gut flora (Chang et al., 2014). Insensitivity to antibiotic substances among commensal gut bacteria is a significant pathway for spreading resistance among pathogenic microorganisms (Chee-Sanford et al., 2012). Human and animal microbial ecosystems are inextricably linked; thus, antibiotic resistance easily crosses these boundaries (Witte, 1998). The transmission of resistant bacteria from livestock to humans was first noticed over 40 years ago. High rates of antibiotic resistance have been found in the gut flora of animals and farmers (Bartlett et al., 2013; Ventola, 2015). Three possible scenarios are identified whereby antibiotic-resistant microorganisms may be transmitted from livestock to humans and pose a risk to human health. The first possibility is direct infection with the resistant pathogen through contact with a live animal or after consuming contaminated meat and other animal products, with no possibility of transmission to another human being. The second scenario involves infection with a resistant microorganism of animal origin followed by continuous human-to-human transmission. Such a mechanism implies that the pathogen breaks the interspecies barrier. A third possibility is the transfer of resistance genes arising in the agricultural

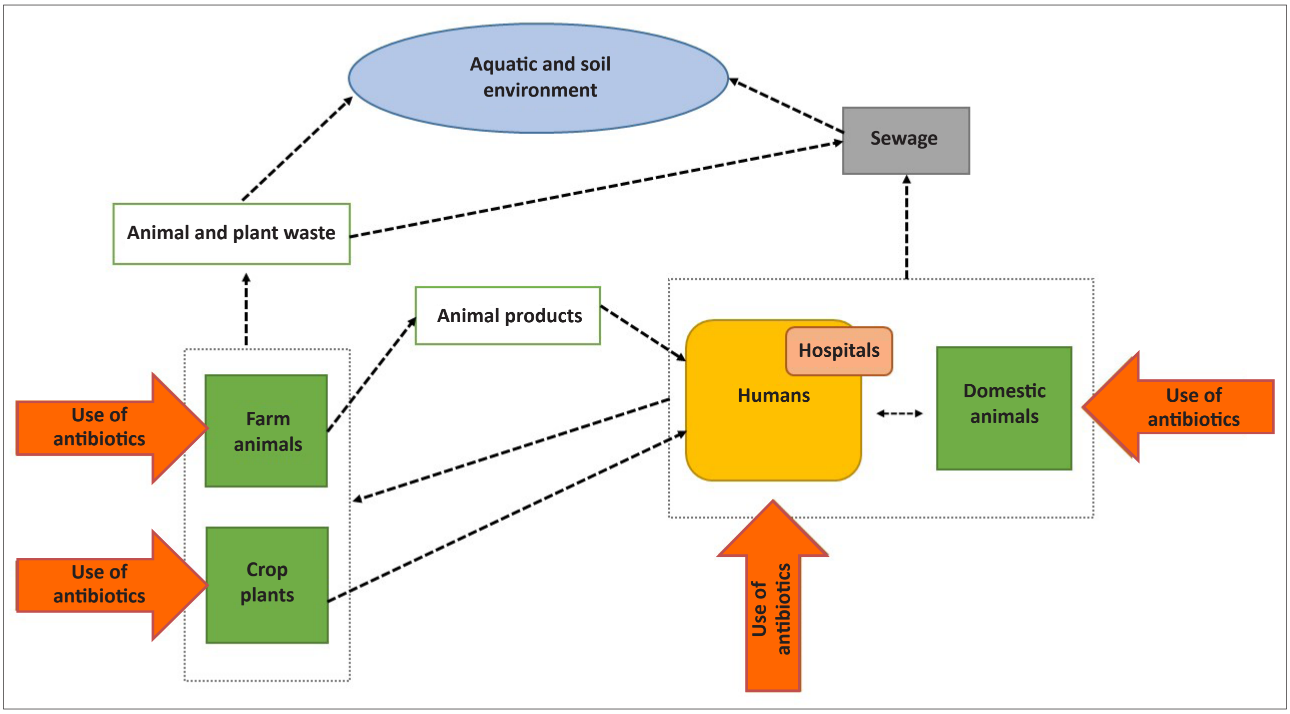

Figure 1. Diagram showing the transfer of antibiotics in the environment (own elaboration based on http://www.effort-against-amr.eu/page/activities.php).

environment to human pathogens through horizontal gene transfer (Chang et al., 2014).

The pollution of the environment

An estimated 90% of antibiotics administered to livestock are excreted by them in an unmetabolised form (Taylor, Reeder, 2020) and end up in sewage (Gulkowska et al., 2008). Furthermore, antimicrobials and drug-resistant bacteria reach manure, commonly used as fertiliser. The substances it contains enter the soil and surface water and are taken up by crops (Kümmerer, 2004; Grote et al., 2007; Zalewska et al., 2017). Animals also excrete antibiotics as metabolic products. Some metabolites are more potent than antibiotics, while others may revert to their parent compounds during manure storage (Massé et al., 2014). Dust from piggeries or other farm buildings is also a source of environmental pollution. Such dust comes from the feed, bedding, faeces of reared animals, among others, and can pose a respiratory health risk due to its content of antibiotics, microorganisms, and allergens (Hamscher et al., 2003; Kemper, 2008). Also, the antibiotics used in aquaculture are not fully utilised. Almost 80% of the fed agents are not eaten or absorbed by aquatic organisms, and 75% are excreted by them (Silva et al., 2021). The unused antibiotics in the feed and the excrements of aquatic organisms accumulate in the sediments. They can also be washed by currents to distant locations, leading to consumption by wild fish, crustaceans, and other aquatic organisms (Cabello, 2006).

Antibiotics threaten ecosystem functioning and health (Cabello, 2006). They cause potential toxic risks to microorganisms, plants, animals, and ultimately humans (Gothwal, Shashidhar, 2015). Antimicrobial substances released into soil and water can affect local microorganisms causing changes in their composition and metabolism (Martinez, 2009). They can inhibit the activity of urease, acid phosphatase, and dehydrogenases (Wei et al., 2009; Du, Liu, 2012) and affect elemental cycles, including denitrification (Roose-Amsaleg, Laverman, 2016). Antibiotic residues accumulating in sediments can have a toxic effect, affect bacterial populations' composition, and reduce phytoplankton and zooplankton diversity (Silva et al., 2021).

Soil fauna, including earthworms (*Eisenia fetida*), are also adversely affected by environmental pollution with antibiotics. Studies have demonstrated that some antibiotics, including tetracyclines and chlortetracyclines, lead to DNA damage and cause changes in enzymatic activity in earthworms exposed to these substances (Dong et al., 2012; Gothwal, Shashidhar, 2015).

Antimicrobial compounds are likely to be taken up by plants with water from polluted areas and get accumulated. Toxicity of antibiotics may then manifest itself in inhibition of growth and chlorophyll synthesis (Patyra, Kwiatek, 2018), adverse effects on plant morphology, and photosynthesis (Gothwal, Shashidhar, 2015).

The content of antibiotics in the contaminated environment is much lower than the minimal inhibitory concentration (MIC), determining the lowest drug concentration that completely inhibits the growth of the microorganism (Wojnicz, 2008). Subinhibitory concentration (more down than MIC) can influence many features of bacterial cells, including their morphology, outer membrane structure, and virulence factors (Lück et al., 1998, Wojnicz et al., 2010). The concentrations also contribute to the spread of drug resistance due to the intense stimulation of horizontal gene transfer processes (Zablotni, Jaworski, 2014).

The contamination of agricultural raw materials

The potential risk to human health from inappropriate antibiotics in animal husbandry is significant. It has been found that livestock treatments with antibiotics can result in their accumulation in edible livestock products (Majewski, Anusz, 2018). Furthermore, resistant microorganisms that proliferate via antibiotic-treated animals can be widely distributed in products for consumption (Landers et al., 2012).

Contamination of agricultural products with pharmaceuticals is primarily related to non-compliance with regulations. Antibiotics applied in animal husbandry in therapeutic quantities carry specific mandatory withdrawal periods due to their penetration into the bloodstream and then into the animal's muscle tissues (Migdał, 2007). Non-compliance with such periods and inappropriate dosing of therapeutic products can contaminate meat and animal products such as eggs and milk (Posyniak, 2011; Różańska et al., 2014). Excessive drug exposure in aquaculture farms has been observed to cause accumulation in the tissues of aquatic organisms (Stec, 2015). Another example is the inappropriate treatment of bee diseases with antibiotics, resulting in honey contamination. This deteriorates its quality and can be harmful to health (Bargańska, Namieśnik, 2012).

As a result of spreading organic fertilizers contaminated with antibiotics, there is a risk of their accumulation in plants (Patyra, Kwiatek, 2018). Studies have revealed that some vegetables are able to absorb antibiotics (Du, Liu, 2012), becoming a risk to humans. Vegetable and fruit products can become contaminated with antibiotic-resistant bacteria due to cross-contamination resulting from irrigation of agricultural fields with water-containing pathogens (Koch et al., 2021). A negative effect of antibiotic accumulation in animal products is their potential carcinogenicity, mutagenicity, and teratogenicity (Chen et al., 2020). Consumption of raw materials contaminated with antimicrobial substances is also associated with the risk of causing, among others, disorders in the intestinal flora, allergies, or nephropathy (Zablotni, Jaworski, 2014).

THE DEGRADATION OF ANTIBIOTICS IN THE ENVIRONMENT

Pharmaceutical substances, including antibiotics, have been recognised worldwide as a new class of pollutants (Patyra, Kwiatek, 2018, Adamek et al., 2019). Antimicrobial substances are degraded in the natural environment due to biotic and abiotic processes in the polluted environment (Kümmerer, 2009; Koch et al., 2021). Biotic factors are associated with the activities of microorganisms. The biodegradation of contaminants depends on temperature, substance concentration, bioavailability, time of exposure to the substance, availability of other nutrients, and enzymatic properties of the existing microbial population (Chee-Sanford et al., 2012). Abiotic factors are related to hydrolysis, sorption, photolysis, oxidation, and reduction processes. The susceptibility to this type of degradation depends on the chemical structure of the substrate (Cycoń et al., 2019; Kumar et al., 2019).

The degradation time of antibiotics in the environment varies and is determined by many factors (Table 3). The decomposition of antibiotics further depends on the humidity, pH, sorption capacity, and chemical composition of the environment (Popowska, 2017). In addition, some ecosystems are exposed to a continuous release of antibiotics (e.g., hospital wastewater, farm residues) and are persistently contaminated regardless of the degree of degradation (Martinez, 2009).

Table 3. Time of decomposition of selected pharmaceuticals in the natural environment (based on Thiele-Bruhn, Beck, 2005; Jessen et al., 2019).

Group of antibiotics	Use in agriculture	Rate and time of degradation
Penicyllins	Used in animal husbandry to combat e.g. respiratory and urinary system infections	0–50% in 1–49 days
Fluoroquinolones	Used in animal husbandry to combat, e.g. infections of respiratory, urinary and auditory systems	0–30% in 56–80 days
Sulfonamides	Used in animal husbandry to combat, e.g. acute infections of the respiratory, infections of urinary, reproductive and gastrointestinal tract and foot rot.	0–50% in 22–64 days
Tetracyclines	Used in animal husbandry to combat e.g. respiratory tract infections, eyelid infections.	~24% in 10–180 days

AN ALTERNATIVE TO THE TREATMENT WITH ANTIBIOTICS

The rational use of antimicrobial agents is recommended to minimise the adverse effects and preserve the effectiveness of antibiotic therapy for as long as possible, so the pursuit of new and practical solutions to reduce the use of antibiotics in agricultural production is a critical issue.

An essential concern in animal husbandry is veterinary prevention to counteract diseases, especially infectious ones (Zenkner, 2021). To effectively prevent infections, it is necessary to provide animal husbandry with the right level of welfare through proper nutrition, water quality, and sanitation (Wieczorek, 2019). Another element of preventive measures is biosecurity, comprising activities aimed at reducing or eliminating the risk of introducing pathogens into a livestock farm. Biosecurity activities include fencing the farm, restricting the movement of people outside the staff, changing outer clothing and shoes, and disinfecting hands (Pejsak, Truszczyński, 2018). Vaccination and biosecurity are the most critical elements of veterinary prophylaxis (Zenkner, 2021).

The application of probiotics as livestock feed additives is becoming more widespread. They are used as replacements for antibiotic growth promoters (Niwińska et al., 2018). Probiotics consist of one or more selected microbial strains. The most commonly used as feed supplements are bacteria of the genus: *Bacillus, Enterococcus, Lactobacillus, Pediococcus*, and *Streptococcus* (Markowiak, Śliżewska, 2018). Probiotics have a beneficial effect on the composition of the intestinal flora, which is associated with the more efficient utilisation of nutrients contained in the feed. They effectively influence the growth and development of animals, increase animal production efficiency, and reduce susceptibility to infections (Kukier et al., 2018).

The harnessing of bacteriophages in the treatment of bacterial diseases may offer an alternative to antibiotics. Bacteriophages, viruses infecting bacteria and archaea, may also have applications in agriculture (Wojnarowski, 2019). By replacing antimicrobials, bacteriophages are emerging as a promising option in animal production, influencing the reduction of antibiotic resistance prevalence and zoonotic pathogens (Svircev et al., 2018). Studies have demonstrated the effectiveness of a bacteriophage mixture in controlling necrotic enteritis in chickens. Lower bird mortality and higher feed conversion and weight gain rates were observed (Miller et al., 2010). Similar experiments have shown that bacteriophages improve growth performance in pigs (Kim et al., 2014). Phages may also provide an alternative to antibiotics used in aquaculture. For example, researchers have proven that phage therapy can replace antibiotics in the fight against vibriosis in fish farming (Silva et al., 2014). Research has also been conducted on bacteriophages in the battle against fire blight. In addition, positive results were obtained regarding the efficacy of phages against *Erwinia amylovora* bacteria, compared to the effect of streptomycin (Boulé et al., 2011).

LEGAL REGULATION FOR THE USE OF ANTIBIOTICS IN AGRICULTURE

Antibiotic growth promoters (AGPs)

The use of antibiotics in animal husbandry was initially regulated by the Council Directive of 23 November 1970, which included using these substances as feed additives. The effect of the emergence of drug resistance due to the widespread use of antibiotics in animal husbandry was first described in the so-called Swann Report (Pejsak, Truszczyński, 2006; Truszczyński, Pejsak, 2006). The document published in 1969 suggested limiting antibiotics as feed additives, especially those compounds intended for human treatment (Truszczyński, Pejsak, 2006; Przeniosło-Siwczyńska et al., 2015). Sweden became the first country to ban the use of antibiotic growth promoters. In 1986, the government prohibited using all antibiotics as feed additives to increase growth or productivity in livestock. In 1995 Denmark and Norway banned the application of AGPs (Lipińska, 2020). Following the example taken by the Scandinavian countries, other Member States have started to ban the addition of antibiotics used in human medicine as feed additives (Przeniosło-Siwczyńska, Kwiatek, 2013). Based on the results of studies showing a decrease in the number of resistant bacteria under the influence of the cessation of AGPs use in different countries, the European Union has forbidden the use of antibiotic growth promoters in all Member States since 1 January 2006 (Regulation (EC) No 1831/2003; Truszczyński, Pejsak, 2006). Since that year, antibiotics in animal husbandry can only be therapeutically treated.

Medicinal products

In Poland, one of the legal provisions ordering medicinal products, including antibiotics, is the Act of 6 September 2001, Pharmaceutical Law (Ustawa z dnia 6 września 2001). It defines the use of medicinal products in humans and animals, establishes the rules for the manufacture and marketing authorisation of medicines, or regulates the conduct of clinical trials (Giedrojć-Brzana et al., 2017; Cywińska et al., 2020). The Act of 11 March 2004 on protecting animal health and combating infectious diseases (Ustawa z dnia 11 marca 2004) requires veterinarians to keep veterinary medical records of the treatment performed. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC defines the application of antimicrobials in the treatment of animal diseases. The regulation informs, in particular, not to use these substances routinely and to compensate for poor hygiene and poor husbandry conditions. The prophylactic use of antibiotics can be performed on individuals or a limited number of animals when the risk of infection is high and has serious consequences. The metaphylactic use of such agents is justified when the risk of spreading infection or infectious disease in a group of animals is high, and there are no alternatives. The provisions of this directive will enter into force on 28 January 2022. However, none of the above legal requirements prohibit the therapeutic use of antimicrobial substances but only restrict their unjustified implementation.

Plant protection products

In many countries, preparations containing streptomycin have been used as plant protection products. In Poland, the only such preparation containing streptomycin sulphate was Hortacin 18 SP, intended for the control of fire blight (Puławska et al., 2009). By Commission Decision of 30 January 2004 concerning the non-inclusion of certain active substances in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing these substances, streptomycin was withdrawn as a plant protection products in the European Union.

Content in foodstuffs intended for consumption

The Act of 25 August 2006 on food and nutrition safety (Ustawa z dnia 25 sierpnia 2006) provides information on the general conditions and actions that must be taken at all stages of food production to ensure human health. One of the criteria is not exceeding the acceptable level of residues of veterinary products (Majewski, Anusz, 2018). The term maximum residue limit (MRL) is used for drugs authorised for food-producing animals. The steps leading to the determination of MRLs for medicinal substances in food products of animal origin are formulated in Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 (Różańska et al., 2014). Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin sets maximum residue levels for antibiotics in food source animals (Majewski, Anusz, 2018).

SUMMARY

Antibiotics are regarded as one of the most outstanding scientific achievements. Since their discovery, they have become an integral part of medicine, veterinary medicine, and agriculture, helping fight infections and improve the quality of agricultural products. Unfortunately, overuse and misuse have made them a real threat to health and the environment over the years. The spread of antibiotic resistance-bacteria and the pollution of ecosystems are the most severe consequences of the widespread use of antibiotics. Awareness of the danger posed by the excessive use of antibiotics has led to stricter regulations that aim to control the consumption and correct use of antibiotics in agriculture.

Raising awareness about antibiotics among the general public is also very important. For example, the European Commission established the European Antibiotic Awareness Day, celebrated annually on 18 November. Meanwhile, in 2015, the World Health Organisation (WHO) introduced World Antibiotic Awareness Week, from 16-22 November. The aim is to organise events to educate the public about antibiotics and the growing problems associated with the loss of effectiveness of antibiotic therapy and the spread of antibiotic resistance among bacteria (Mazińska, 2019).

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