PAN Germany
Pestizid Aktions-Netzwerk e.V.

Antibiotic resistance threatens human and animal health!

Antibiotics in Livestock Farming

What can be done to reduce environmental threats and avoid the development of antibiotic resistance?

The use of antibiotics in intensive livestock farming promotes the development of antibiotic resistance and the spread of resistant bacterial strains. This is a serious problem for both public health and the environment. Today, 700,000 people worldwide die from bacterial infections each year because antibiotics are no longer effective. If decisive action is not taken to combat increasing antibiotic resistance, the number of deaths is expected to increase steadily and reach 10 million annually by 2050[1].

Efforts to counter this development are being undertaken at international[2], European,[3] and national[4] levels. It is clear that measures aimed at solving this problem will only be effective if all parties involved – legislators, the pharmaceutical industry, doctors, patients, livestock farmers, and consumers – play their part. The livestock industry has a special responsibility in the fight against antibiotic resistance and the environmental impacts of veterinary pharmaceuticals.

This background paper is the English translation of the PAN Germany publication "Antibiotika in der Tierhaltung. Wie lassen sich Umweltbelastungen reduzieren und Resistenzen vermeiden"[4a]. In most cases where the "national level" is mentioned, this refers to the situation in Germany.

What are antibiotics and what are they used for?

Antibiotics are substances that either kill bacteria or inhibit their proliferation. Antibiotics differ in terms of their spectrum of activity – in other words, their effectivenes against different kinds of bacteria as well as their absorption, distribution, and degradation in the body of the animal treated and their possible side effects. Antibiotics are administered in a number of ways, for example, as medicated feed additives, as depot injections or in drinking water. Available classes of approved animal antibiotics include aminoglycosides, cephalosporins, (fluoro-)quinolones, macrolides, penicillins, phenicols, pleuromutilins, polypeptides, ionophores, sulfonamides and tetracyclines. Some of these antibacterial substances were developed exclusively for veterinary use, whereas others are also administered to humans.

For decades, treatment with antibiotics of diseases caused by bacterial infections such as diarrhoea, pneumonia, tuberculosis, and certain skin diseases has been highly successful. In recent years, however, serious infections in humans and livestock have again been on the rise. One reason for this is the spread of antibiotic-resistant microorganisms.

What is antibiotic resistance and why does it pose a problem?

The development of antibiotic resistance is a natural process, but it can become a problem. Every time an antibiotic is administered, bacteria sensitive to the specific substance are killed. Bacteria that are less susceptible survive initial applications of the antibiotic used. This means that each application of antibiotics contributes to the selection of resistant bacteria. To kill off all target bacteria, it is essential that the correct dosage and duration of treatment be observed. Mass medication, unnecessary or incorrect treatment, insufficient doses, and failure to complete the full course of treatment promote the development and spread of antibiotic-resistant microorganisms. Once pathogens become resistant to an antibiotic, treatments with it become ineffective. The development of bacterial strains that are resistant to several classes of antibiotics is particularly problematic. These strains are referred to as multidrug-resistant bacteria.

An official report from North Rhine-Westphalia published in 2014 revealed that nine out of ten turkeys were treated with antibiotics, including colistin and enrofloxacin, which are both important in treating human diseases.

According to DBU (German Federal Environmental Foundation), 90 % of Escherichia coli found on turkey farms are antibiotic resistant.

Multidrug-resistant MRSA bacteria were detected in 41.8 % of stocks of breeding pigs in Germany.

Antibiotic resistance on animal farms are a threat to human health

Resistant bacteria from livestock farming can spread and be transmitted to humans through contaminated meat products, direct contact with animals, and through the environment. As a result, treatment of infectious diseases in humans can be impeded or even become completely ineffective. In regions with a high livestock density like north-western Germany, resistant bacteria from livestock farming have been detected in a significantly higher percentage of hospital patients than in patients from other regions.

One example from livestock farming is resistance in Staphylococcus aureus bacteria to the antibacterial substance methicillin (methicillin-resistant S. aureus – MRSA), which is widespread in Germany's populations of breeding pigs. Colonisation with LA-MRSA CC39877 has been detected in 77 to 86 % of German farmers exposed to pigs. The rate of colonisation in people with no direct exposure to livestock is 0.5 to 1 %. Studies have shown that in humans, LA-MRSA CC398 multidrug-resistant bacteria can cause wound and bone infections, pneumonia, and other bacterial infections.[4b]

Antibiotic residues in eggs, meat, and milk

Maximum residue limits (MRLs) in food have been set not only for pesticides but also for veterinary medicinal products. EU Regulation No 37/2010[5] lays down the maximum residue limits in food of animal origin for all authorised veterinary medicinal products, including 59 agents used against bacterial infections. For example, traces of the antibiotic tetracycline may not exceed 100 micrograms per kilogram (µg/kg) in muscle tissue, 100 micrograms per litre in milk, 200 µg/kg in eggs, and 600 µg/kg in kidney tissue. Only in cases in which these maximum residue limits are exceeded do foodstuffs lose their market authorisation, meaning that they may no longer be sold. Every year, the German Federal Office of Consumer Protection and Food Safety publishes data on unacceptable residues in food of animal origin as part of the National Residue Control Plan (NRCP).[6] At first glance, the contamination of foodstuffs with veterinary medicinal products seems to be relatively low. In 2014, "non-compliant" antibacterial residues were detected in 0.15 % of the food samples tested. The most frequently found substances were tetracyclines, followed by penicillins, quinolones, aminoglycosides, sulphonamides, diaminopyrimidines, and macrolides. However, pharmaceuticals can also have a significant impact in lower concentrations and in combination with other substances, and some have been shown to be consistently highly toxic. Cumulative effects and children's special vulnerability to bacterial infections and their eating habits have not been taken into account in setting maximum residue limits.[7]

In Germany, more than 13 million turkeys are conventionally farmed.[10] About 88 % of these turkeys are kept in livestock facilities that house 10,000 or more birds.

Last-resort antibiotics

Last-resort antibiotics are antibacterials that are of vital importance for the preservation of human health. Most organisations use this term for antibiotics described by the WHO as "critically important antimicrobials". These include antibiotics for the treatment of serious infections in humans which are particularly problematic as far as the transmission of bacteria (between animals and humans) and development of resistance is concerned and for which there are no or hardly any alternative substances. WHO lists macrolides, ketolides, glycopeptides, (fluor)quinolones, and third- and fourth-generation cephalosporins as antimicrobials of the highest priority for the protection of human health.[8]

The EU banned the use of antibiotics as growth promotors in livestock farming in 2006. The use of antibiotics to promote growth is still permitted in the USA and Asia.

In 2014, about 200 mg of antibiotics were used in Germany to produce 1 kg of meat. This makes Germany one of the EU's top users of antibiotics in livestock farming.

The use of pharmaceuticals to compensate for deficits in accommodations, breeding, management, and hygiene contradicts the principles of responsible livestock farming.

Enterococci, streptococci, and staphylococci were detected in the exhaust air of piggeries; 98 % of these bacteria were resistant to between two and four different classes of antibiotics.

The polypeptide antibiotic colistin is now also classified as a last-resort antibiotic for humans. This means that the high volume of colistin (82 tonnes) used in livestock farming is a cause for concern. Colistin is used mainly to treat intestinal infections in poultry and pigs. Colistin resistance has been increasing in recent years, for example, in *Escherichia coli* found in poultry fattening operations. In spite of its considerable side-effects, colistin is increasingly being used in humans as a last-resort treatment option, for example against carbapenem-resistant bacteria such as *Escherichia coli* and *Acinetobacter baumanii*, which can cause serious wound infections and pneumonia and have already caused numerous deaths in German hospitals.

What is the extent of the use of antibiotics in German livestock farming?

In Germany, the amount of antibiotics marketed has been documented and published since 2011. According to the Federal Office of Consumer Protection and Food Safety, 805 tonnes (t) were sold for use in livestock farming in Germany in 2015. The highest volumes of antibiotics marketed were reported for penicillins (299 t), tetracyclines (221 t), polypeptide antibiotics (colistin) (82 t), sulfonamides (73 t), macrolides (52 t), and amphenicoles (5 t). This indicates that 50 % less sales of antibiotics were reported in 2015 in comparison to the 2011, the first year such transactions were monitored. At first glance, this is an encouraging development, but on closer inspection we see that these figures reflect only part of the total amount of antibiotics used in livestock farming. They do not include the antibiotics, such as Lasalocid A, monensin sodium und narasin, contained in premixes used to produce medicated feed. Moreover, the reported reduction in the total amount of antibiotics marketed is offset by an increase of 29 % in the use of last-resort antibiotics. In view of the spread of antibacterial resistance, this is highly problematic. The highest resistance to fluoroquinolone ciprofloxacin at 74.2 % was found in 2014 in the carcasses of turkeys.[9] Since 2014, operations that fatten cattle, pigs, chickens, and turkeys with populations that exceed a certain size are required to document the frequency of antibiotic applications, and those that use excessive amounts of antibiotics risk sanctions. However, although antibiotics are also used by dairy farms, hatcheries, other specialised breeding farms, and in aquaculture, these operations are exempt from the requirement to document "individual figures on the frequency of antibiotic applications". This data therefore does not include all livestock operations. Moreover, monitoring the number of antibiotic applications indirectly promotes the use of last-resort antibiotics, since the frequency of use of these substances is often lower.[11]

Antibiotics in dairy farms

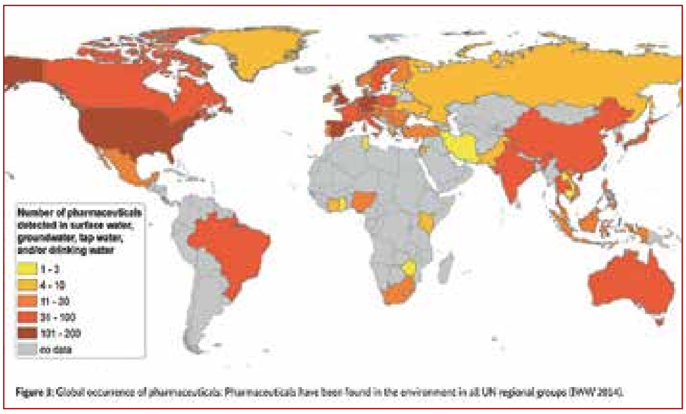
Antibiotics are given to 80% of dairy cows in Germany prior to their giving birth, as a pharmaceutical aid to reduce milk production; this is referred to as "drying off". Dairy cows are also given antibiotics to treat udder, uterine, and claw infections – all of which are diseases that tend to develop more often when cows are bred to have udders "compatible" with milking systems, when high yields are an important priority, and when deficits in hygiene and herd management occur.[12]

A reported 75 to 90 % of the antibiotics excreted by animals are not metabolised and remain active in the environment.

Soils regularly fertilised with pig manure have tetracycline concentrations that sometimes exceed 100 micrograms per kilogram of soil.

Africa, Asia, America and Europe – pharmaceuticals pollute the environment around the world

Pharmaceutical residues have become a global environmental problem. To date, 631 pharmaceutical substances have been detected in the environment in 71 countries around the world.[13] Comprehensive and systematic environmental monitoring for pharmaceuticals would no doubt reveal considerably higher figures. The substances detected enter the environment as a result of applications in hospitals and by private individuals, from effluents from pharmaceutical manufacturing plants, and from livestock farming. The following database compiled by the German Federal Environment Agency provides an overview of human and animal pharmaceuticals found in the environment worldwide: http://www.umweltbundesamt.de/en/node/42170.



Number of pharmaceutical substances detected in surface water, groundwater, and drinking/tap water (IWW 2015).

Why are pharmaceuticals a threat to the environment?

To be effective in an organism pharmaceuticals must, for example, remain stable at acidic pH values and resist certain enzymes. Pharmaceuticals administered to an animal are only partially metabolised or degraded in its body. Depending on the active ingredient, 30 to 90 % of the active substances are excreted unchanged and remain active in the environment.

The environmental behaviour of pharmaceuticals varies, depending on environmental conditions, the particular site characteristics, soil conditions, hydrology, temperature, etc. Many pharmaceuticals are persistent and accumulate in the environment. Many substances are water soluble and mobile

The intended therapeutic action of pharmaceuticals, for example the destruction of bacteria or parasites, can lead to undesirable and adverse effects on non-target organisms in the environment.

in aquatic ecosystems and can now be detected in nearly all flowing waters.[14]

Authorisation procedures require that the environmental impact of new medicinal products is examined prior to approval. But for most of the antibiotics that have been in use for many years, including many “top selling” products sold in very large quantities, data on how these substances behave in the environment and assessments of possible risks are either non-existent or obviously inadequate.[15]

Antibiotics pollute waters

Four of the active medicinal substances found in German surface waters in concentrations higher than 0.1 µg/l were antibiotics from livestock farming: sulfadimidine, sulfamethoxazole, erythromycin, and trimethoprim. Bodies of water are also ecosystems. Antibiotics such as erythromycin and tetracycline have been shown to inhibit the growth of algae and blue-green algae (cyanobacteria) in surface waters, and there is evidence of a negative impact of sulfamethoxazole on rainbow trout.[16] Even low concentrations of medicinal substances below 1 µg/l have been shown to have an effect on organisms. Bacteria in marine sediments display increased levels of antibiotic resistance when exposed to antibiotics. Marine sediment bacteria have key functions in the nitrogen and carbon cycles and are therefore important for global environmental processes such as eutrophication and climate change. There has been only limited research on the environmental consequences of increased resistance rates in sediment bacteria and their long-term exposure to pharmaceuticals to date.[17]

PAN calls for an extension and adaptation of the existing legally binding limits for pesticides and biocides in groundwater, which permit residues of 0.1 µg/l of individual pesticides and biocides and a cumulative amount of 0.5 µg/l, so that they also apply to pharmaceuticals.

Pharmaceuticals have also been detected in groundwater, including veterinary medicinal products such as sulphonamides (the basis for sulfamethoxazole and sulfamethazine) and tetracycline (tetracycline, chlortetracycline, oxytetracycline), trimethroprim, and tylosine. In Germany recorded groundwater concentrations are still low and the presence of these substances rarely detected. However, the fact that residues of veterinary medicinal products have been detected in groundwater is a wake-up call. Groundwater, as Germany's main source of drinking water and a sensitive ecosystem, should be completely free of contaminants.

Effect on microorganisms in soils

Antibiotics attack microorganisms that have useful functions in ecosystems. Antibiotics end up in agricultural soil through fertilisers such as manure, via fermentation residues from digestion plants, and as exhaust air from livestock buildings; once in the soil, they interact with microorganisms there. Some antibiotics, such as fluoroquinolones and tetracyclines, which are widely used in livestock farming, bind to soil particles. Tetracycline substances cause an increased selection of antibiotic-resistant soil bacteria in soils, leading to changes in the composition of soil microflora. Some antibiotics are very toxic for useful soil fungi such as mycorrhiza, which play an important role in supplying nutrients to the plants with which they live in symbiotic relationships. However, it is difficult to prove that antibiotic residues from veterinary and human medicinal products cause lasting harm to soil functions. We cannot yet predict the long-term effects on soil fertility and yields, making precautionary measures all the more important.

From barn to beak

Studies have shown that earthworms ingest veterinary medicinal products such as trimethoprim, a type of antibiotic, and other harmful substances in soils that have been fertilised with pig manure. This not only affects the earthworms but also birds and their offspring, as well as other animals that feed on earthworms.[18]

Antibiotics are absorbed by plants and can be harmful to them

Since the 1980s, numerous studies have examined the effects of antibiotics on plants and confirmed that antibiotics can adversely affect root growth, nutrient uptake, germinability, photosynthesis, and chlorophyll production in plants.[19] The

There are no legally binding limits for pharmaceuticals in foodstuffs of plant origin.

residue levels measured to date have been very low and, so far, have not been considered hazardous to human health. However, in regions where wastewater contaminated with antibiotics is used for irrigation, higher concentrations of antibacterial substances may be present in crops, as testing of cucumbers, paprika, cabbage, and other plants has shown.[20]

Extreme environmental pollution in the vicinity of pharmaceutical manufacturing plants

The immediate surroundings of pharmaceutical manufacturing plants are hotspots for environmental pollution caused by medicinal products and the resistant bacteria they lead to. As early as 2007, Swedish researchers examined effluent from 90 pharmaceutical manufacturing plants in India and detected, among other things, concentrations of as much as 31,000 µg/l of the antibiotic ciprofloxacin. They calculated that through the wastewater of the manufacturing plant studied, up to 45 kilograms of the antibiotic were discharged into adjacent waters per day.[21] With publication of the report Bad

Measures must be implemented in livestock farming to reduce the amounts of antibiotics used overall. Breeding, management, and feeding must ensure that animals can be raised in good health without the use of last-resort antibiotics.

In effluent from pharmaceutical manufacturing plants, 86 % of the bacterial strains detected were resistant to at least 20 different types of antibiotics.

Medicine in 2015, a wider public became aware of the extent of environmental pollution in the vicinity of manufacturing sites in India and China. The report not only documents pollution near manufacturing plants but also reveals that many reputable European pharmaceutical companies source their medicinal products from manufacturers who cause massive environmental pollution and contribute substantially to the spread of antimicrobial resistance.[22] To end this contamination in future, environmental organisations, including PAN Germany, demand that the criteria for Good Manufacturing Practice (GMP)be expanded to incorporate environmental standards[23].

The "cocktail effect" increases toxicity

Organisms in the environment, whether microorganisms, insects, fish, or birds, are exposed to not just one but any number of potentially harmful substances. The potential combined effect of such mixtures is a problem that is still ignored or underestimated in risk assessments. Studies have shown that when several antibiotics are mixed, they can have a stronger impact on organisms, even if the concentrations of the individual active pharmaceutical substances are very low.[24] One example is the combined effect of erythromycin and trimethoprim, both antibiotics, and triclosan, an antibacterial and antifungal agent suspected of disrupting hormonal development in humans and animals. Whereas the mixture of these substances resulted in significant changes in the sex ratios of water fleas, this did not occur when the water fleas were exposed to the same substances separately.[25]

Reduced antibiotic use for healthy animals and a healthy environment

Anyone who holds animals is responsible for ensuring that they do not suffer. Using pharmaceuticals to do so is appropriate and necessary. However, many of the diseases farm animals suffer from result from the way they are bred and raised and are thus home-grown and avoidable.

Most chickens, pigs, and cattle are bred to produce maximum yields of eggs, meat, and milk, in order to supply people with cheaper food. These intensively farmed animals are usually kept in huge facilities and under extremely crowded conditions with thousands of other animals and without sunlight or freedom of movement. This makes them susceptible to diseases and promotes the rapid spread of pathogens. In intensive farming, diseased animals are not separated and

not treated individually for economic reasons. Instead, entire groups of animals are mass medicated (metaphylaxis), even if only a few animals are ill, meaning that thousands of healthy animals are treated with antibiotics unnecessarily. Intensive animal farming is a system that creates a high demand for medicinal products, exacerbates environmental pollution, and promotes the spread of antibiotic resistance.

Policy and legislation – necessary measures have not yet been implemented

Under the programmatic slogan "Reduce, Replace, Rethink", the European Food Safety Authority (EFSA) summarises the steps that need to be taken to cut back on the use of antibiotics in livestock farming.[26] EFSA's goal is to reduce the use of antibiotics, replace them with alternative treatments, and rethink the livestock production system. PAN Germany welcomes this approach but highlights shortcomings in its implementation. Heightened efforts are required, especially with regard to necessary changes in the livestock farming system. A lot must be done if animals are to be farmed in way that will ensure they are raised in good health and treated individually if they contract an illness. To this end, breeding must prioritise animals that are more robust, even if this leads to somewhat reduced performance and yield. Moreover, livestock accommodation and good management practices are needed that allow animals to behave as they would naturally. Responsible staff with sufficient time and a high level of expertise, as well as numerous other factors must also be taken into account. Many of the measures needed are thus beyond the scope of the current legal framework for veterinary medicinal products. But existing legal provisions for veterinary pharmaceuticals also offer opportunities to bring about improvement. However, the proposal for a revised legal framework for veterinary medicinal products [27] currently being negotiated does not go far enough, especially with regard to restricting the use of antibiotics in livestock farming. The proposed legislation should also be revised with respect to documentation and access to relevant data (for example, documentation of the amounts of all medicinal products used should be publicly available, access to key ecological data on pharmaceuticals, monitoring the occurrence and impacts of medicinal products in the environment, etc.).

PAN Germany's demands

To combat the spread of antibiotic resistance and protect people and the environment from the adverse effects of antibiotics used in animals, PAN Germany calls for

- ► a shift in the priorities in breeding goals for livestock in favour of more robust and disease-resistant breeds and overall lifetime yields
- ► realisation of appropriate conditions for livestock and attention to animal welfare
- ► reduction of animal density per facility and per region with legally binding limits (ratio of animals to available area)
- ► further reduction of the application of antibiotics in livestock farming and effective monitoring measures
- ► restriction of the methaphylactic use of antibiotics
- ► prohibition of the use of last-resort antibiotics in intensive livestock farming with exceptions permitted only within very strict limits
- ► documentation and reporting for all antibiotics used, including those in feed additives, and for all forms of animal breeding and husbandry, and publication of all data collected
- ► introduction of legally binding limits and standards for residues of pharmaceutical substances (individual substances and combinations and mixtures) to protect surface water, ground and drinking water, and the soil
- ► incorporation of enhanced protection of the environment into the legal framework for veterinary medical products
- ► implementation of systematic and comprehensive monitoring of the occurrence and impacts of pharmaceuticals in the environment
- ► systematic environmental risk assessment (ERA) of pharmaceuticals introduced before the ERA became mandatory, in keeping with the precautionary principle
- ► strict regulatory procedures and monitoring for pharmaceutical substances which specifically affect the environment
- ► inclusion of environmental standards in Good Manufacturing Practices to ensure a high level of environmental protection applies in pharmaceutical production

More information on this issue

PAN Germany on veterinary medical products in the environment

- http://www.pan-germany.org/ keyword: veterinary pharmaceuticals
- Frequently asked questions regarding pharmaceuticals in the environment (in German) http://www.pan-germany.org/download/tierarzneimittel/FAQs-Tierarzneimittel.pdf
- Demands for improved protection of the environment from the adverse effects of veterinary medical products; PAN Position Paper http://www.pan-germany.org/download/veterinary_pharmaceuticals/Enhanced_Protection_of_Environment_from_Veterinary_Medicinal_Products.pdf
- How to tackle environmental pollution from veterinary pharmaceuticals; PAN Position Statement. http://www.pan-germany.org/download/tierarzneimittel/Position-Statement_ENGL_F.pdf

Further information from other NGOs

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More about the issue (in English)

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Information on antimicrobial resistance (English/German)

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