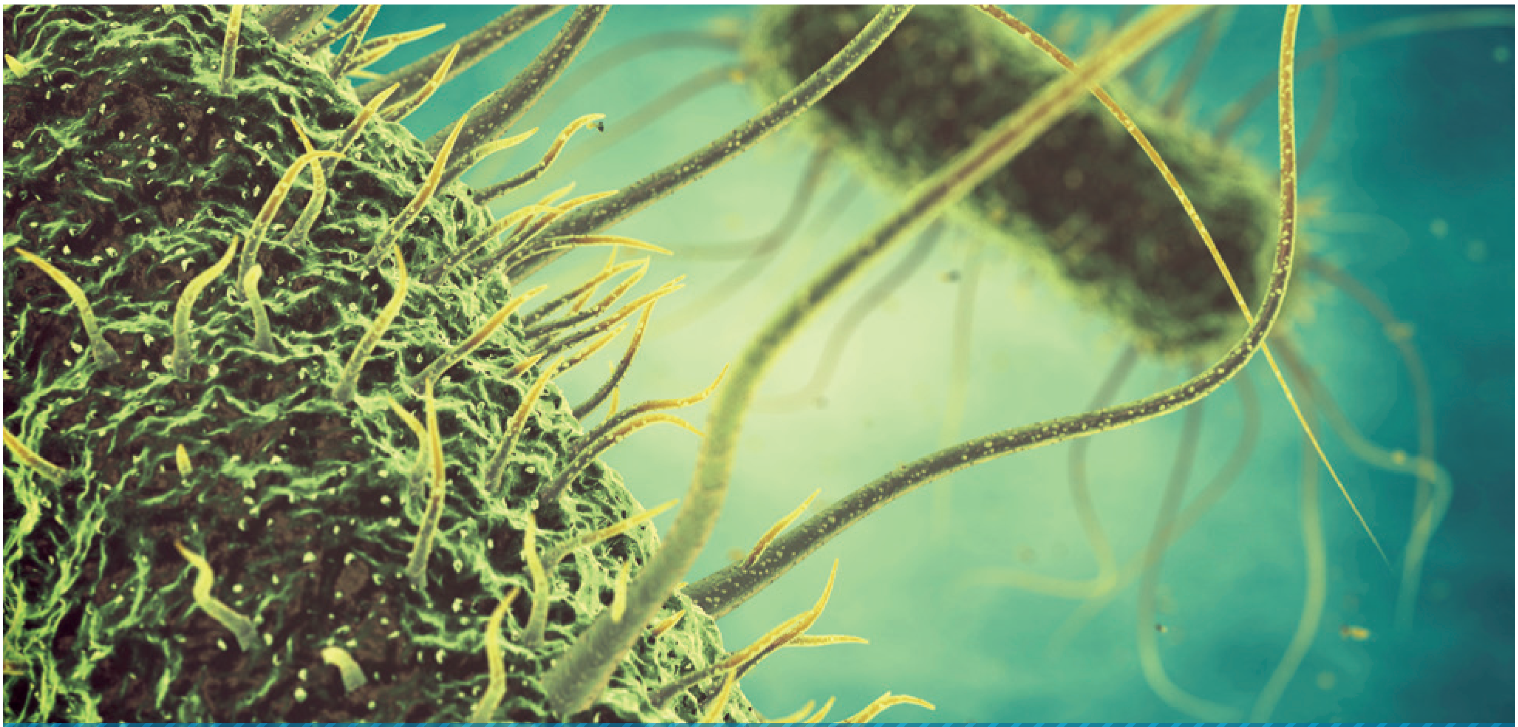

BACKGROUND // OCTOBER 2018

Antibiotics and Antibiotic Resistances in the Environment

Background, Challenges and Options for Action

German Environment Agency

Umwelt Bundesamt

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Antibiotics and Antibiotic Resistances in the Environment

Background, Challenges and Options for Action

List of abbreviations

AR
Antibiotic resistance

AS
Antibiotic substance

ARB
Antibiotic-resistant bacteria

ARG
Antibiotic-resistance gene

BMBF
German Federal Ministry of Education and Research *(Bundesministerium für Bildung und Forschung)*

BMG
German Federal Ministry of Health *(Bundesministerium für Gesundheit)*

BMEL
German Federal Ministry of Food and Agriculture *(Bundesministerium für Ernährung und Landwirtschaft)*

DART
German Antibiotics Resistance Strategy *(Deutsche Antibiotika-Resistenzstrategie)*

DIMDI
German Institute of Medical Documentation and Information *(Deutsches Institut für Medizinische Dokumentation und Information)*

E. coli
Escherichia coli (intestinal bacteria)

EMA
European Medicines Agency

ESBL *E.coli*
E. coli, which form Extended Spectrum ß-lactamases. These enzymes effectuate the resistance towards certain antibiotics (including penicillins and 1st to 3rd generation cephalosporins)

LAWA
German Working Group of the Federal States and the Federal Government on Water Issues *(Bund/Länderarbeitsgemeinschaft Wasser)*

MRGN
Multi-resistant Gram-negative bacteria

MRSA
Methicillin-resistant Staphyllococcus aureus

HA-MRSA
MRSA, which typically occurs in hospitals (hospital-associated)

LA-MRSA
MRSA, which typically occurs in livestock (livestock-associated)

REACH
Registration, Evaluation, Authorisation and Restriction of Chemicals

SMX
Sulfamethoxazole

EQS
Environmental Quality Standard *(Umweltqualitätsnorm)*

WHO
World Health Organisation

Table of contents

1 Introduction

The presence of antibiotic-resistant bacteria in the environment has been widely reported and is a current topic of discussion in Germany. However, sometimes the documented findings of antibiotic substances and antibiotic-resistant bacteria in the environment are not correctly distinguished. The objective of this paper is to summarise the existing scientific knowledge about antibiotic substances and antibiotic-resistant bacteria in the environment and to highlight knowledge deficits and options for action which, from the perspective of the German Environment Agency (UBA), need to be taken into account during the current political discussions. The role of the different environmental media such as soil and waters as a "sink" for antibiotic substances is considered in terms of them being a medium of transmission and reservoir for antibiotic-resistant bacteria. To understand the meaning of antibiotic-resistant bacteria and their presence in the environment and to be able to better differentiate them from the documented findings of antibiotic substances in the environment, these topics are considered separately in section 2. Due to the relevance of the topic for human health, the interface between the environment and people is highlighted in section 3. Following from this, in section 4, research needs, preventive measures and options for action to protect people and the environment are discussed.

On the basis of the reports of the WHO, the EU Commission presented its "One Health" plan of action for controlling antimicrobial resistances (https://ec.europa.eu/health/amr/action_eu_en) in June 2017. In this respect, "One-Health" constitutes an interdisciplinary approach which describes the complex relationships between people, animals, the environment and human health and the close collaboration between all stakeholders. The Commission has asked the Member States to implement measures for controlling antimicrobial resistances as quickly as possible. In terms of the environment, the EU Commission states that better documented findings about the role of the environment in the development and the spread of antimicrobial resistances in people and animals are required. The Commission has therefore planned the following steps for the transposition (a.) the adoption of a strategic EU approach to minimize pharmaceuticals in the environment; (b.) the maximisation of data from monitoring measures, and (c.) strengthening the role of the Scientific Committee on "Health and Environmental Risks".

In Germany, the Federal Ministry of Health (BMG) together with the Federal Ministry of Food and Agriculture (BMEL) and the Federal Ministry of Education and Research (BMBF) developed the German Antibiotics Resistance Strategy "DART 2020". It was adopted in May 2015. DART 2020 assembles measures that are required for the reduction of resistances to antibiotics. Its objective is to stronger monitor and reduce the presence of resistances to antibiotics and the use of antibiotics in human medicine, veterinary medicine and agriculture, and to implement additional measures for the prevention and controlling of resistances. In this respect, the sector-spanning cooperation, i.e. the "One Health" approach, is centre stage. Within this framework, the role of the environment and environmentally-related measures have so far only been considered to a limited degree. This is addressed more closely in section 4 of this paper.

In recent years, there has been an increasing number of media reports regarding the elevated presence of pharmaceuticals and antibiotics in the environment, but also the associated risks to the environment and health (Bio Intelligence Service 2013, Beek et al. 2016). To reduce the entry of pharmaceuticals and therefore antibiotics into the environment, the EU Commission is currently developing a strategic approach to prevent the contamination of waters with medicinal products. The input of antibiotics in terms of the occurrence of antibiotic-resistant bacteria (ARB) is also likely to be addressed in the strategy of the EU.

In 2016, the stakeholder dialogue on the "Trace substance strategy of the German federal government" was opened. It concerns the protection of waters from anthropogenic trace substances such as medicinal products, household chemicals and industrial chemicals. The initial results of the dialogue are available in the policy paper "Recommendations from the multi-stakeholder dialogue on the Trace substance strategy of the German federal government" (BMU/UBA 2017). The objective of the dialogue is to prevent and/or minimise the entry of trace elements, more precisely defined as micro-pollutants, into the aquatic environment. In this respect, the dialogue addresses reduction measures at source, during use, and end-of-pipe measures such as advanced treatment of waste water. In this context, antibiotic substances and antibiotic-resistant bacteria have not explicitly been considered.

In the interests of preventing and reducing future contamination of waters with micro-pollutants such as medicinal products, the UBA has compiled its current background paper "Recommendations on the reduction of micro-pollutants" (UBA, 2018). In these recommendations, both the entry paths of medicinal products and other micro-pollutants are analysed, critical substance properties are identified, and specific steps for a comprehensive water protection are proposed for the areas of production, use and the treatment of waste water. In focusing on antibiotics and antibiotic resistances, the paper at hand supplements this UBA position.

DEFINITIONS

Antibiotics are active substances which impede and/or kill the growth of bacteria. In this paper, the terms antibiotics and antibiotic substances have the same meaning.

Antibiotic-resistant bacteria (ARB) are considered to be bacteria which do not react especially sensitively to one antibiotic or several antibiotics, i. e. they are resistant to the impact of these substances. This means that their growth is no longer impeded by the antibiotic. Therefore, infections with such bacteria are more difficult to treat with the currently available antibiotics. The resistance of bacteria to antibiotics can be a naturally existing property or it can be a gained property. Bacteria can develop a resistance through mutation and through the transfer of genes from resistant bacteria. Documenting ARB in the environment occurs through the cultivation and characterisation of the bacteria.

Antibiotic resistance genes (ARG) are the area of genetic material (DNA) in which the capacity for antibiotic resistance is located. Documenting resistance genes in the environment occurs through molecular biological methods. When documenting resistance genes based on samples from the environment, it is not generally possible to determine whether they are resistance genes from environmental bacteria, pathogens or free DNA.

Antibiotic resistances (AR): An umbrella term relating to both ARB and ARG.

2 How do antibiotics find their way into the environment? How do antibiotic-resistant bacteria develop in the environment? Where can they be found?

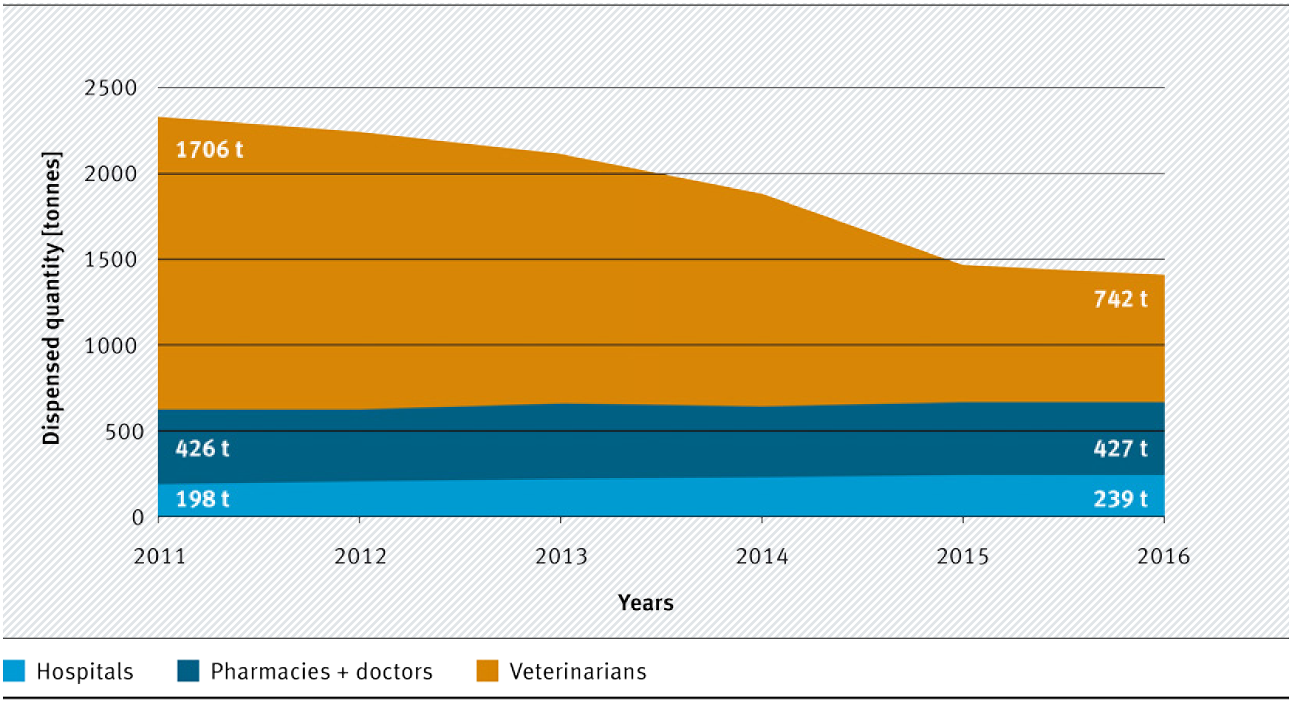
2.1 Dispensed quantities of antibiotics in Germany

Antibiotics are used for the treatment of bacterial infectious diseases in human and veterinary medicine. A detailed description and listing of all groups of antibiotic substances is provided in Küster et al. 2013. as a consequence of an increasing occurrence of antibiotics in the environment and the resulting discussion about antibiotic resistances, the dispensed quantities of veterinary and human medicines have been documented for some years. In human medicine, 666 tonnes of antibiotics were dispensed by hospitals, doctors and pharmacies in Germany in the year 2016 (Fig. 1). In total, from 2011 (642 tonnes) to 2016, the dispensed quantity increased slightly. A sector-based analysis shows that this increase can almost exclusively be attributed to antibiotics in hospitals. β-lactams (penicillin, amino-penicillin and cephalosporin) are most frequently used in human medicine. In this respect, the increased use of reserve antibiotics is considered to be especially critical, i. e. substances which are restricted to the treatment of serious infections for which standard antibiotics such as tetracyclines or amino-penicillins can no longer be used due to the development of resistance. The fall in the overall quantities between 2011 and 2016 was, however, accompanied by an increase in the dispensed quantities of fluoroquinolones and cephalosporins of the 3rd generation. Their use in the area of veterinary medicine is considered very critically due to their particular importance as reserve antibiotics in the field of human medicine (Wallmann et al. 2016). In 2010, almost one in two prescriptions for antibiotics constituted a reserve antibiotic in Germany (Schröder 2011).

Comparable quantities have been recorded in the area of veterinary medicine, and in 2016, the quantity of antibiotics dispensed by veterinarians amounted to 742 tonnes. Since 2011, according to the Medicines Ordinance by the German Institute of Medical Documentation and Information (DIMDI), the

Figure 1

Dispensed quantities of antibiotics from human and veterinary medicine.



Source: © Federal Office of Consumer Protection and Food Safety (BVL) and IMS HEALTH; compilation by UBA pharmaceutical industry must document the quantities of antibiotics dispensed to veterinarians each year and report this data to a central register. The Federal Office of Consumer Protection and Food Safety (BVL) evaluates the data every year. A positive development: between the years 2011 (1,706 tonnes) and 2016, the dispensed quantity of antibiotics as a veterinary medicinal product fell by 56.5 percent. A wide range of groups of antibiotic substances are used in veterinary medicine. In 2016, the biggest quantities that were dispensed were from the groups of penicillins (279 tonnes), tetracyclines (193 tonnes) and sulphonamides (69 tonnes). These quantities clearly decreased in comparison to quantities in 2011. The dispensed quantities of cephalosporins of the 4th generation (1.1 tonnes), of polypeptide antibiotics (69 tonnes) and macrolides (55 tonnes) also declined. In this respect, it is necessary to remember that the dispensed quantity for polypeptide antibiotics is almost exclusively attributable to the active substance of colistin, which is listed as a reserve antibiotic for human medicine (Wallmann et al. 2016).

2.2 How do antibiotic-resistant bacteria develop in the environment?

The resistance of bacteria to antibiotics is a natural property (D'Costa 2011, Bhullar 2012). ARB are therefore ubiquitous in the environment. Despite this, bacteria can also develop an antibiotic resistance through mutation and through the horizontal transfer of genes from resistant bacteria. Of considerable clinical and publicly-relevant importance in this respect are those ARB that have gained resistance, such as methicillin-resistant staphyllococcus aureus (MRSA), extended spectrum ß-lactamases (ESBL *E. coli*) or multi-resistant Gram-negative bacteria (MRGN). These develop especially in places where antibiotics are used because there they have a survival advantage. Hotspots for the occurrence of ARB therefore include hospitals and agricultural livestock keeping. From these hotspots, ARB are able to enter the environment via waste water or through the spreading of sewage sludge, slurry or fermentation residues.

Since the first medical use of antibiotics in the 1940s, the resistance levels have increased significantly in comparison with the natural environment. In a comparison of soils in 2008 with archived soils dating from 1940, a more than 15-fold increase of individual ARG was demonstrated (Knapp et al. 2010). This clearly illustrates the anthropogenic influence on the development and spread of ARB.

A further accumulation and spread of ARB can occur in the environment. With waste water, sewage sludge, slurry or fermentation residues, not only are ARB released into the environment, but also antibiotic substances, which exert a selection pressure on bacteria and are therefore able to foster the development of ARB. In this respect, it is necessary to bear in mind that even limited concentrations of antibiotic residues are sufficient to provide resistant bacteria in the environment with a selection advantage compared to non-resistant bacteria (Gullberg et al. 2011). In addition to this, the horizontal transfer of genes between bacteria species in waste water can be fostered by the high nutrient content and the high bacterial density in biofilms (a layer of mucus consisting of micro-organisms which can also contain ARB and ARG). In this respect, pathogens which were previously not resistant can also acquire resistance genes from bacteria.

Another mechanism through which ARB occur in the environment is co-selection through substances such as biocides or heavy metals that are also present in waste water, sewage sludge, slurry or fermentation residues (Westphal-Settele et al. 2018). The combination of a high nutrient content, a high bacterial density and the existence of various antibiotics and heavy metals in such media creates the ideal conditions for a transfer of genes between bacteria. Recent studies demonstrated the spread of ARG to environmental bacteria. Following their application on soils, ARG from slurry has been verified in soil micro-organisms (Ghosh and LaPara 2007, Jechalke 2014) as well as in bacteria in ground and surface waters (Chee-Sanford et al. 2009). For this reason, these media are to be considered hotspots for the spread of antibiotic resistances in the environment (Sengeløv et al. 2002; Marti et al. 2014).

INTERACTIONS OF ANTIBIOTIC SUBSTANCES AND ANTIBIOTIC RESISTANCES IN THE ENVIRONMENT

Even limited concentrations of antibiotic residues in the environment are sufficient for giving antibiotic-resistant bacteria a selection advantage compared with non-resistant bacteria (selection pressure). This selection can also be fostered by other environmental pollutants, such as biocides, heavy metals (zinc, copper) and antibiotic mixtures. If bacteria carry several resistance genes, located on the same mobile genetic element, this single genetic element can promote the resistance against different substances. In this way, the presence of a heavy metal in the environment for example, may facilitate the distribution of resistance genes against heavy metals alongside with the antimicrobial resistance genes among bacteria. This phenomenon is referred to as the co-selection of resistance genes.

In nutrient-rich waste water, sewage sludge and slurry, the density of the bacterial colonisation is often very high. This high cell density can additionally support the transfer of genetic material between the bacteria, i. e. the horizontal gene transfer.

If all of these factors occur simultaneously along the entry pathways of antibiotics, this fosters the development of antibiotic-resistant bacteria in the environment.

2.3 The environmental assessment of antibiotics and resistances within the authorisation of human and veterinary medicinal products

The EU Directives 2001/83/EC for Human Medicinal Products and 2001/82/EC for Veterinary Medicinal Products as well as the Regulation 726/2004/EC set out the statutory requirements for the authorisation of new human and veterinary medicinal products. These stipulate that during the course of new applications for authorisation, it is necessary to verify the environmental risks posed by medicinal products, and to derive special risk reduction measures. In contrast, pharmaceutical products that are already authorised, are not subject to a retrospective environmental assessment, meaning a conclusion on the risk to the environment is not possible. In Germany, the national Medicines Act (AMG) stipulates that the authorisation of medicinal products which pose a risk to the environment has to include conditions concerning environmental protection. In contrast to veterinary medicinal products, there are no current statutory provisions for a rejection of the authorisation of human medicinal products due to identified risks to the environment. For veterinary medicinal products a rejection of the authorisation for environmental reasons is possible from a legal perspective, but with regard to the risk-benefit analysis a rejection is hardly implemented. Assessment concepts in the form of a harmonised European guideline (EMEA 2006, VICH 2000, VICH 2004) form the joint basis for the environmental assessments of human and veterinary medicinal products, and therefore antibiotics, for public authorities and industry. In the scope of the authorisation of antibiotics, the UBA verifies and assesses the studies that have been submitted concerning the behaviour and impact in the environment.

The methods and criteria for assessing the development of antibiotic resistance in the environment have not yet been included in the environmental risk assessment of antibiotics. A previously discussed measure for the environmental risk assessment is the assessment of the specific concentrations in which antibiotic substances are able to foster or cause the development of resistances in bacteria in the environment. Some initial proposals with respect to this have been described in the literature (Bengtsson-Palme and Larsson 2016). Addressing antibiotic resistance as part of the post-authorisation control of antibiotic products, commonly known as “pharmacovigilance”, has also been discussed. In the course of pharmacovigilance, the side effects of a medicinal product are to be monitored and compiled subsequent to the authorisation. During authorisation these two measures, can be used to either verify the development, dissemination and transfer of resistances in the environment before the antibiotic is placed on the market or after it is used. However, a systematic assessment of these measures in the scope of the environmental risk assessment is not yet in place.

2.4 The entry of antibiotics into the environment

Antibiotic substances can find their way into the environment in different ways (Fig. 2). Antibiotics are only partially metabolised in peoples' and animals' bodies ("processed by the metabolism"), which means they are sometimes excreted in the form of the initial active substance. Depending on the antibiotic, the excreted ratio varies between 10 and 90 % of the initial active substance. Antibiotics which are used in human medicine can enter the sewers from private households as well as from healthcare and nursing facilities, reaching waste water treatment plants without pre-treatment, and subsequently entering waters via treated waste water. The technology used at municipal waste water treatment plants is not, however, currently configured for eliminating micro-pollutants and therefore antibiotics (UBA 2017). If sewage sludge from waste water treatment plants is applied to soil, active substances can find their way onto fields and meadows. Antibiotics can also enter the groundwater from rivers, lakes and streams or via the soil. In places where antibiotics are manufactured or formulated (i. e. where antibiotic substances mixed with auxiliary products), they can reach the environment directly through the waste water discharged from the facility, or indirectly, i. e. via municipal waste water treatment plants. The relevance of this input path for Germany is yet to be clarified. In livestock keeping, antibiotics enter the environment through animal dung and urine. Through the application of slurry and dung, sometimes in the form of fermentation residues from biogas plants, or through direct excretion by free range livestock that have been treated, antibiotic residues can find their way onto fields and meadows, soil, rivers and lakes, and can therefore enter the groundwater. As the entry pathways of antibiotics from human and veterinary medicine are very different, the respective entry also require different reduction measures. Our options for action that we have identified (see section 4) therefore partially distinguish between antibiotics from human medicine and those from veterinary medicine. It is also necessary to remember that in many cases, it is not possible to attribute the documented findings of antibiotics in the environment exclusively to use by humans or for animals. Cephalosporins or penicillins are for example used both by humans and for animals, and therefore enter the environment through different pathways.

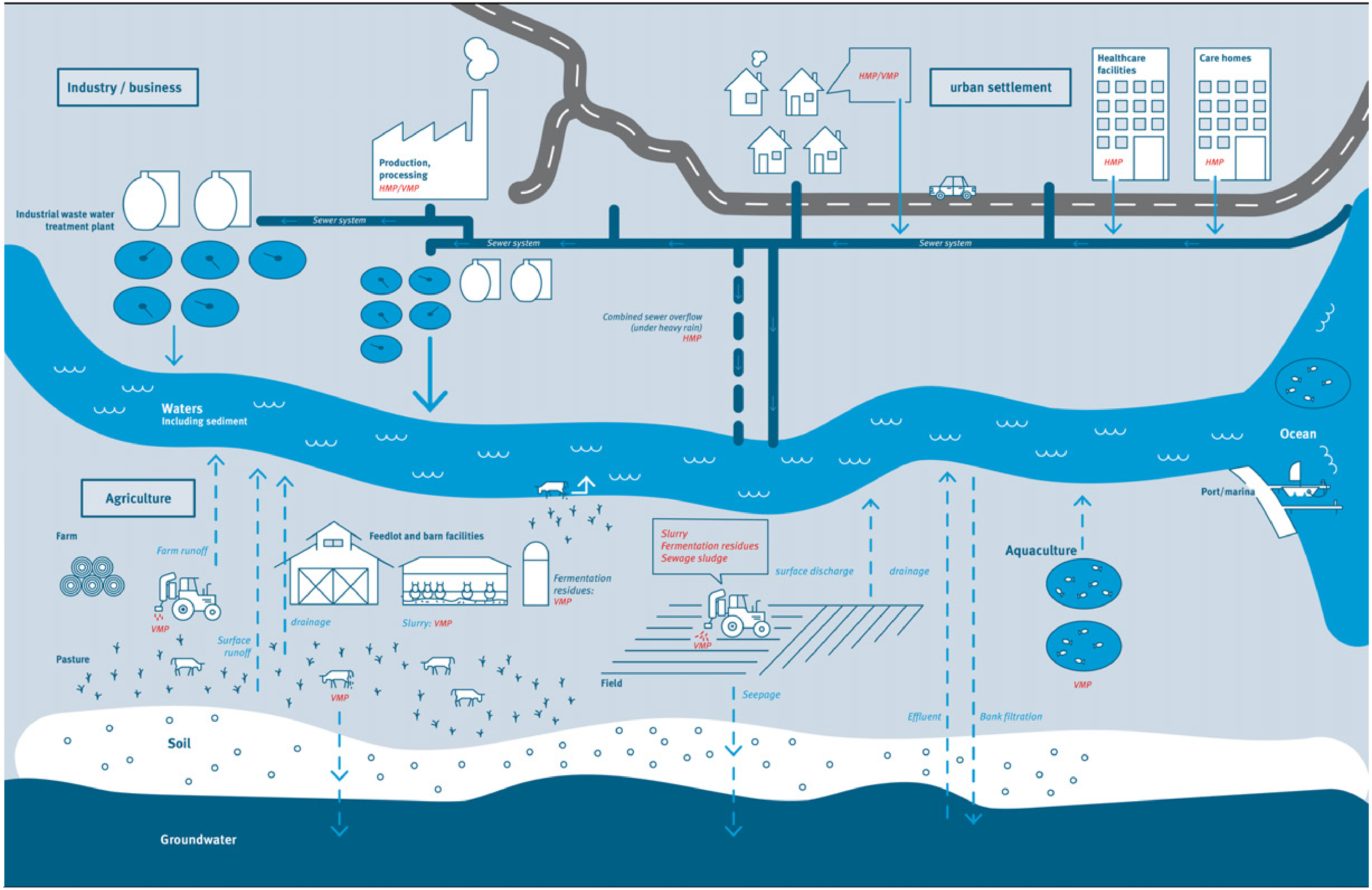
2.5 Dissemination of antibiotic-resistant bacteria in the environment

In recent years, the entry of ARB into the environment that exceeds the naturally existing antibiotic resistances has been covered in numerous publications for all environmental compartments. In principle, the input paths of ARB are identical to those for antibiotic substances (Fig. 2). Bacteria with an acquired antibiotic resistance especially occur in the environment where water and soils is contaminated by faeces. The currently discussed hotspots for the dissemination of antibiotic resistances are above all fertilisers (slurry, fermentation residues, sewage sludge) and municipal waste water, particularly waste water with indirect entry from healthcare facilities (hospitals, care homes, old people's homes). In this respect, slurry, sewage sludge and fermentation residues as well as the municipal waste water are generally contaminated directly with ARB through excretions from people and animals. At present, there is an increasing focus on waste water from airports and slaughterhouses as input paths for ARB. However, there are currently no overview and data regarding the dissemination of ARB in the environment in Germany. In 2015, the HyReKA[1] research project was launched by the BMBF to address these aspects. By 2019, the entry of ARB into the environment through waste water from hospitals, municipal waste water or waste water from livestock rearing farms, for instance, is to be researched on a qualitative and quantitative basis. The objective of the project is to identify the contamination situations and methods of dissemination and to estimate the potential risks. In addition, the risk of transmission from the environment, from agriculture or agricultural livestock keeping and back to people in contact with contaminated water or food products should be quantified and characterised.

1 Comparisons: http://www.hyreka.net

Figure 2

Entry pathways of antibiotics into the environment from human and veterinary medicine



Inputs from various sources: surface discharge, drainage, seepage into the groundwater

Point sources: entries in sewer system and from waste water treatment plants

HMP Human medicinal products; VMP Veterinary medicinal products

Source: German Environment Agency

2.6 Documented findings of antibiotics and antibiotic-resistant bacteria from human medicine in the environment

Although no comprehensive, systematic monitoring of antibiotics and antibiotic-resistant bacteria in the environment currently takes place in Germany, in recent years, antibiotic substances have been found in various environmental media, especially from human medicine. ARB are increasingly found in the environment as well. However, a systematic monitoring is still missing.

2.6.1 Documented findings in waste water from treatment plants

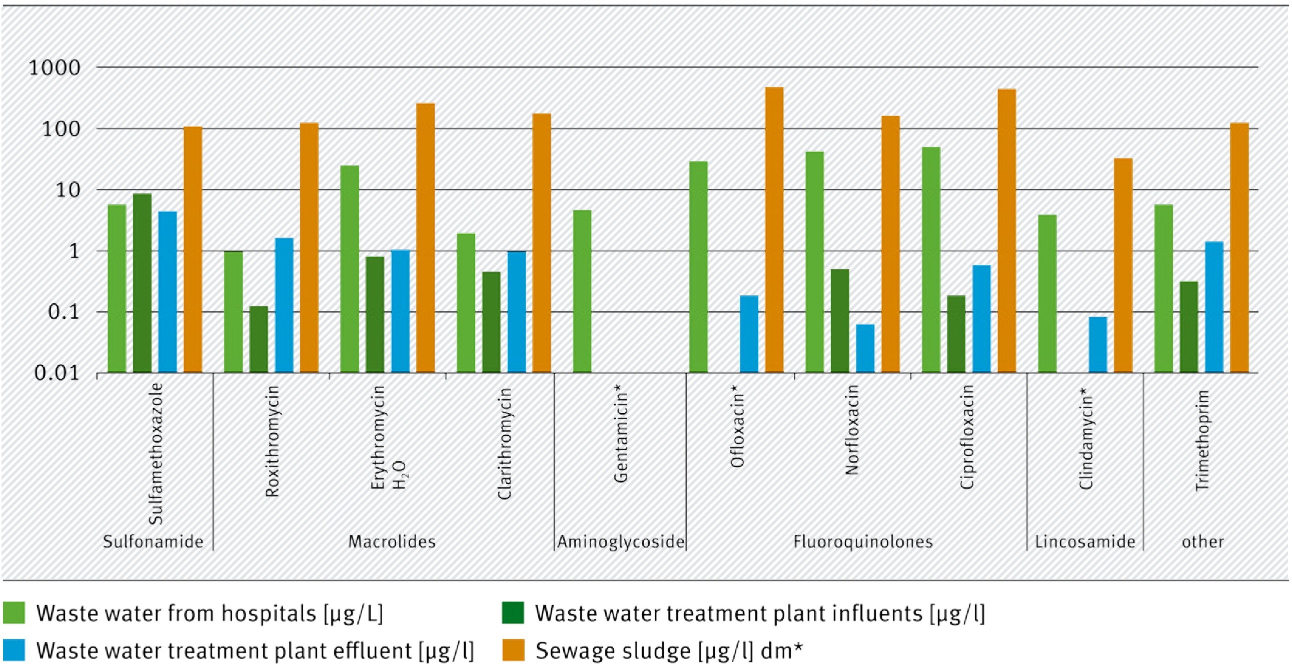
Antibiotics.

Antibiotics find their way into waste water treatment plants through the municipal sewerage system. In general, antibiotics are not completely retained by waste water treatment plants, because conventional plants apply a three-stage waste water treatment process, the technology of which is not optimised for the reduction of micro-pollutants such as medicinal products. As a rule, waste water from households, hospitals, care facilities and old people's homes is discharged together to a waste water treatment plant. Waste water from antibiotic production facilities can enter waste water treatment plants both directly and indirectly. This means that the production facility may discharge into its own waste water treatment plant or it can be connected with the municipal sewerage system. Due to the residues of antibiotic substances present in waste water, the bacteria in the waste water treatment plants can acquire resistance to the active substance. For this reason, waste water which is treated in municipal waste water treatment plants is one of the key entry pathways of antibiotics into waters. Fig. 3 shows a selection of antibiotics from human medicine in waste water from hospitals (Ohlsen 2003), municipal waste water effluent and sewage sludge in Germany. For this purpose, the maximum concentrations of antibiotic substances from a variety of studies were compiled, which means the data regarding the influents and effluents from the waste water treatment plants cannot be directly compared. It is evident that waste water from hospitals and waste water treatment plants can contain high concentrations of antibiotics. In addition, many antibiotic substances accumulate in the sewage sludge, which is a pollutant sink in the waste water treatment plant.

To date, little evidence of certain antibiotics, such as β-lactames (e. g. penicillins, cephalosporins and carbapenems) has been found in the environment although

Figure 3:

Maximum concentrations of antibiotic substances used in human medicine in waste water from hospitals, in the influents and effluents from waste water treatment plants and in sewage sludge in Germany.



*data are available for the presented matrices only.
** dry matter (DM = dry mass)

Source: Amended according to Schönfeld et al. (2017)

they are prescribed in large quantities. Among others, this reflects the considerable differences in the stability and biodegradability of the antibiotic substances. For several years the concentrations of antibiotics in the influents and effluents of waste water treatment plants have been monitored and published on a voluntary basis. A publicly accessible collection of measured data from healthcare institutions discharging waste water indirectly, such as care homes and old people's homes, but also manufacturing facilities, slaughterhouses and airports, does not exist due to the lack of a statutory obligation. In several countries in the EU, certain active medicinal substances, including sulfonamides and the antibiotic substances lincomycin and bacitracin have been found in high concentrations in waters downstream from production facilities (see overview in Larsson et al. 2014). The production of antibiotics in Germany could therefore constitute a possible input path into the environment for antibiotic substances. Since there is no data on production facilities in Germany yet, its relevance cannot be assessed at present.

Antibiotic resistances.
In Germany, the regulatory requirements regarding waste water discharges from municipal waste water treatment plants take cumulative parameters such as the biochemical oxygen demand (BOD) or the chemical oxygen demand (COD) into account. The emissions of pathogens, ARB and ARG are regulated neither in terms of national regulatory law (Waste Water Ordinance) nor in terms of charges (Waste Water Charges Act). Since waste water from households, hospitals, care facilities and old people's homes generally finds its way to a common waste water treatment plant, treated waste water from municipal waste water treatment plants also constitutes a key input path of ARB into waters. A collection of data regarding the incidence of ARB in relation to different sectors, including the production facilities for antibiotics, does not yet exist for Germany.

2.6.2 Documented findings in sewage sludge from municipal waste water treatment plants

Antibiotics.
Depending on the waste water treatment techniques used in waste water treatment plants and the attributes of the antibiotics, some of the antibiotic substances accumulate in sewage sludge. In this respect, a written report on the monitoring data of pharmaceuticals in the environment completed on behalf of the UBA showed documented findings of the antibiotics ciprofloxacin, norfloxacin, clarithromycin, roxithromycin and trimethoprim in sewage sludge (Bergmann et al. 2010).

Antibiotic resistances.
Sewage sludge is a reservoir for ARB and ARG. High bacterial densities and sufficient nutrient contents provide the ideal conditions for the adaptation of bacteria through horizontal gene transfer processes. In particular, substances with a selective impact such as antibiotics, but also heavy metals for example, bring growth benefits for resistant bacteria and therefore support the dissemination of ARG. The storage conditions of sewage sludge as well as the high nutrient content and high bacterial density also support the propagation of these resistant bacteria. When used as fertilisers, both the antibiotic residues and ARB reach the soil, thus ARB can be directly spread further in the environment. A study by UBA examined the occurrence of resistance genes in the case of the presence of different antibiotics as a consequence of the use of sewage sludge in agriculture and the horizontal dissemination of these ARG. The results show that the spreading of sewage sludge leads to a significant increase of ARG in the soil, and that these ARG can be proven to exist in the soil over an extended period of time. It is also possible for multi-resistant soil bacteria to be transferred to potential pathogens.

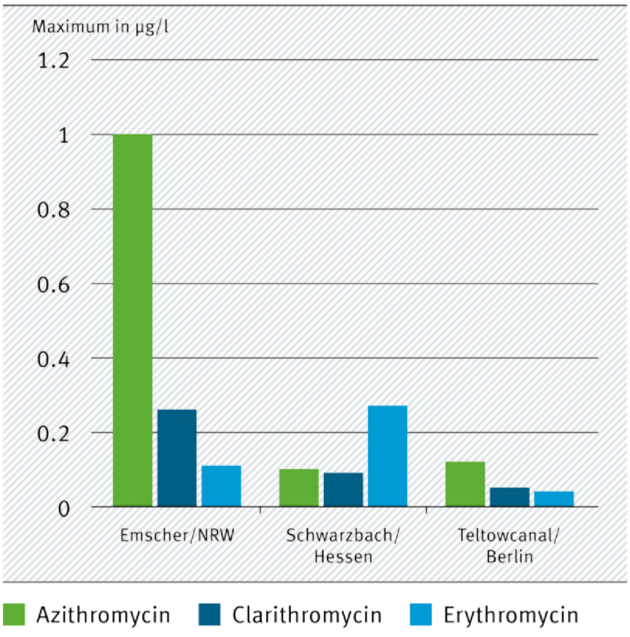
2.6.3 Documented findings in surface waters

Antibiotics.

In waters, antibiotics can occur in concentrations which have a harmful impact on the aquatic habitats and their occurrence may require more advanced water treatment processes. Therefore there are proposals for environmental quality standards (EQS) that can be used to assess the protection of the ecological habitat and human health in case of fish consumption. Macrolide antibiotics (azithomycin, clarithromycin, erythromycin) and sulfamethoxazole cause damage to aquatic plants such as algae and cyanobacteria in the water ecosystem. This can disturb the equilibrium of the natural food chain in waters and damage the entire ecosystem. For this reason, the regulatory authorities in the German federal states and German Federal Institute of Hydrology have been measuring pharmaceuticals in surface waters for several years. From 2014 –2016, it was possible to measure 13 antibiotics and two transformation products in the monitoring network of the German Working Group of the Federal States and the Federal Government on Water Issues (LAWA) above the limit of determination. A report by LAWA (2016) highlights that EQS proposals regarding sulfamethoxazole and clarithromycin are exceeded at the effluents of municipal waste water treatment plants. Under low-flow conditions and high proportions of waste water in surface waters, further exceedances of the EQS proposal are possible.

Figure 4

Maximum concentrations of antibiotics in surface waters.



Source: UBA according to report data from 2016 on implementing decision 2015/495 of the EU Commission

ENVIRONMENTAL QUALITY STANDARD (EQS)

An environmental quality standard is understood as being the concentration of a specific pollutant or a specific group of pollutants which cannot be exceeded in the environment, neither in water, sediment nor in species, to be able to achieve a good chemical and ecological status. To date, there have been proposals for EQS for antibiotics, but no legally binding EQS for surface waters.

Figure 4 shows the maximum concentrations measured in the waters of the Teltow Canal in Berlin, the Schwarzbach in Hesse and the Emscher in North Rhine Westphalia, all of which contain high concentrations of waste water. While the antibiotic azithromycin exceeds the EQS proposal at the Teltow Canal, at the Emscher the EQS proposals for azithromycin and clarithromycin are also exceeded. It has not as yet been possible to verify the origins of these antibiotics. However, an identification of the causes is indispensable for a reduction of entries. Antibiotics are increasingly being measured and detected in the oceans (HELCOM, 2017). The occurence of the antibiotics sulfamethoxazole and clarithromycin in the coastal waters of Mecklenburg-Western Pomerania has been reported since 2009.

Antibiotic resistances

A recently published literary study shows the prevalence of ARB in lakes worldwide (Yang et al., 2012). Accordingly, ARB are found in high concentrations in lakes as well as in rivers into which waste water is discharged or in lakes and rivers with agricultural use in the catchment area. An overview of the dissemination of ARB in surface waters in Germany is not currently available. The current HyReKA research project aims to make a contribution to this (see section 2.5). Individual measurements show a considerable amount of ARB in the surface waters in Germany.

Of considerable importance for the possible transfer of ARB from the environment to people are bathing waters. Appropriate details are available in the recommendations of the UBA, which have been compiled with the collaboration of the Working Group for Bathing Waters of the German federal government and federal states and the Bathing Waters Commission of the UBA[2]. The poorer the quality of the water, the higher the risk of ARB or pathogens being prevalent. As expected, in the course of sample-based studies in the federal states, different ARB were documented in bathing waters. An overview of the incidence of ARB in bathing waters in Germany has not yet been made available. Only a limited number of international studies have addressed the specific topic of ARB in bathing waters. In 2001, a study was carried out in Greece regarding the incidence of enterococci that are resistant to antibiotics in 120 bathing waters (Arvanitidou et al. 2001). Approx. 30 % of the 316 enterococci isolates which were studied demonstrated resistance to at least one of the antibiotics to be tested and approximately 20 % were multi-resistant. A resistance to vancomycin was not documented in any of the isolates, however. The authors attribute these high prevalences of antibiotic resistances to the exceptionally widespread use of erythromycin and other macrolide antibiotics in the population. In a current large-scale study in Great Britain, the dissemination of a certain class of ARB (*E.coli* with resistance to the 3rd generation of cephalosporins) in coastal bathing waters was examined (Leonard et al. 2015). It was possible to document these ARB in 11 of 97 samples. At 0.12 %, the share of these antibiotic resistant *E.coli* in these samples in the total *E.coli* bacteria was low, however (Leonard et al. 2015). The overwhelming majority of the documented findings of these ARB was in samples with poor water quality, while the documented findings in excellent or good quality bathing waters were very limited.

2.6.4 Documented findings in the groundwater

Around 75 % of the drinking water in Germany is abstracted from the groundwater. It is therefore very important to make sure that the groundwater is free from contaminants such as antibiotic residues and ARB.

Antibiotics.

Antibiotics from human medicine primarily enter surface waters through the sewerage system. However, human antibiotics have also been found in the groundwater (Ma et al. 2015). They reach the ground water, for example, through the application of sewage sludge on agricultural soils, via the passage of sediment from surface waters, or through small-scale waste water treatment plants which run off into the groundwater. In the scope of a UBA research project (Hannappel et al. 2016), from 2012–2016, for example, high concentrations of sulfamethoxazole (SMX) were repeatedly measured in the groundwater (found at two of 38 measurement stations, max. concentration 950 ng/L). SMX is an antibiotic which is primarily used for the treatment of urinary tract infections in human medicine, but also finds use in veterinary medicine. For the active substances that are found, a clear allocation of the cause of input (human or veterinary medicine) is frequently very difficult and complicated, and requires a detailed root cause analysis. In the case of the aforementioned research project, the root cause analysis demonstrated, for example, that the active substance originated from human use, and found its way into the groundwater via the irrigation system of a nearby small-scale agricultural waste water treatment plant.

Antibiotic resistances.

There are no systematic studies on the incidence of ARB in the groundwater in Germany. It is exceptionally unlikely for bacteria with acquired antibiotic resistance to be prevalent in well-protected groundwater aquifers because bacteria from surface waters are unable to enter them. In less well-protected groundwater, however, an input of faecal contaminants and therefore of ARB can occur. For instance, in a current study in Ireland looking at different catchment areas, ARB with resistances to typical human antibiotics or veterinary antibiotics were found in samples of water from individual wells (O'Dwyer et al., 2017). In this respect, the HyReKA research project of the BMBF should also provide findings relevant to Germany (see section 2.5).

2.7 Documented findings of antibiotics and antibiotic resistances from veterinary medicine in the environment

The use of antibiotics in veterinary medicine is characterised by animal welfare considerations and determined by the objective of manufacturing healthy food products. The use of antibiotics aims to treat individual animals, groups or holdings of livestock at an early stage so that the health of the animals and the quality of foodstuffs such as meat, milk and eggs is guaranteed. With regards to the prevailing conditions in fattening farms in particular, a metaphylactic ("preventive") use of antibiotics is usually unavoidable.

2 Compare: https://www.umweltbundesamt.de/themen/wasser/schwimmen-baden/badegewaesser/faq-antibiotikaresistente-bakterien-in#textpart-1

Metaphylaxis can be understood as the treatment of large groups of animals or even the complete holding of livestock because the holding has already been infected by a pathogen, and although only a few animals are sick, it is necessary to prevent a wave of infections (Wiesner and Ribbeck 2000). This means that considerably bigger quantities of antibiotics are used and potentially transferred into the environment than with the treatment of individual animals. With regards to the selection of ARB in livestock facilities, differences exist between conventional and ecological animal husbandry. Far fewer ARB occur in ecological animal husbandry (Tenhagen et al. 2018).

2.7.1 Documented findings in barn air

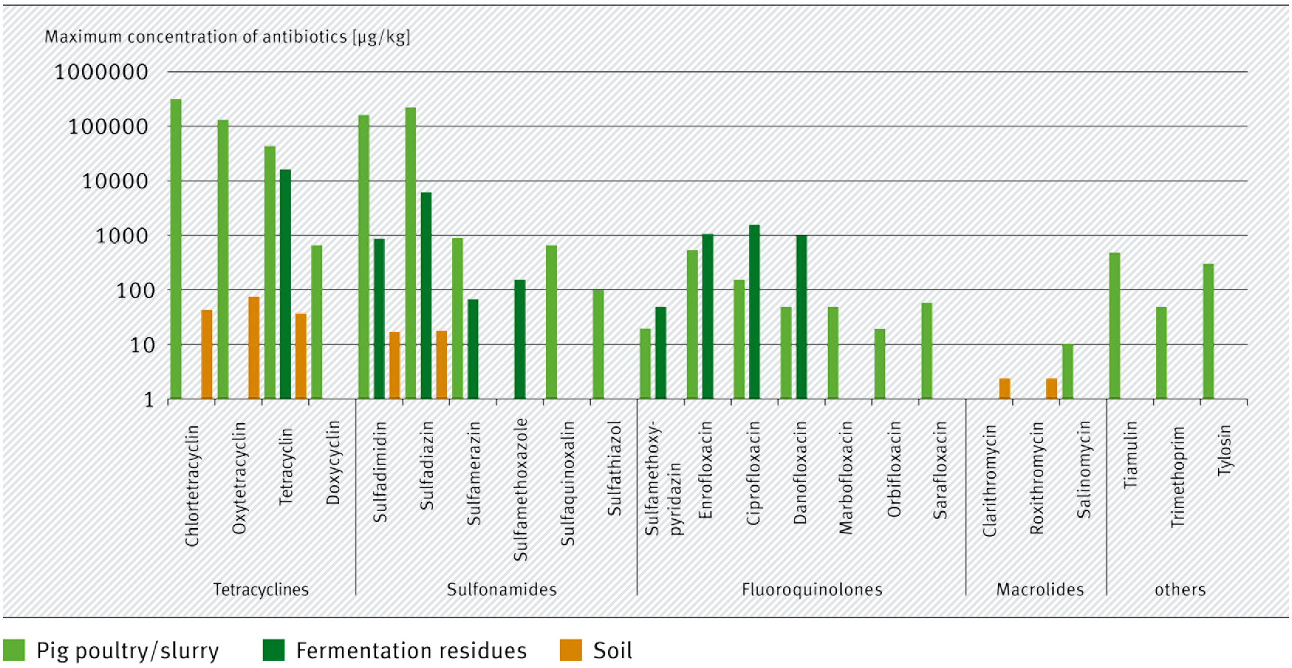
Antibiotics.
Through the administration of preparations in powder form, antibiotics can find their way into barn air and the environment of the barn facilities through waste air filtration systems. A long-term study (1981–2000) was able to provide documented findings of up to six different antibiotics (chloramphenicol, chlortetracyclin, oxytetracyclin, sulfamethazin, tetracyclin, tylosin) in most of the samples of barn dust examined (Hamscher et al. 2003). Other studies (Stahl et al. 2016) have demonstrated that an administration of sulfadiazin to pigs in powder form leads to higher concentrations of the active substance in barn air than is the case with administration in the form of granules or pellets. These are generally filtered out with the cleansing of the used air. Antibiotics can find their way into the environment due to insufficient filtering or open barn facilities, however.

Antibiotic resistances.
ARB which arise in livestock keeping can also enter the environment via the air from barns. In this respect, multi-resistant bacteria (LA-MRSA) have been documented in the environment of barns in a variety of studies (Friese et al. 2012). In a German study, LA-MRSA was documented in the barn air at 85 % of pig fattening facilities and 79 % of poultry fattening facilities (Friese et al. 2012). The transfer of LA-MRSA through the air as well as deposits in the soil at a distance of up to 300 m away from the barn was also detected (Friese et al. 2012). The bacteria are primarily transferred via physical contact, and the inhalation of the contaminated dust in the barns is also possible. Studies show that a nasal colonisation of LA-MRSA to be present in 86 % of the farmers and veterinary surgeons who work in MRSA-positive facilities. The risk of an MRSA colonisation is 138 times higher for people who come into direct contact with animals compared with unexposed persons in the same

Figure 5

Occurrence of antibiotics from veterinary medicine in slurry and fermentation residues.

the details for slurry (pig or poultry), fermentation residues (composite samples with proportion of slurry) and soil refer to µg/kg of dry matter.



The respective maximum values of the measured concentrations of antibiotic are shown. The data have been collated from a variety of research projects.

Source: UBA 2017, data from (Ratsak 2013, Wohde 2016, LAUBW 2002, Hembrock-Heger 2011, Göbel 2005, Hannappel 2017)

environment (Cuny et al. 2013). Techniques are available for the reduction of dust emissions from barn facilities. With their waste air purification systems, these can also contribute to a reduction of bioaerosols. However, no limit values are to date available that have been derived from dust from barns. The precise composition of dust particles (including their content of antibiotic residues and ARB, for example) is not being considered any further at present either.

2.7.2 Documented findings in slurry and fermentation residues

Antibiotics.

A considerable number of antibiotic substances of relevance to veterinary medicine have been found in slurry (fig. 5), and therefore reflect the entire range of active substances used in veterinary medicine (Westphal-Settele et al. 2018). In particular, the groups of tetracyclines, sulfonamides and trimethoprim are found in very high concentrations, sometimes of more than 100 mg/kg, especially in pig and poultry slurry, and in individual cases, in cattle slurry as well. Among other reasons, the high quantities of these groups of active substances occur in slurry because they have to be applied in high dosages in order to be effective.

Not to be underestimated are the low concentrations of fluoroquinolones such as enrofloxacin and its active transformation product ciprofloxacin, as these are very effective and therefore also active in very limited dosages in comparison with many other antibiotics. It has also been possible to document high quantities of antibiotics in fermentation residues which arise due to the fermentation of the affected slurry in biogas plants (Ratsak 2013).

Antibiotic resistances.

Slurry and fermentation residues also tend to be contaminated with ARB through excretions from animals that have been treated with antibiotics. It is therefore concerning that slurry and fermentation residues are not just contaminated with antibiotic mixtures, but also other pollutants such as zinc, copper and antimicrobial biocides which also support the formation of new combinations of these resistances in environmental bacteria (Sattelberger 2005, Ratsak 2013).

2.7.3 Documented findings in soil

Antibiotics.
Antibiotics from livestock keeping find their way into soil which is used for agricultural purposes via farm fertiliser (slurry, urea, liquid manure, fermentation residues), sewage sludge (see section 2.6.2) or from livestock pastures (see fig. 2). Through being worked in and with the leachate, these antibiotics reach the lower layers of the soil, where they are able to accumulate, before moving to deeper soils and penetrating the groundwater. In the form of an initial step into a more detailed characterisation of the environmental relevance of veterinary medicinal products, 15 years ago, UBA supported a research project of the Agricultural Investigation and Research Institute (LUFA) in Oldenburg and Weser-Ems Chamber of Agriculture (Winckler et al. 2004). In this project, the input of active substances from veterinary medicinal products into soils used for agricultural purposes was quantified, and an exposure assessment was carried out for the lead substance of tetracycline. Numerous studies on the input and behaviour of antibiotics in the soil are now available. Tetracyclines in particular, which find very frequent use in veterinary medicine, bind very strongly to soil particles, and have therefore been discovered in numerous studies (including Hamscher 2012, Jeschalke et al. 2014). Their documented concentrations are in the range of a few micrograms per kilogram of soil. In the scope of a current UBA report on the assessment of the impact of antibiotic mixtures on soil (Thiele-Bruhn, 2018), research was conducted into the impact of individual substances on soil organisms. In terms of the mode of action of antibiotics, a transposition of the structural composition of the soil microflora is apparent in the soil (oral communication of Thiele-Bruhn, 2018). It is necessary to remember that antibiotics are rarely applied on or into soils as an individual substance with slurry, but generally as a mixture of differing active substances, which are expected to have an additive or synergy-based impact on soil organisms.

Antibiotic resistances.
Soil microflora constitute one of the evolutionary origins of the known antibiotic resistance mechanisms (D'Costa 2011). For this reason, they are currently considered to be a reservoir of ARG which can be exchanged with clinical pathogens (Forsberg et al. 2012). Soil does not just come into direct contact with antibiotics which are used during the rearing of cattle and crop production (Heuer et al. 2011; McManus et al. 2002). It is also a natural habitat for bacteria (e. g. Streptomyces types) which produce antibiotics (Kieser et al. 2000). In recent years, there has been increased evidence of the exceptional increase in resistances (up to 15 times) in comparison with the natural backdrop since the beginning of the use of antibiotics in medicine, such as it has been possible to demonstrate in soils in the Netherlands (Knapp et al. 2010). To date, no comprehensive and systematic overview of the current dissemination of ARB is available for soils in Germany. The application of sewage sludge to agricultural soil as fertiliser, however, results in the entry of ARB which can survive in the soil for several months (Pietsch et al. 2015).

2.7.4 Documented findings in surface waters

Antibiotics and antibiotic resistances.
No routine measurements are carried out in surface waters for veterinary medicinal products that are used as antibiotics or the resistances which result from their use, as there is no statutory obligation to do so. Due to the insufficient data, it is not possible to provide a nationwide overview of the situation regarding the contamination in rivers, streams and lakes. The current HyReKA research project aims to make a contribution to this (see section 2.5).

2.7.5 Documented findings in the groundwater

Antibiotics.

Depending on their physical and chemical attributes, it is possible for antibiotics from veterinary medicine to enter the groundwater via the soil. Sulfonamides in particular have a high degree of mobility and solubility in water, and have been found in the groundwater in the course of different studies (including BLAC 2003, Bartelt-Hunt et al. 2011). With the objective of examining the degree of contamination of near-surface groundwater by antibiotics from veterinary medicine, from 2011–2016, UBA carried out two research projects in regions of northern Germany characterised by intensive livestock keeping (Hannappel et al. 2014, Hannappel et al. 2016). First, particularly at-risk monitoring points from the groundwater monitoring network were chosen and examined for selected antibiotics. The results show that at present, there is no comprehensive contamination of the near-surface groundwater by veterinary medicinal products in Germany. The majority of the measurement stations examined were free from the active substances under investigation. Antibiotics were documented in the groundwater at nine of the 38 monitoring points examined, however. To clarify the causes of the findings, these measurement sites were therefore analysed in more detail. In this respect, most of the concentrations of the documented sulfonamides (sulfamethoxazole, sulfadimidine and sulfadiazine, as well as their metabolites and transformation products) were in the lower nanogram/litre range ($< 0.1\ \mu g/L$) and largely originated from livestock keeping. This is also confirmed by subsequent examinations that were carried out on behalf of the Lower Saxony Water Management, Coastal Defence and Nature Conservation Agency.

Antibiotic resistances.

There are no systematic studies on the incidence of ARB in the groundwater for ARB which are based on use in veterinary medicine (for further details, see section 2.6.4).

2.7.6 Documented findings from the production of veterinary medicinal products

Antibiotics and antibiotic resistances.

The production of antibiotics for veterinary medicine constitutes a possible input path into the environment for antibiotic substances (for further details, refer to the section on human medicines). The federal states are responsible for the monitoring of production facilities in Germany. To date, no information about production facilities in Germany or the measurement results regarding antibiotics and ARB in the waste water from German production facilities has been available to the UBA.

2.8 The UBA medicinal products database – a research tool for the occurrence of antibiotics in the environment

In 2015, the UBA compiled the global findings of pharmaceuticals in the environment in the form of a publicly accessible UBA database, "Pharmaceuticals in the environment".[3]. The database contains more than 120,000 measured values for pharmaceuticals in the environment (from documented findings in the groundwater, to effluents from waste water treatment plants, to the soil) and is updated on a regular basis. As a result, occurrence of pharmaceuticals was documented in the environment in 71 countries. By 2011, it was possible to collate more than 600 active medicinal substances in concentrations that exceeded their limit of determination in the literature. The top 15 pharmaceuticals to be documented included 5 antibiotics: sulfamethoxazole, trimethoprim, ciprofloxacin, ofloxacin and norfloxacin. The results show that in the literature, there were 47 documented findings of sulfamethoxazole, 29 documented findings of trimethoprim, 20 documented findings of ciprofloxacin, 16 documented findings of ofloxacin and 15 documented findings of norfloxacin at worldwide monitoring points (Beek et al. 2016). The most frequently stated input sources of antibiotics are urban waste water, followed by hospitals, agriculture, aquaculture and the production facilities for medicinal products. The entries in the database show antibiotics in the environment to be a global problem, as they are not just found in industrialised nations, but also developing and emerging countries. Since its publication, the UBA database has been used regularly by scientists, regulators and associations for research purposes. Since 2017, it has been linked with the information platform for chemical monitoring (IPCHEM) of the European Union (https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html).

3 Compare: https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0

SUMMARY

Following excretion by people and animals, antibiotics that are used in human and veterinary medicine can find their way into the environment through waste water and organic fertiliser. Antibiotics can also enter the groundwater from rivers, lakes and streams or via the soil. Nowadays, antibiotics can be found in all of the affected environmental compartments, and can harm other organisms in the water ecosystem, for example. This can disturb the equilibrium of the natural food chain in waters and have consequences for the entire ecosystem.

The input paths of antibiotic-resistant bacteria are generally identical to those for antibiotics. In particular, antibiotic-resistant bacteria occur in the environment where the faecal contamination of the water or soil takes place. Even limited concentrations of antibiotic residues in the environment are sufficient for exerting a selection pressure and encouraging the existence of ARB in the environment. The antibiotic-resistant genes of environmental bacteria can then be transferred to pathogens which were not previously resistant. As a consequence antibiotic treatments for bacterial diseases are no longer effective.

To date, little research has been carried out regarding the role of the environment as a reservoir for the existence and dissemination of antibiotic resistances. To protect the environment, the interactions should be known to prevent possible short- and long-term consequences for the ecosystem.

3 The interface between people and the environment – what needs to be taken into account?

Epidemiology and formation mechanisms as well as the dissemination of antibiotic resistances are very varied. There are several paths for their transfer to people. On the one hand, ARB can be transferred from people to people or from animals to people through direct contact. Through the transfer of ARB to people, a colonisation of the intestines or the nose with ARB can occur. This does not necessarily lead to an illness, however. Studies have shown that five to seven percent of the European population have antibiotic-resistant bacteria (ESBL *E. coli*) in their intestines. In addition to this, some ARB such as MRSA occur as a component of the bacterial flora in the nose and throat area of 2–3 % of the German population. Farmers who keep livestock have particularly intensive contact with ABR. Therefore, they are colonised with certain ARB (LA-MRSA) more frequently than the normal population. In the area of human medicine, hospitals and care homes are considered to be particular "hotspots" for contact with resistant bacteria. During a course of treatment with antibiotics, resistant ARB can form in the patient's intestines which can then be transmitted to other patients through the faecal-oral route.

On the other hand, ARB from the environment can also be transferred to people at any place where contact with contaminated water or soil takes place. This can occur due to bathing in poor-quality waters; or via food, such as lettuce, irrigated with contaminated water or cultivated on soil that has been treated with sewage sludge. In those cases ARB can reach leaves of the plants. For this reason, the transfer of ARB in the area of food production should also be taken into account.

As previously described, antibiotic-resistant pathogens occur in the environment in considerably lower concentrations than in hospitals and care homes. The ingestion of a sufficient amount of pathogens for a colonisation or infection is only possible in the event of contact with water or soil that has a high degree of faecal contamination. This is possible, in the case of surface water which is heavily contaminated with waste water, or soil on which sewage sludge or slurry has been recently applied. In bathing waters that are of excellent or good quality by contrast, the concentrations are so low that an ingestion and colonisation with antibiotic-resistant pathogens and other bacteria that have acquired resistance to antibiotics is unlikely in the case of healthy people. In just one study (Söraas, 2013) from Norway, swimming in fresh water was described as a risk factor for the development of a urinary tract infection with ARB, but no details were provided concerning the water quality.

The increased concentrations of antibiotic resistances, antibiotics, biocides and heavy metals in the environment are a cause for concern, however, because they can lead to the formation of new combinations of these resistances in potential pathogens or also in environmental bacteria. These new antibiotic-resistant bacteria can be absorbed by people from the environment in the aforementioned ways. In the intestines, ARB can also be transferred to further bacteria in the intestinal flora. This means that the human gastrointestinal tract can be a reservoir for bacteria with antibiotic resistances. ARB can remain in the intestines for several months (Zimmermann 2013, Birgand 2013), and people can function as a vector ("carrier") for ARB. In the worst-case scenario, new, multi-resistant pathogens build up in the environment or in the intestines which are resistant to several antibiotics and can no longer be fought. Patients who have such pathogens in their intestines are able to bring them into hospitals or care homes as patients or visitors, where they can be transferred to sensitive patients who can also fall ill. Because of the antibiotic resistance, such infections are very difficult to treat, or in extreme cases, impossible to treat. To date, the risk of transferring ARG from waste water to environmental bacteria, for instance, and from there to pathogens, has only been studied on a rudimentary basis. The relevance of this pathway to the occurrence and dissemination of antibiotic-resistant pathogens is currently studied via HyReKa.

3.1 The reuse of reclaimed waste water

The European Commission currently supports the use of reclaimed waste water from municipal waste water treatment plants for the purposes of agricultural irrigation. From the perspective of UBA, this is associated with risks because reclaimed waste water can contain pathogens and chemicals. In this respect, antibiotics are not completely eliminated and can find their way into the environment through agriculture. Studies show that antibiotics can accumulate in soils which are irrigated with treated waste water (Fatta-Kassinos et al. 2011, Christou et al. 2017a). The absorption of antibiotics by plants has also been documented (Christou et al. 2017a). Field studies of tomatoes which were watered with reclaimed waste water over the course of three successive years provided documented evidence of the antibiotics sulfamethoxazole and trimethoprim in the soil and in the fruits of the tomatoes (Christou et al. 2017b). Findings of antibiotics in the groundwater can also be attributed to the application of reclaimed waste water to agricultural areas (Kinney et al. 2006, Ternes et al. 2007).

Since waste water treatment plants are a hotspot for the dissemination of antibiotic substances and antibiotic resistances, there is cause for concern that the use of treated waste water is a possible path for the dissemination of ARB and ARG. Targeted research into this topic is currently under way (e. g. Pina et al. 2018, http://www.nereus-cost.eu/).

3.2 Antibiotic-resistant bacteria in waste water from production facilities in third countries[4] and the import of such resistances to Europe

Waste water from the production of antibiotics in India or China is increasingly being discussed as a possible multiplier for the development of resistances. Very high concentrations of antibiotic substances are often found in the direct environs of production locations or in the surrounding environment, such as rivers. Samples from waters in Hyderabad and its surrounding environment in Southern India demonstrate (Lübbert et al. 2017) that an insufficient management of waste water in the production facilities can lead to the exceptionally high contamination of the water resources with antibiotic substances. This is associated with the selection and dissemination of specific antibiotic-resistant pathogens (such as carbapenemase producing pathogens). Carbapenems are used in Germany as reserve antibiotics for serious infections. There have also been increasing numbers of reports, mainly from doctors, about the increase in "imported" ARB in Germany due to growing levels of tourism in these regions. As a consequence of globalisation, EU citizens can be confronted with antibiotic resistances, that developed in non-EU countries e.g. due to emissions of antibiotic production sites and/or widespread use. In this respect, for example, 70 % of tourists from India are carriers of multi-resistant bacteria (Lübbert 2017)[5]. The initial results from the HyReKa project show that in this context, waste waters from airports are also a hotspot for ARB.

4 Third countries are generally countries which do not belong to the European Economic Area, which means countries that are not members of the European Union, not including Iceland, Liechtenstein and Norway.
5 https://www.umweltbundesamt.de/saicm-epi-fachgespraech-2017-zu-pharmaka-in-der#textpart-1

3.3 Antibiotic-resistant bacteria in drinking water

A majority of the drinking water in Germany is derived from protected bodies of groundwater which generally contain pathogens or ARB in exceptionally limited concentrations. Therefore, this drinking water does not need to be treated, or only to a limited degree. The treatment of the drinking water is oriented to the quality of the untreated water. In the case of protected groundwater, straightforward treatment without disinfection is sufficient. Surface waters or pristine groundwater, which is used for the extraction of drinking water is protected against anthropogenic influences such as faecal contamination through what are referred to as water protection zones. It is also subjected to comprehensive treatment which largely removes micro-organisms and pathogens effectively through a variety of differing step-by-step treatment stages such as bank filtration or flocculation filtration and disinfection (WHO 2017). The same applies to antibiotic-resistant bacteria. Drinking water is also monitored for potential faecal contamination that might be discharged into rivers via waste water effluents. is also monitored for potential faecal contamination that might be discharged into rivers via waste water effluents. In this respect, harmless intestinal bacteria such as *E. coli* and intestinal enterococci are used as indicators. If just one bacteria is found in 100 millilitres of water, the limit value is exceeded and an alarm is activated. The limit value for *E. coli* is in complied with in almost all of the samples in Germany[6]. At present, it is very unlikely for bacterial pathogens to find their way into the drinking water. At the same time, however, it is not possible to rule out the fact that according to the current levels of knowledge, for infections of people with antibiotic-resistant micro-organisms, as an infection path, drinking water is not relevant. It is, however, necessary to examine the extent to which resistance genes can break the barriers to the extraction and treatment of drinking water.

6 https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/umwelt_und_gesundheit_02_2015_trinkwasserbericht_des_bmg.pdf

SUMMARY

Antibiotic resistances can be passed from person to person (especially in hospitals) and from animals to people (e.g. in agriculture). From the environment, antibiotic resistances can be transferred to people through contact with poor-quality waters or with soils that have been treated with fertiliser. Antibiotics and ARB may also be ingested by people through food from cultivated areas which have been irrigated with reclaimed waste water. Through the simultaneous occurrence of increased concentrations of ARG, antibiotics, biocides and heavy metals in the environment, the formation of new combinations of these resistances in environmental bacteria can occur (also see p. 15). As a result of this, new ARB can occur and be transferred to the human intestinal flora. All of these contexts have so far only been examined on a rudimentary basis and require detailed clarification in order to minimise the transfer of antibiotic resistances from the environment to people. At present, the transfer of ARB to people through the consumption of drinking water is unlikely in Germany.

4 Research requirements and options for action to reduce the entry of antibiotics and antibiotic-resistant bacteria

Directly documented findings of both antibiotics and ARB in municipal waste waters, sewage sludge and slurry, as well as in environmental media such as soil, surface and groundwater, are methodologically determinable and have been submitted several times. It is more challenging to create a direct causal relationship between the use of a certain antibiotic and the increased dissemination of antibiotic resistances in the environment. The quantification of the associated risks for the individual and general health of the population is similarly difficult. Due to the high and increasing relevance, among others, caused by an increasing consumption of medicinal products, these contexts require urgent further research with regards to the existence and spread of antibiotic-resistant bacteria.

From the perspective of the UBA, despite open questions, action is now urgently necessary, as antibiotic residues from human and animal medicine as well as resistant bacteria and resistance genes have already been documented in the environment. In order to formulate effective options for actions, we differentiate between four levels of risk:

1. the impact of antibiotic substances in the environment on the affected ecosystems
2. the impact of antibiotic substances (in combination with co-selective substances such as metals) in the environment on the horizontal gene transfer;
3. the role of the environment as a reservoir for the antibiotic resistances and the associated build up of resistance;
4. the transfer of antibiotic resistances from the environment to people and the consequences for health.

The UBA considers a systematic monitoring of the input of antibiotics and antibiotic resistances into the environment to be urgently necessary. In addition to this, non-statutory, measures and statutory measures are very important. The latter require a considerable amount of time to prepare and transpose, which means they need to be anchored very early. The relationships between antibiotics and antibiotic resistances in the environment are currently being discussed in the EU and Germany. In this respect, the aforementioned German Antibiotics Resistance Strategy (DART), the "One Health Concept" of the EU, the announced European Union strategic approach to pharmaceuticals in the environment, the pending evaluation of the European Water Framework Directive, the revision of the European Urban Waste Water Treatment Directive and the "non-toxic environment" strategy are of considerable importance. Unfortunately, urgently necessary options for legislative action have not been included in the mentioned documents. For this reason, in this paper, the UBA has summarised the current level of knowledge on antibiotics and antibiotic resistances in the environment and defined areas of research and options for action.

4.1 Status of the research and research requirement from the perspective of the UBA

The principles of the input of antibiotic substances, antibiotic-resistant bacteria and resistance genes from hotspots have been researched in Germany in a limited number of investigations and studies. The results of the UBA research projects can be read in the final reports (see annex). In the TransRisk research project of the BMBF (sub-project of RiSKWa 2011–2014), it became clear that resistances are spread in the receiving waters of waste water treatment plants. The Academic Office of the German Federal Parliament (Deutscher Bundestag, 2018) has summarised research projects and studies on multi-resistant germs in the water and the possibility of their reduction through the treatment of waste water for Germany. In this respect, reference is also made to the joint HyReKA project supported by the BMBF (funding period: February 2016 to January 2019) which addresses the biological and/or hygienic relevance and control of antibiotic-resistant pathogens, antibiotic resistance genes and antibiotic residues in clinical, agricultural and municipal waste water, as well as rivers and lakes, and last but not least, drinking water. In this context, contamination situations and distribution pathways (risk assessment) should be identified and initial countermeasures should be formulated.

The UBA is currently compiling a report on the effects of antibiotic mixtures in soil. The literary research already shows that a mixture of different antibiotic substances frequently exists in slurry which is then applied to soil as fertiliser. The antibiotic mixtures have a negative influence on the biodiversity and functioning of soil micro-organisms and therefore contribute strongly to the development of resistances (Hegreness et al. 2008).

From the perspective of the UBA, several questions on the role of the environment as a medium for the occurrence and transfer, and as a reservoir for antibiotic resistances remain open:

- How stable are antibiotic-resistant bacteria in the aquatic and terrestrial environment? How long do they keep their resistance genes, also with additional stress factors such as heavy metals, biocides and antibiotic mixtures?
- What effects do antibiotic mixtures in the soil have on the function and composition of soil bacteria and soil fertility?
- What is the impact of stress factors such as heavy metals, biocides and antibiotic mixtures on the occurrence and transmission of resistance genes (co-selection)?
- Are long-term consequences for the ecological equilibrium to be expected due to the presence of increased amounts of resistant bacteria (reservoir function of the environment), and if yes, then which?
- In the area of the municipal and industrial treatment of waste water, what processes and combinations of processes are the most suitable for reducing antibiotics, resistance genes and antibiotic-resistant bacteria?
- Can the frequency of antibiotic resistances be limited due to ecological livestock keeping in comparison with conventional livestock keeping?
- How effectively are resistance genes reduced during the filtration processes for the treatment of drinking water (bank filtration, sand filtration)?
- Which resistance genes can be used as indicators for the presence of antibiotic-resistant bacteria?
- What are the results of a monitoring of resistant environmental bacteria, pathogenic bacteria or mobile elements that carry resistance genes in the environment and how are they to be assessed in health terms?
- What regulatory conclusions can be drawn from the results of the monitoring? Are maximum values for the concentration of resistant bacteria and free resistance genes necessary in bathing waters, for example? What measures should these trigger off?
- How stable are antibiotics, antibiotic metabolites and transformation products in the environment (water, sewage sludge, slurry, soil)? What impact do they have on environmental bacteria (including the meta-analysis of numerous publications to clarify gaps in the knowledge and the definition of open research questions)?
- What steps are urgently necessary to allow for a superior quantitative assessment of the risk posed to the population through an infection with multi-resistant pathogens as a result of resistance reservoirs and direct contact in the environment?
- How are sensitive groups of people (children, sick people, elderly people) to be taken into consideration, especially with the evaluation of the risk posed by the transfer of antibiotic-resistant bacteria and free resistance genes, e. g. the assessment of the safety of bathing waters?
- To what extent can resistance genes break through the barriers to the extraction and treatment of drinking water?

4.2 Options for action from the perspective of the German Environment Agency

Although the UBA continues to see a need for research, in terms of the precautionary principle, appropriate options for action should now be defined which take the ongoing discussions at the national and European level into account and are to be implemented throughout Europe.

The input paths of antibiotic active substances are in some cases identical to those of resistant bacteria. In certain cases, necessary options for action to reduce the entry of (i) resistant bacteria and/or (ii) active substances might differ.

In the following, options for action to reduce the entry of antibiotic substances and to reduce the occurrence of antibiotic resistances are presented. The variety of options for action ranges from notification measures for consumers, through to options for action for the improvement of the knowledge base, through to technical measures to reduce the input of antibiotics and the occurrence of antibiotic resistances.

The goal is to highlight options for action which encompass on a short- and long term horizon, non-statutory and statutory measures for reduction. Due to the relevance and urgency of the topic, as many options for action from this compilation as possible should be taken at the same time in order to prevent and/or limit the further occurrence and dissemination of antibiotic resistances in the environment.

I. PREVENTION

I. 1. The use of antibiotics should be limited to the medically necessary level. For this purpose, improved awareness and information is required in the area of human and veterinary medicine.

To minimize antibiotics and antibiotic resistances that enter the environment, antibiotics should be taken with caution. Consistent hygiene measures and the professional use of antibiotics for humans and animals should therefore be key for awareness rising.

I. 2. A species-appropriate animal husbandry can help to prevent illnesses. Pharmaceutical forms for application should be adapted to reduce the residues of antibiotics in excreta.

A risk-oriented, preventive form of health management is urgently necessary in the keeping of agricultural livestock, as antibiotics which are not used in the first place cannot contaminate the environment. Above all else, the preventive measures include husbandry conditions which prevent illnesses, the strengthening of the animals' immune systems, and the systematic monitoring of their health (www.uba.de/tierarzneimittel). During the prescribing and administration of antibiotics, savings in the quantities of active substances can be made by choosing the appropriate pharmaceutical form for the application (e.g. by changing from oral to injection, since some active substances are better absorbed by the intestinal passage, leading to fewer residues in the excreta). Providing farmers with detailed advice on the precise dosage, the duration and regularity of use, the correct storage and disposal and compliance with veterinary advice help to ensure the success of the therapy and prevent unnecessary harm to the environment.

II. COMMUNICATION

II 1. Doctors, pharmacists, veterinarians and farmers must be informed and trained on the topic of antibiotics in the environment in a target-group-specific way.

A comprehensive programme of information and training on the topic of antibiotics and the environment should contribute to the enlightening of specific target groups. In addition to an EU strategic approach, at the national level, it is necessary to clarify how the relevant groups which prescribe and use the antibiotics can be informed and trained on a targeted basis. The UBA published conceptual deliberations and recommendations on the provision of target group oriented training and information in 2017 (Vidaurre et al. 2017). The UBA information page "Veterinary pharmaceuticals in the environment" also provides a variety of tips for minimising the input of antibiotics as well as information for farmers, veterinarians and consumers (www.uba.de/tierarzneimittel).

II 2. Campaigns on the correct disposal of antibiotic residues are necessary.

Information on the correct and environmentally sound use and disposal of antibiotics should be available for all participants in the area of healthcare as well as for farmers, veterinarians and patients. This should also be integrated in a target group specific form of education and training. Campaigns throughout Germany should also highlight the role of the environment as a "reservoir" for the input of antibiotic substances and the resulting consequences. The role of the environment in the horizontal transfer of genes and the reservoir function should be integrated in the education and further training of doctors and veterinarians.

III. THE AUTHORISATION OF ANTIBIOTICS AS A MEDICINAL PRODUCT

III. 1. Develop and implement assessment methods and criteria for antibiotics and antibiotic resistances.

For the possible encouragement of the occurrence of resistances due to the input of the assessed antibiotics into the environment, it is necessary to develop assessment methods and criteria which should be included in the guidelines for the environmental risk assessment of human and veterinary medicinal products.

III. 2. Develop and implement a risk assessment for the occurrence of resistances in the scope of the post-authorisation control of antibiotics and antibiotic resistances in human and veterinary medicinal products.

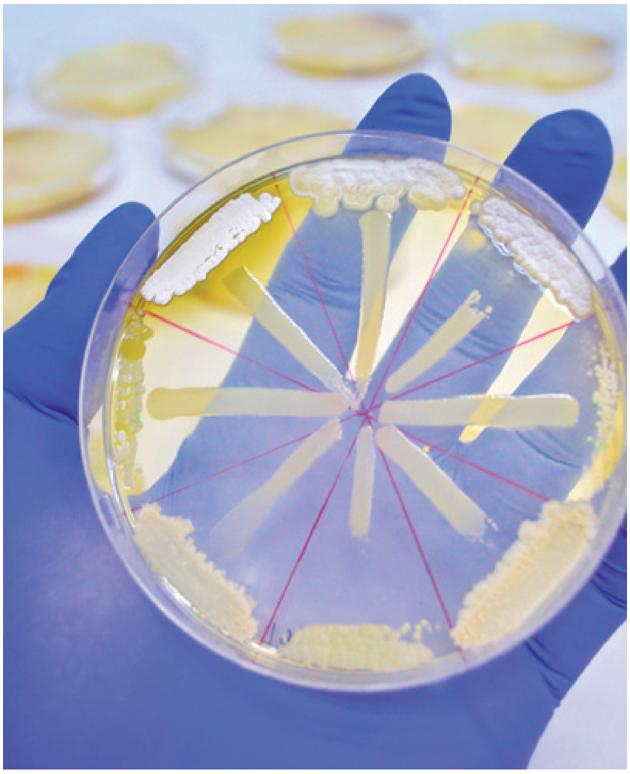
To date, there has been a lack of methodical principles that would enable a forecasting of the existence, development and spread of antibiotic resistances in the environment. It remains unclear which concentration of an antibiotic substance is able to foster resistance, either in a living organism or in an environmental compartment. Therefore, measurements of antibiotics and antibiotic resistances are required in the scope of the post-authorisation control. It is equally necessary to develop standardised test methods as well as risk assessment approaches to document the extent of the emissions.

III. 3. Publish environmental data from the authorisation of antibiotics.

The environmental risk assessment for the authorisation provides valuable substance-related information which can be used for the deriving of environmental quality standards as regards the legislation on water. However, such environmental data from the authorisation is not yet available to the public and should therefore be urgently collated in a publicly accessible, Europe-wide database.

III. 4. Develop a substance-based environmental assessment for antibiotics (monographs) and publish harmonised end points.

The assessment criteria for medicinal products require urgent improvement by moving away from a product-based environmental assessment and towards an active substance-based (monographs system) view. In this respect, the environmental data concerning active substances should be included in "master files" which provide an overview of the environmental characteristics of substances. In this way, it is possible to identify gaps in the data for antibiotics which have already been on the market for a very long time and which did not have to pass an environmental risk assessment upon their authorisation.



III. 5. Include environmental considerations in the risk-benefit analysis for the authorisation of antibiotics for human medicine.

As is already the case with veterinary medicinal products, risks to the environment should be considered in a risk-benefit analysis, so that the risk of the occurrence of antibiotic resistances can be taken into account during the authorisation, and possible risks can be adequately documented in the post-authorisation control of antibiotic products (pharmacovigilance).

IV. DIRECT AND INDIRECT DISCHARGE OF WASTE WATER/MUNICIPAL AND INDUSTRIAL WASTE WATER TREATMENT PLANTS

IV. 1. Identify hotspots for the discharge of antibiotics and antibiotic resistances.

Prior to the implementation of measures for the reduction of antibiotic substances and antibiotic-resistant bacteria from municipal waste water [waste water from (urban) settlements and waste water discharged by production facilities via municipal waste water treatment plants], a screening of the relevance of entry paths should initially take place in order to identify possible "hotspots". There should also be a focus on healthcare institutions, such as hospitals and care homes, as well as airports, but also on slaughterhouses.

IV 2. Develop monitoring guidelines to be able to better monitor the discharge of antibiotics and antibiotic resistances into municipal and industrial waste water

In addition to this, a systematic monitoring of differing antibiotic substances, ARB and ARG must also occur in order to be able to forecast the actual scope of the environment as a reservoir for antibiotic resistances. Guidelines for these measurements and analyses require urgent development so as to obtain harmonised results. It is also necessary for biofilms (a layer of mucus consisting of micro-organisms which can also contain ARB and ARG) to be examined in the area of these facilities as well as sewage sludge, if it is intended for application on agricultural land. At the same time, the quantity and variety of the antibiotic substances and ARB that enter into the environment should also be taken into account. On the other hand, facilities where the treated waste water is discharged into sensitive waters (bathing waters, drinking water resources) should be examined as a priority.

IV 3. Address antibiotic residues and antibiotic resistances adequately in the statutory waste water provisions.

To date, there have not been any specific requirements concerning medicinal products and/or antibiotics regarding their discharging from municipal waste water in the European Urban Waste Water Treatment Directive (91/271/EEG, UWWTD) and in the German Waste Water Ordinance (Abwasserverordnung, AbwV). Cumulative parameters regarding the discharging of waste water from production, such as the chemical oxygen demand (COD), are stated in the annex to the German Waste Water Ordinance. The COD parameters serve the purpose of the documentation of the degradation efficiency and/or elimination performance of biological waste water treatment plants; with the cumulative parameters, the specified toxicity values towards specific organisms may not be exceeded. Specific requirements concerning individual antibiotic substances (individual substances) are yet to be determined. Following verification, these loopholes should be closed in the pending review, where necessary.

IV. 4. Extend the assessment criteria and quality characteristics for the treatment performance and quality of the effluent from municipal and industrial waste water treatment plants.

Equally, to date, no specific requirements concerning medicinal products, or hygiene-microbiological parameters have been determined in current European law or the German Waste Water Ordinance (AbwV). To date, the quality of effluent from waste water treatment plants is insufficiently examined to make statements concerning the input of antibiotics, ARB and ARG from waste water treatment plants.

In Germany, to date, emissions of pathogens, antibiotic-resistant bacteria and antibiotic resistance genes have not been regulated, either in terms of regulatory law (Waste Water Ordinance) or tax law (Waste Water Charges Act). Conventional waste water treatment plants only reduce bacteria – including ARB and ARG – by 2–3 decimal power. Since the concentrations in untreated waste water, primarily from "hotspots" are very high, the reduction by conventional waste water treatment plants is insufficient. The current assessment criteria of the treatment performance of municipal waste water treatment plants should therefore be extended with new chemical, eco-toxicological and microbiological parameters (also see TransRisk). If the treated waste water is discharged into sensitive waters (bathing waters, drinking water resources), a more advanced treatment of the waste water may also be necessary.

IV. 5. Improve the technology at waste water treatment plants.

The technology used at municipal waste water treatment plants is not currently configured for the complete elimination of poorly biodegradable compounds such as certain antibiotics (UBA 2018), nor for a sufficient reduction of pathogens or ABR. It is only possible to remove a wide range of antibiotics with an appropriately more advanced level of treatment. It is also necessary to remember that the processes for the reduction of antibiotic substances (e. g. low concentrations of ozone and activated carbon) are unable to effectively minimise bacteria (including ARB) in the waste water.

The UBA therefore recommends the introduction of the more advanced treatment of waste water at large-scale waste water treatment plants (size category 5, approx. 50 % of the volume of waste water in Germany) and smaller waste water treatment plants which discharge into waters with sensitive uses (e. g. the extraction of drinking water and bathing waters). In this respect, the applied technology must be determined on site and at the different sources as well as based on the composition of the differing micro-pollutants, pathogens and antibiotic resistances.

IV. 6. Compile the production locations and examine the emissions from production facilities.

The production of antibiotics in Germany constitutes a possible input path into the environment for antibiotic substances. At the national level, the federal states are responsible for the monitoring of production facilities. To date, no measurement results are available, as there is no statutory requirement for measurements concerning individual antibiotic substances. For this reason, the production locations should be listed, and a systematic monitoring of the waste water should be carried out.

IV. 7. Revise the reference document on the best available techniques for the production of organic fine chemicals (OFC) and/or corresponding reference documents, and update them regarding emissions from the production of antibiotics.

At the European level, the environmental requirements concerning the production of medicinal products are governed by the Industrial Emissions Directive (IE Directive). Specific environmentally-related requirements, such as the monitoring requirements or the limiting of emissions for different parameters specifically for the individual sectors and/or categories of activities listed in Annex I of the IE Directive, and/or for individual production processes, are set out in the “best available technique reference documents” (BAT documents).

At present, antibiotics are recorded as medicinal products in the BAT document for the production or organic fine chemicals (OFC BREF). With regard to emissions from water, the CWW BREF (Best Available Techniques for Common Waste Water and Waste Gas Treatment/Management Systems in the Chemical Sector) also applies to all chemical facilities. In the future, the WGC BREF (Common Waste Gas Treatment in the Chemical Sector) will apply to the treatment of exhaust gases. In Germany, this is implemented in Annex 22 of the Waste Water Ordinance and/or in the Technical Instructions on Air Quality Control (TA Luft), the requirements of which also apply to the production of medicinal products. In the pending reviews of the statutory provisions at the national and EU level, antibiotic substances and antibiotic resistances in the waste water from production facilities should be measured, and documented in the respective reference documents.

IV. 8. Implement environmental considerations in the "Good Manufacturing Practice" requirements for the production of antibiotics and in trade agreements.

The production of antibiotic substances for the European market, particularly of generic medical drugs, primarily takes place in Asia, where to date, environmental considerations have not been respected, or only to a limited degree. The emissions of antibiotics and antibiotic resistances during the production of active substances as well as through the "formulation" of medicinal end products in Germany, the EU and third countries should therefore be measured and reduced as required. The environmental emissions should also be incorporated in the guidelines regarding good manufacturing practice (GMP), i.e. quality assurance. These requirements could also be taken into account in trade agreements with third countries. These measures can prevent ARB and ARG which occur through production in third countries from entering the EU and/or Germany through goods or tourism.

V. SURFACE WATERS/BATHING WATERS/ GROUNDWATER

V. 1. Develop monitoring guidelines and assessment concepts for the monitoring of antibiotic resistances in surface and bathing waters (if the indicator parameters are not considered sufficient).

The Bathing Waters Directive contains indicator parameters (*E. coli* and intestinal enterococci) for the extent of faecal contamination. Since most of the clinically relevant ARB result from faecal contamination (due to either direct input or an increase in the concentration of nutrients), these indicator parameters provide a reference to the likelihood of the occurrence of ARB. The question of whether a special monitoring of ARB is necessary in bathing waters must be discussed subsequent to the availability of the results of the HyReKa and the measurement programmes of the federal states concerning ARB in bathing waters.

V. 2. Include antibiotics and antibiotic resistances in the Water Framework Directive.

Antibiotic substances which are measured in waters are considered to constitute chemical contamination. These substances must be monitored and reduced on a continuous basis through the determination of environmental quality standards. At present, the aforementioned antibiotic substances azithromycin, clarithromycin and erythromycin (see section 2) are measured by the federal states in the scope of the watch list mechanism of the EU. To date, however, no overview of the antibiotic resistances in waters has been made available for Germany and the EU. The Surface Waters Ordinance (OGewV) must therefore be adapted at the national level, and the list of "priority substances" at the EU level, so that the relevant substances can be measured on a regular basis and their concentrations can be reduced.

V. 3. Take antibiotic resistances into account in the deriving of environmental quality standards.

To date, antibiotic resistances in waters have not been systematically documented or subjected to statistical evaluation. The objectives of the Water Framework

Directive refer to the protection of water and the protection of human health. Human health can be put at risk, for example, through the consumption of fish which contain antibiotics or antibiotic resistances. When deriving environmental quality standards for antibiotics, their ability to trigger resistances should therefore be taken into account.

V. 4. Reduce the input of antibiotic resistances into surface and bathing waters, e. g. through the widening of riparian strips and the designation of water protection zones.

The input of antibiotic resistances and antibiotic resistance genes into water which is attributable to human activity, particularly livestock keeping, can be reduced at the local level through the widening of riparian strips, which prevents run-off and drifting into waters from the application of slurry. A consistent designation of water protection zones at the regional level is also a possible measure for reducing the input of antibiotic resistances.

V. 5. Introduce a threshold value for antibiotics in the legislation concerning groundwater.

For precautionary reasons, the UBA recommends the introduction of a threshold value at the national and European level for antibiotics for groundwater which is equivalent to the limit values for plant protection products and biocides. On this basis, in the event of exceedance, the statutory basis would be provided for the regular verification of the groundwater and measures of a more advanced nature.

VI. FERTILISERS USED IN AGRICULTURE

VI. 1. Prohibit the application of sewage sludge onto soil and use sewage sludge for the recovery of phosphorous (this also reduces the contamination by antibiotics in P-recycling products)

Through the revised version of the Sewage Sludge Ordinance (AbfKlärV), in the future, the direct use of sewage sludge for fertilising purposes is to be prohibited for large-scale waste water treatment plants with more than 50,000 population equivalents (PE), and the recovery of phosphorous is to be scheduled at the same time. From 2029 and/or 2032, the soil-related recovery of sewage sludge from waste water treatment plants > 100,000 and/or > 50,000 PE will no longer be possible. Smaller waste water treatment plants can continue to recover for soil-related purposes, however. Detailed assessments of the risk of the use of sewage sludge as a fertiliser should therefore be carried out. A research project of the UBA shows that phosphorous recyclates contain considerably more limited residues of antibiotics and medicinal products than the initial sewage sludge. In particular, the thermal recovery of phosphorous leads to the simultaneous sanitisation of the sludge. In the long term, there should be efforts to complete withdraw from agricultural use of sewage sludge on the national and EU level.

VI. 2. Needs-based fertilisation – demand assessments for fertilisers on the basis of in-house analyses (soil analysis, nutrient content of farm fertiliser).

By reducing the quantities of farm fertiliser used, the fractions of antibiotics in the environment can be directly decreased. With a constant level of application and without the use of a mineral-based supplementary fertiliser, this can only be achieved on the basis of a clear increase in the effectiveness of farm fertiliser, however. For this purpose, a realistic and location-adapted needs assessment for fertiliser is urgently necessary. In this respect, the provisions in the revised national Fertilisers Ordinance are an initial basis, but can still be adapted in several places. Therefore, the in-house values of soil analyses and measurements of the nutrient content of farm fertiliser must be preferred over the standard values.

Measures to reduce the quantities of agricultural fertilisers indirectly serve the purpose of reducing fractions of antibiotics in the environment. The less slurry applied, the fewer antibiotics find their way into the environment, where they have the risk of having an unwanted impact. In the regions of Germany in which the intensive keeping of livestock takes place, there is a considerable excess of Nitrogen and Phosphorous. This makes it clear that excessive amounts of fertiliser are being used which are superfluous to the requirements of the crops. Therefore, a further tightening of the legislation on fertilisers is not just able to reduce the excessive use of fertiliser, it can also minimise the input of antibiotics.

VI. 3. Introduce the compulsory documentation of the antibiotics used in livestock stables and the co-selectors of zinc and copper used as animal feed during the respective production period of the slurry.

Since the occurrence and dissemination of resistances is to be expected, even with low concentrations of antibiotics, and is strengthened by zinc and copper, it is above all important to know the antibiotic substances and the quantities of zinc and copper present in the slurry. The documentation of the quantities of antibiotics present in slurry can be linked with the compulsory documentation on the use of antibiotics in the rearing of livestock without the requirement for further analysis. Specifically, the total quantities used and the types of antibiotic substances should be collated and documented together with the quantity of zinc and copper used as feeding stuffs in the respective operations for the time taken to produce a sufficient quantity of slurry for one whole slurry tank. This could be supplemented in the already compulsory documentation of the nutrient contents (Art. 3, 4 and 10 of the Fertilisers Ordinance), and is possible with a relatively low level of effort.

The Ordinance on the Marketing and Transport of Farm Fertiliser governs the requirements and principles surrounding the distribution of farm fertilisers. As part of the documentation of the contents of the farm fertilisers the antibiotic content of the slurry could also be determined. It would also be possible to document the copper and zinc content in externally purchased feeding stuffs. This documentation of the contamination situation is also important in order to prevent the mixing of farm fertilisers that are contaminated with different antibiotic substances, e. g. through their intermediate storage or use in biogas plants, and/or to link them to hygiene measures.

VI. 4. In the form of slurry delivery notes, pass on information concerning the production and transport of slurry and its application on the soil.

On the basis of this requirement for documentation, the quantity of antibiotics used, the antibiotic substances as well as the zinc and copper contents, together with the other slurry parameters required for documentation (including the N and P content) could be included in a slurry delivery note, and transferred throughout the life cycle of the slurry up until its application on the soil. This allows for a more specific monitoring of the farm fertilisers that are contaminated with antibiotics and which are used by several different farmers.

VI. 5. Develop guidelines for methods and assessment concepts for the monitoring and verification of hygiene-microbiological parameters for stable manure, slurry, fermentation residues and composts made from slurry as well as sewage sludge

To date, prior to their use as farm fertiliser, slurry, manure, fermentation residues and sewage sludge as well as waste water have not generally been verified for antibiotic residues, ARB or ARG. In the framework of the circular economy, cost-effective and easy-to-use methods for the measurement of antibiotics, ARB and ARG should be developed and legally specified, and specific parameters should be monitored. Continuous systems for the storage of slurry, for example, possibly in biogas plants, are particularly critical. Here, the slurry is moved back and forth over long periods without completely emptying the system. This makes the development and spread of a reservoir of multi-resistant bacteria possible. The development of antibiotic resistances in biogas plants that are operated with contaminated slurry should also be monitored on a regular basis.

VII. SOIL

VII. 1. Examine the dissemination of antibiotic residues and antibiotic-resistant bacteria through sampling at selected arable farmland locations throughout Germany, and define precautionary and possible limit values for antibiotics as well as zinc and copper in the soil.

Although documented findings are available on the impact of antibiotics on soil organisms and their activities, as well as the structural composition of soil organisms (Thiele Bruhn 2005), the current data basis is insufficient for the derivation of environmental quality standards or precautionary values for antibiotic residues in the soil in the scope of the Federal Soil Protection and Contaminated Sites Ordinance (BBodSchV). For this reason, selected locations identified as being subject to the regular application of sewage sludge and slurry should be examined at which known co-factors for the forming of resistances occur. On such a basis, in a next step, suitable measures can be derived and implemented, such as prohibiting the application of slurry and sewage sludge at especially noticeable locations.

Precautionary values for the concentrations of antibiotics in slurry should be developed in order to prevent what is known as an “accumulation” of persistent antibiotic residues in the soil due to the repeated application of slurry. The derivation of a cumulative parameter on the basis of indicator substances for individual groups of antibiotic substances which would be incorporated in the development of the cumulative parameters via toxicity equivalents according to their intensity would be conceivable. The input of zinc and copper (used as feed additives) into the soil via the slurry also enforces the selection pressure and the spread of antibiotic resistances. As zinc and copper remain in the soil for a very long time, it is also appropriate to define upper limits for the application of zinc and copper in the soil so as to prevent an accumulation of these substances.

4.3 Summary of the Options for action

In the following, the options for action from section 4.2 for reducing the environmental input of antibiotic substances and antibiotic resistances are summarised in a table. From the perspective of UBA, the non-statutory measures need to be complemented by statutory measures. The following table provides information on the regulatory framework and timetable as well as the necessary target groups/level for the respective measures. Due to the relevance and urgency of the topic, as many options for action from this compilation as possible should be implemented at the same time in order to prevent and/or limit the further occurrence and dissemination of antibiotic resistances in the environment.

Tabelle 1

Measures for the reduction of the environmental entry of antibiotic substances (AS), antibiotic resistances (AR) from human (HMP) and veterinary medicinal products (VMP)

Option for action	Entry of/ Reduction goal	HMP or VMP	Legal background	Effectiveness horizon*	target group/level
I. 1. Prevention The use of antibiotics should be limited to the medically necessary level. For this purpose, improved awareness and information is required in the area of human and veterinary medicine.	AS, AR	HMP, VMP		short term	Doctor / Veterinarian
I. 2. Prevention A species-appropriate animal husbandry can help to prevent illnesses. Pharmaceutical forms for application should be adapted to reduce the residues of antibiotics in excreta.	AS	VMP		short term	Farmer / Veterinarian
II. 1. Communication Doctors, pharmacists, veterinarians and farmers must be informed and trained on the topic of antibiotics in the environment in a target-group-specific way.	AS	HMP, VMP		short – medium term	EU, national, regional
II. 2. Communication Campaigns on the correct disposal of antibiotic residues are necessary.	AS	HMP, VMP		short – medium term	EU, national, regional
III. 1. Authorisation Develop and implement assessment methods and criteria for antibiotics and antibiotic resistances.	AS, AR	HMP, VMP	2001/82/EC 2001/83/EC (EC) No 726/2004 AMG	medium term	EU

Option for action	Entry of/ Reduction goal	HMP or VMP	Legal background	Effectiveness horizon*	target group/level
III. 2. Authorisation Develop and implement a risk assessment for the occurrence of resistances in the scope of the post-authorisation control (pharmacovigilance) of antibiotics and antibiotic resistances in human and veterinary medicinal products.	AR	HMP, VMP	2001/82/EC 2001/83/EC (EC) No 726/2004 AMG	medium term	EU
III. 3. Authorisation Publish environmental data from the authorisation of antibiotics.	AS	HMP, VMP	2001/82/EC 2001/83/EC (EC) No 726/2004 AMG	short – medium term	EU
III. 4. Authorisation Develop a substance-based environmental assessment for antibiotics (monographs) and publish harmonised end points.	AS	HMP, VMP	2001/82/EC 2001/83/EC (EC) No 726/2004 AMG	short – medium term	EU
III. 5. Authorisation Include environmental considerations in the risk-benefit analysis for the authorisation of antibiotics for human medicine.	AS, AR	HMP	2001/83/EC (EC) No 726/2004 AMG	medium term	EU
IV 1. Waste water treatment plants Identify hotspots for the discharge of antibiotics and antibiotic resistances.	AS, AR	HMP			
IV. 2. Waste water treatment plants Develop monitoring guidelines to be able to better monitor the discharge of antibiotics and antibiotic resistances into municipal and industrial waste water.	AS	HMP	91/271/EEC 2010/75/EU Waste Water Ordinance	medium term	EU, national
IV 3. Waste water treatment plants Address antibiotic residues and antibiotic resistances adequately in the statutory waste water provisions.	AS, AR	HAM, TAM	91/271/EEC 2010/75/EU Waste Water Ordinance	medium term	EU, national
IV. 4. Waste water treatment plants Extend the assessment criteria and quality characteristics for the treatment performance and quality of the effluent from municipal and industrial waste water treatment plants.	AS	HMP, VMP	91/271/EEC 2010/75/EU Waste Water Ordinance	medium term, long term	EU, national
IV 5. Waste water treatment plants Improve the technology at waste water treatment plants.	AS, AR	HMP, VMP	91/271/EEC 2010/75/EU Waste Water Ordinance	medium term, long term	EU, national
IV. 6. Waste water treatment plants Compile the production locations and examine the emissions from production facilities.	AS	HMP, VMP	2010/75/EU Waste Water Ordinance	medium term	International, EU

Option for action	Entry of/ Reduction goal	HMP or VMP	Legal background	Effectiveness horizon*	target group/level
IV. 7. Waste water treatment plants Revise the reference document on the best available techniques for the production of organic fine chemicals (OFC) and/or corresponding reference documents, and update them regarding emissions from the production of antibiotics.	AS	HMP, VMP	2010/75/EU	medium term	EU
IV. 8. Waste water treatment plants Implement environmental considerations in the "Good Manufacturing Practice" requirements for the production of antibiotics and in trade agreements.	AS	HMP, VMP	2001/82/EC 2001/83/EC (EC) No 726/2004 2003/94/EC 1991/412/EEC	medium term	EU
V 1. Waters Develop monitoring guidelines and assessment concepts for the monitoring of antibiotic resistances in surface and bathing waters.	AR	HMP, VMP	2008/105/EC Surface Waters Ordinance Bathing Waters Ordinance	medium term	EU, national
V. 2. Waters Include antibiotics and antibiotic resistances in the Water Framework Directive.	AS, AR	HMP, VMP	2000/60/EC 2013/39/EU Surface Waters Ordinance	medium term	EU, national
V. 3. Waters Take antibiotic resistances into account in the deriving of environmental quality standards.	AR	HMP, VMP	2000/60/EG 2013/39/EU OGewV	medium term	EU, national
V. 4. Waters Reduce the input of antibiotic resistances into surface and bathing waters, e. g. through the widening of riparian strips and the designation of water protection zones	AR	HMP, VMP		short – medium term	regional, municipal
V. 5. Waters Introduce a threshold value for antibiotics in the legislation concerning groundwater.	AS	HMP, VMP	2006/118/EC Groundwater Ordinance	medium term	EU, national
VI. 1. Agriculture Prohibit the application of sewage sludge onto soil and use sewage sludge for the recovery of phosphorous.	AS, AR	HMP	86/278/EEC Sewage Sludge Ordinance	medium term	National, EU
VI. 2. Agriculture Needs-based fertilisation – demand assessments for fertilisers on the basis of in-house analyses (soil analysis, nutrient content of farm fertiliser).	AS	VMP	(EC) no. 162/2007 Fertilisers Ordinance	medium term	EU, national

Option for action	Entry of/ Reduction goal	HMP or VMP	Legal background	Effectiveness horizon*	target group/level
VI. 3. Agriculture Introduce the compulsory documentation of the antibiotics used in livestock stables and the co-selectors of zinc and copper used as animal feed during the respective production period of the slurry.	AS, AR	TAM	(EC) no. 162/2007 Fertilisers Ordinance Fertilisers Act	short term	EU, national
VI. 4. Agriculture In the form of slurry delivery notes, pass on information concerning the production and transport of slurry and its application on the soil.	AS, AR	VMP	(EC) no. 162/2007 Fertilisers Ordinance	medium term	EU, national
VI. 5. Agriculture Develop guidelines for methods and assessment concepts for the monitoring and verification of hygiene-microbiological parameters for stable manure, slurry, fermentation residues and composts made from slurry as well as sewage sludge.	AS, AR	VMP	(EC) no. 162/2007 Fertilisers Ordinance	medium term	EU, national
VII. 1. Soil Examine the dissemination of antibiotic residues and antibiotic-resistant bacteria through sampling at selected arable farmland locations throughout Germany, and define precautionary and possible limit values for antibiotics as well as zinc and copper in the soil with respect to the impairment of soil functions.	AS, AR	HMP, VMP	Soil Protection Ordinance	medium term	national

*effectiveness time frame: short term ‹ 5 years, medium term ‹ 10 years, long term › 10 years

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FKZ 201 61 211:
Nachweis der Übertragung Antibiotika-resistenter Bakterien und ihrer Resistenzgene auf den Menschen über verschiedene Umweltmedien wie pflanzliche Nahrungsmittel oder Oberflächenwasser in Badegewässern (2001–2003).

FKZ 3711 71 240:
Risikoanalyse der bodenbezogenen Verwertung kommunaler Klärschlämme unter Hygieneaspekten. (2011–2014)

FKZ 3712 61 209:
Hygienische Risiken bei der landwirtschaftlichen Verwertung von Klärschlamm durch die Aufnahme von Infektionserregern in Kulturpflanzen (2012–2016).

FKZ 3717 34 342 0:
Erarbeitung anspruchsvoller Standards für die mittelfristige Fortführung der bodenbezogenen Verwertung von Klärschlämmen aus Abwasserbehandlungsanlagen mit kleiner Ausbaugröße (2017–2019).

FKZ 3711 63 423:
Entstehung und Ausbreitung von Antibiotika-Resistenzen in Mikroorganismen unter umweltrelevanten Arzneimittel-Konzentrationen, Berücksichtigung dieser Umweltwirkung bei der Umweltrisikobewertung von Arzneimitteln (2011–2013).

FKZ 3713 63 402:
Antibiotika-Resistenzentwicklung als Endpunkt in der Umweltrisikobewertung antibiotischer Wirkstoffe; experimentelle Methodenüberprüfung (2013–2017).

Project No. 92954:
Literaturstudie zum Umweltrisiko durch Antibiotikagemische in Böden (2017–2018).

FKZ 3715 33 4010:
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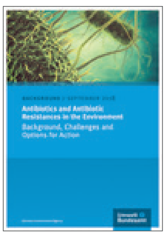

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