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position paper

Pharmaceuticals in the environment

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Foreword

The policy perspective of BUND/Friends of the Earth Germany and the “BUND Positions”

The world is facing tremendous ecological and social challenges. BUND/Friends of the Earth Germany designs and promotes solutions to these challenges which conform to ecological and social sustainable development criteria. As an environmental and nature protection NGO, BUND/FoE Germany is fighting, in particular, to limit global heating to 1.5°C and for climate justice, to end the loss of biodiversity, and for the protection and appreciation of nature. For this behalf, we demand policies initiating and catalysing transitioning towards a truly sustainable agriculture without genetic engineering (regardless if old or new GMO¹ technologies are involved), immediate decommissioning of nuclear power, decarbonizing economy and society within 20 years, and reducing the consumption of resources. BUND's campaigns aim at ending the domestic and global dumping of industrial and household waste, terminating the poisoning of our environment with pesticides, giant numbers of potentially harmful substances in innumerable mixtures, including micro- and nano-plastics. As Germany's largest sustainability NGO, BUND/FoE Germany works for social and ecological justice, fights poverty and promotes human rights and democracy. Our experience has shown us that you cannot achieve one without the other.

Such goals cannot be achieved by just fully exploiting all environmental and socially sustainable options for increasing resource use efficiency. To reduce human resource extraction from the environment in absolute terms we also need sufficiency: we have to consume not only differently, but also less. Pivoting towards a sustainable change in the way of life of all citizens is not an individual responsibility, but a joint and social one. Enhancing the common good requires not only to have more participation rights, but, above all, a supportive political framework. This is why for a long time BUND/FoE Germany has been calling for energy savings to cut final energy consumption by

at least half so that the remaining needs can be met from renewable energy sources – studies by the German Federal Environment Agency confirm these demands.

To halt the extinction of more and more species and to protect our natural spaces, then the ever-increasing use of land for roadways as well as commercial and residential infrastructure must finally be ended, while agriculture needs to be transformed to comply with environmental and animal welfare criteria. The consumption of raw materials must be drastically reduced in the course of this century, for example by a factor of 10 or more. A rapid and massive lowering would help overcoming the climate crisis, stopping the loss of biodiversity and giving future generations the same development opportunities in all countries.

Our economic system has to become leaner in terms of material and energy use. This is a huge challenge, but it can be accomplished. However, mastering this task will become impossible if politics continues to prioritise economic growth over the preservation of the basics of nature and human subsistence. Economic growth policy, whether succeeding in stimulating economic growth or not, is the driver of havoc being wrecked on nature and the planetary health. Examples include the expansion of infrastructure with excessive land consumption (airports, roads, expansion of waterways), the promotion of export-oriented agriculture with animal stocks that are far too high, and much more. Economic growth policy calls for and causes low-wage sectors, income polarization and a predatory global economy. Democratic decisions and citizen participation are increasingly being eroded, undermined by regulations accelerating spatial planning and by weakening citizen rights to legally holding government to account. Governments on all levels, inspired by neoliberal policies, have enacted such

¹ GMO: Genetically Modified Organism

regulations believing this would accelerate economic growth.

The necessary socio-ecological transformation offers the chance to live a good life within the planetary boundaries under living and working conditions characterised by more justice and community spirit, and less egoism, competition and exploitation. A lot of fellow citizens has recognized how necessary such a turn to the good life is, not least in the pandemic crisis since 2020. Working relations and conditions and ways of life will change, and be have to change, driven by new technologies as much as by strong sustainable consumption and by new, sustainable forms of good remunerated and voluntary work. This will require not only new job profiles and qualifications, but also that status, pay and social security are improved in many areas of business and administration.

BUND/FoE Germany stands not only for ecological, but also for social, institutional and economic sustainability – that is why publications from our Positions paper series include approaches contributing to social justice, good work and sustainable economic activity. Thinking outside the box, BUND/FoE Germany develops new perspectives together with the partner organizations in our international network, Friends of the Earth Europe and Friends of the Earth International, and with other civil society organizations which share our vision. As BUND/FoE Germany is not linked to any political party and – proudly – also financially independent from government funding and business donations, and enters no partnerships with commercial groups or entities, we are free to choose the right partners among, for instance, consumer, development, feminist or peace NGOs, trade unions and religious organisations.

There are alternatives to a policy that is approaching a dead end at ever higher speed! BUND/FoE Germany presents such alternatives in the Position papers, which are conceptualised and drafted by 20 scientific working groups at the national level and refined by Scientific Board in an inter- and transdisciplinary process, before they are finally adopted by the BUND/FoE Germany board. In the scientific working groups, academic and non-academic expertise work together at eye level, and in the Scientific Board the draft Positions are interdisciplinarily cross-examined by experts from 20 subject disciplines or subject areas. BUND/FoE Germany has been practicing and refining inter- and transdisciplinary science for more than 40 years now. Hence the BUND/FoE Germany Positions are based on socially robust and evidence based interdisciplinary scientific knowledge as the basis for suggestions and demands for political and social solutions to sustainability problems. They are the knowledge base for campaigning, public mobilisation, environmental education, political lobbying, managing high biodiversity value land and other BUND/FoE Germany activities.

Each Position, including this one, is an important element contributing to an overall strategy for a socio-environmental transformation towards a sustainable economy, society and private life.

Abstract

Medicinal products are physiologically highly active substances that enter the water and soil, particularly through human and animal excretion. They are being detected in the environment to a greater and greater extent, often in concentrations that are not harmless to humans and other living organisms. The consumption of pharmaceuticals is increasing, mainly due to the aging of the population. Consequently, measures to reduce environmental pollution are therefore necessary.

The widespread use of antibiotics in farm animal husbandry poses a particular problem, as it may promote the development of (multi)resistant bacteria. Antibiotic residues in water and soil can even contribute to the formation and spread of resistance. Since almost no new classes of antibiotic substances are being developed and approved, the administration of reserve and broad-spectrum antibiotics to animals in particular is posing a major problem for the treatment of human infections. Widespread mass animal husbandry is inconceivable without the intensive use of veterinary medicines. A fundamental change in husbandry conditions is thus necessary, not only to promote animal welfare.

Since 2006, the assessment of environmental risks has been part of the approval process for medicinal products, – a significant advance. However, the procedure is deficient and – in the case of medicinal products for human use – toothless. Combination effects are not being taken into account, nor are special modes of action or the development of resistance to antibiotics. Existing medicinal products that were approved before 2006 are still on the market without being assessed for environmental risks.

A comprehensive package of measures is needed to improve the situation. This must include the strengthening of environmental assessment as part of the approval process, as well as an environmental classification system for drugs to enable doctors to

administer the least environmentally harmful drugs. Measures implemented at source to avoid discharges into wastewater and the gradual expansion of minimum at large wastewater treatment plants to reduce water pollution must be included in planning, as the collection of drug residues by pharmacies, comprehensive information for doctors, nurses and consumers, a ban on advertising non-prescription drugs and the expansion of preventive health care. Monitoring programmes for the water and soil with regard to pharmaceuticals and resistances and requirements for the production of pharmaceuticals according to the best available techniques (BAT) as well as the promotion of research into the development of environmentally compatible active ingredients complete the range of measures. In accordance with the polluter-pays principle, the manufacturers and distributors of pharmaceuticals must be involved in financing these measures.

1. Summary of BUND/FoE Germany demands and recommendations

Active substances in drugs are increasingly being detected in the environment, sometimes at levels of concentration that are cause for serious concern. In response to this, BUND/FoE Germany recommends a comprehensive package of measures in order to reduce the harmful impact of pharmaceutical substances on the environment. These include, most importantly:

- Making the environmental risk assessment of pharmaceuticals a firmly established legal requirement. Pharmaceuticals approved before the implementation of the environmental risk assessment (old drugs) must be assessed and removed from the market if they pose risks.
- The monitoring of pharmaceutical active ingredients and of antibiotic-resistant bacteria must be developed and further extended.
- The development of environmentally friendly active substances must be made a key focus of research and be promoted by incentives ("green pharmacy").
- Strict environmental controls should be applied in the production of pharmaceuticals, both internationally and nationally.
- Doctors, pharmacists, caregiver and farmers should receive targeted in-service training on measures for reducing the use of pharmaceuticals.
- Both livestock husbandry and aquaculture must be changed in such a way that the pollution of water and soil is reduced and animal welfare is promoted. A binding transformation of animal husbandry to improved animal welfare, expanded environmental protection and fewer veterinary drugs is needed. Biological husbandry conditions require less use of medication.
- An environmental classification system should be introduced which will enable doctors to prescribe environmentally friendly alternative medicines in the future.
- A general advertising ban for non-prescription drugs should be introduced.
- Strict rules must apply to the keeping of livestock and the agricultural utilization of farm manure, and these must also be monitored nationwide.
- Pharmaceutical residues must not be disposed of in the wastewater but should be collected by pharmacies. Consumers must be informed on this.
- Wastewater flows with particularly high levels of pollutants must be treated before being discharged into the sewer system. In the case of contrast media, the patient's excretions must be separately collected, e. g., in urine bags, and disposed of.
- In the event of higher pollution, sewage treatment plants must be gradually expanded (4th stage of wastewater purification) so that they effectively reduce the drug concentrations in wastewater discharges.
- Further increases in consumption of medications should be prevented in the future by expanding preventive health care.
- Manufacturers and other polluters must make an appropriate contribution to the financing of the measures (polluter pays principle).

2. What is it about? Problem outline

2.1 Pharmaceuticals in the environment

Since the mid-1980s, scientists have been reporting more and more discoveries of pharmaceuticals in the environment. When endocrine substances came into focus more strongly in the 1990s, the discussion also turned to hormonal medication for, among other things, contraception, and its environmental impact. In addition, there was concern about the more frequent identification of antibiotic-resistant bacteria, which are associated with the use of antibiotics in human and veterinary medicine (PAN 2015). Although active agents in pharmaceuticals are no less biologically active than those in agricultural and non-agricultural pesticides, this issue has received less public attention because medication is usually associated with health.

For a study on behalf of the Federal Environment Agency (UBA), on the emerging policy issue “Pharmaceuticals in the environment” within the scope of the “Strategic Approach to an International Chemicals Management” – SAICM of the United Nations Environment Programme (UNEP), over 1,000 publications and data sources were evaluated (UBA 2016). The UBA database developed from the study mentioned above, which is constantly updated, now contains over 178,000 entries from approximately 1,500 publications. This means active substances or their transformation products from 75 countries in all the regions of the world are currently accessible in the database. A total of 771 different pharmaceutical substances were detected in environmental media, of which 269 were in Germany and a total of 596 active substances in the countries of the EU. Most of the substances were found in the effluent from wastewater treatment plants. Throughout the world 528 detectable active substances were measured in surface water, ground water and drinking water, and 159 in Germany. There were 19 active pharmaceutical substances detected in the aquatic environment in all five UN regions (UBA 2020).

The most frequent sources were municipal wastewater, hospitals, farm manure, aquaculture, and pharmaceutical production plants. The most frequent active substance to occur was the painkiller Diclofenac which was detected in 50 countries, and often in ecotoxicologically relevant concentrations. The UBA study shows that drugs pose a global problem in the environment, not only in industrialized countries, but increasingly also in countries in the Global South (UBA 2016). It should be noted that the most important production facilities for pharmaceuticals are now in India and China.

In December 2014, all UN countries voted to include pharmaceutical residues in the environment as one of eight priority political topics in the United Nations Chemicals Programme (SAICM) in order to search for global solutions (SAICM 2020). The United Nations Sustainable Development Goals (SDGs) also offer a starting point for efforts to find sustainable solutions in the supply and consumption of pharmaceuticals at the global level (SDG 3 – Ensure healthy lives and promote well-being for all at all ages, SDG 6 – Ensure availability and sustainable management of water and sanitation for all, SDG 14 – Conserve and sustainably use the oceans, seas and marine resources for sustainable development, and SDG 15 – Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss) (UN 2015).

The measured concentrations of active pharmaceutical ingredients in the environment are usually below the therapeutic doses of the individual medications (human medicines) or the maximum permissible residue levels in foodstuffs (veterinary medicines) specified for them (BMJ 2009, EU 2009). However, this does not by any means sound the all-clear for the environment. For example, because the acceptable level of valsartan acid in drinking water

had been exceeded for years the Berlin Water Supply System felt it necessary, together with the Berlin State Office for Health and Social Affairs (LAGESO), to call on the doctors to replace it with less harmful substances (DGK 2017, Schimmelpfennig and Dünnbier 2019).

Although pharmaceuticals are among the substances that have been most thoroughly investigated in terms of human toxicology, the ecotoxicological consequences of the comparatively low but continuous pollution of waters, sediments and soils with active pharmaceutical ingredients or their transformation products are largely unknown.

Medicines have to be approved. The conditions for approval are regulated at EU level by Directive 2001/83/EC for medicinal products for human use (EU 2001) and Regulation 2019/6 for veterinary medicinal products (EU 2019). Merely national approvals are rare today. Medicinal products for human use are mostly authorized centrally or decentrally throughout the EU. The approval is usually valid for an unlimited period. Since an amendment to the guidelines in 2004, which was implemented in 2006, an environmental risk assessment has been mandatory, but only for preparations for which approval was sought after that date. Previously approved drugs are available on the market without an environmental risk assessment. Approximately 47% of the drugs approved in Germany require a prescription; the others are available pharmacy-only or over-the-counter (ABDA 2019).

2.2 Human medicine

Exact consumption levels of the drugs used in human medicine in Germany are not available. In various research projects, attempts to obtain reasonably reliable data have been made again and again. Since no official statistics are kept, this is difficult for a number of reasons (see remarks on this in TAB 2019). Bergmann et al. determined that a total of 37,915 t of the approved 2,671 active phar-

maceutical ingredients were sold in Germany in 2001. In 1999 it was 28,878 t with 2,754 substances. The best-selling groups of active ingredients are (for 2001) analgesics (painkillers) (1,837 t), anti-inflammatory drugs (633 t), antibiotics (496 t), anti-epileptics (204 t) and beta(β) blockers (160 t) (Bergmann et al. 2011). Newer reliable figures are not available. These numbers suggest a level of accuracy that does not exist. Consequently, mostly estimates are used today. The Federal Environment Agency (UBA) assumes that there was an annual consumption of human pharmaceuticals in Germany of around 30,000 t in 2012, assuming around 2,300 active ingredients in around 31,000 drugs. Around 1,100 of the active ingredients are viewed as not environmentally relevant per se. They belong to the group of electrolytes, minerals, peptides and vitamins, which are not expected to have any harmful effects on the environment in view of their low persistence and toxicity. Consequently, there is no environmental risk assessment in the approval process. According to the UBA, there are around 1,200 potentially environmentally relevant human medicinal products with an annual consumption of around 8,100 t (UBA 2014, 2018a).

In view of the increasing average age of the population, an increase in drug consumption is expected. A further increase in drug consumption of 43% to 69% is expected by 2045, with a further increase in non-prescription drugs expected in particular (Civity Management Consultants 2017).

Since most of the active pharmaceutical ingredients get into the wastewater in human excretions and are usually only incompletely eliminated in the sewage treatment plants, there is a constant entry of active pharmaceutical ingredients into the environment, albeit in relatively low concentrations. According to estimates by the pharmaceutical industry, the main sources of human medicinal products in surface water are patient excretions (88%), improper disposal in the toilet and sink (10%) and

manufacturing processes (2%). With regard to improper disposal, the UBA assumes that up to 47% of consumers always or occasionally dispose of their drug residues improperly (UBA 2018a).

2.3 Veterinary medicine

Around 430 active ingredients in 2,295 medications are approved as veterinary medicinal products in Germany, 270 of which can be classified as potentially environmentally relevant as they are not among the substances excluded from the environmental risk assessment (see above). Some of the approved active ingredients for veterinary medicinal products are also approved for human medicinal products, so that the source cannot always be clearly identified when they are found in water or in the soil. The most important group of active substances in veterinary medicine are antibiotics (see Section 2.4).

In 2019, the amount of antibiotics given to veterinarians was 670 t (BVL 2020). No reliable data are available for the other groups of active substances (TAB 2019). Other drugs often used in veterinary medicine are medications against parasites (antiparasitics), for the treatment of inflammation (antiphlogistics) and local therapeutic agents for skin, udder and eyes, as well as agents for the treatment of fungal infections (antimycotics) and hormonally active substances, for example for oestrus synchronization in sows (PAN 2015).

Veterinary drugs are mainly used in the agricultural sector for the treatment of farm animals such as cattle, pigs, chickens, turkeys, sheep, goats and horses. Like humans, animals also excrete most of the active ingredients unchanged or in metabolized form. Treatments for companion animals such as dogs and cats are used to a lesser extent and are therefore in most cases not subject to an environmental risk assessment. Exceptions are antiparasitics, which are used

externally against fleas, ticks and mites in companion animals. Active ingredients such as fipronil or imidacloprid are toxic in the ng/l range and can cause damage in contact with water. The EMA is currently discussing the possibility of subjecting such drugs to an environmental risk assessment (EMA 2020).

Remnants of veterinary drugs in animal excrement are spread in agricultural areas as slurry or manure. Consequently, the soil is the most important target medium of these emissions. Depending on the nature of the soil, pharmaceutical residues can seep into the groundwater or enter surface water through runoff during heavy rain events. In the case of grazing animals, the influence of antiparasitics on dung fauna (beetles and flies), without which the faeces cannot decompose, must also be taken into account.

The use of pharmaceuticals in aquaculture activities, which are often in direct contact with surface waters, is a special case. The agents are applied through immersion baths or feed. Feed residues, fish droppings and used immersion baths/basins pollute ponds, rivers or coastal waters (BUND 2013, PAN 2018). Bees are also treated against the Varroa mite with drugs (LAVES 2019). As a rule, however, this pest can be effectively combated using mild methods.

2.4 The special case of resistance to antibiotics

One of the most pressing problems on the agenda at the WHO, the UN and also at political summits like the G7 and G20 is the increase in the incidence of multi-resistant pathogens (e. g., methicillin-resistant staphylococcus aureus – MRSA) and the associated risk of no longer being able to effectively treat a large number of infectious diseases. In fact, the German Robert Koch Institute (RKI) is already anticipating around 10,000–15,000 deaths per year in Germany with 400,000–600,000 nosocomial infections (so-called hospital infections), although only a small proportion of these are currently caused by

multi-resistant bacteria. Around 90,000 deaths per year from nosocomial infections are expected within the European Union (EU) (RKI 2019). The most common bacteria found in Germany are *Escherichia coli*, *Staphylococcus aureus*, *Clostridium difficile*, *Enterococcus faecalis* and *Enterococcus faecium* (NRZ 2017).

Antibiotic-resistant bacteria are detected not only in health facilities and animal stalls but also in the environment, especially in sewage, surface water, bath water and soils. This contamination results from the direct entry of resistant bacteria via slurry, sewage, manure, sewage sludge, etc. (UBA 2018b).

The One Health approach of the World Health Organization (WHO) has meanwhile reached a consensus (WHO 2015), particularly with regard to antibiotic resistance. This not only states that human and veterinary medicine should be considered together, but also that industrialized, emerging and less developed countries must all be considered due to increasing globalization (Heudorf 2016). The WHO has presented a Global Action Plan to Combat Antibiotic Resistance. The multi-resistant pathogens (MRE) were also on the agenda at the last G7 and G20 summits. The EU Commission (One Health Action Plan against AMR) and the German government (German Antibiotic Resistance Strategy – DART 2020) have adopted antibiotic resistance strategies (BMG et al. 2019, EC 2017). However, DART does not address the role of the environment as a reservoir and transmitter of antibiotic resistance.

Due to the special problem of resistance, the quantities of antibiotics dispensed have been recorded separately for some years now. In 2016 these amounted to 666 t/year in the case of human medicinal products (UBA 2018b) and 670 t/year for veterinary medicinal products (BVL 2020). In Germany, between 2011 and 2019 the amount of antibiotics dispensed for veterinary medicine more

than halved from 1,706 to 670 tons (minus 65%). Compared with 2017, however, the total amount of antibiotics dispensed decreased by only 40 tons (5.5%). This was established in the evaluation of the quantities of antibiotics in veterinary medicine collected since 2011 by the Federal Office for Consumer Protection and Food Safety (BVL 2015, 2019 and 2020).

After the amount of fluoroquinolones, which play an important role as the basis for reserve antibiotics in human medicine, had risen in veterinary medicine for a time, all groups of active substances are now, in some cases substantially, dispensed at lower levels than in 2011. The BVL assumes that a new standard procedure for dispensing this group of substances, which has been included in the Veterinary Pharmacy Ordinance, is responsible for the decline. Compared with the first data collection year, 2011, the dispensing of the polypeptide colistin has decreased by approximately 42% and of macrolides by approximately 66% (TAB 2019). While a slight increase in the dispensing of macrolide and polypeptide antibiotics was registered in 2018, there was also a decline in these two drug classes in 2019. Both are classes of active ingredients that have been classified by the WHO and the World Organization for Animal Health (OIE) as particularly important for therapy in humans (BVL 2019, 2020). The new EU Veterinary Medicines Regulation 2019/6 specifies in Art. 37 (3) that antimicrobial agents should no longer be approved as veterinary medicinal products if they are reserved for the treatment of certain infections in humans. Currently, there is a risk that this provision will be undermined by the EU Commission, which, in a draft implementing regulation, provides, among other things, that some reserve antibiotics will be declared essential for animal health and can continue to be used (Häusling 2020).

Earlier, antibiotics were permitted with specified animals as so-called “antibiotic performance

enhancers.” Due to the possible transferability of resistance and the possible promotion of the development of resistant bacteria, antibiotic growth promoting agents have been banned across the EU since January 1 2006, but are still allowed in the USA and Asia (LGL 2020, PAN 2015).

Cocciostats against parasitic protozoa that cause gastrointestinal diseases are still permitted as feed additives with antibiotic or antiparasitic effects. Feed additives are not subject to pharmaceutical legislation. However, an environmental risk assessment by the European Food Safety Authority (EFSA) is foreseen (FEEDAP 2019).

3. How relevant is the problem?

The time to act is long overdue

3.1 Release into the environment

In many cases, human and veterinary pharmaceutical substances are broken down only incompletely – if at all. Differences in the quantities of human and veterinary medicinal products found are mainly due to the different entry paths into the environment. Medicines for humans reach surface waters via the sewage system and sewage treatment plants. Agricultural soils are polluted through the spreading of sewage sludge, which is still permitted in Germany. The new Sewage Sludge Ordinance allows it to be spread on or in soils with fewer than 50,000 population equivalents (PE = number of residents in the catchment area of a sewage treatment plant). Only in the case of higher PE treatment of farmland will be prohibited from 2029 (for more than 100,000 PE) or 2032 (for more than 50,000 PE) (BMUB 2017). In wastewater treatment, sewage sludge is a pollutant sink for substances that are difficult to break down. It thus contains not only valuable nutrients but also an unknown number of pollutants. Thus, a UBA study measured in sewage sludge 3 to 21 mg/kg of dry matter ciprofloxacin, 0.75 to 8.9 mg/kg of dry matter levofloxacin, 0.054 to 1.1 mg/kg of dry matter carbamazepine, 0.023 to 0.16 mg/kg of dry matter clarithromycin, 0.0056 to 1.1 mg/kg of dry matter 17 β -estradiol, 0.074 to 2.1 mg/kg of dry matter diclofenac and 0.044 to 1.1 mg/kg of dry matter metoprolol according to (UBA 2019b).

Most veterinary medicinal products reach agricultural areas with untreated slurry and manure from intensive animal production, from where they seep away and can be flushed into the rivers. When plants absorb micropollutants, they can also find their way into the food chain. With respect to antibiotics, it has been proven, for example in cereals, that uptake occurs via the roots (Freitag et al. 2008). Medicines that are used in aquaculture find their way directly into surface waters and sediments. Additional entry paths such as the production and disposal of active

pharmaceutical ingredients must also be taken into account.

Accordingly, residues of active pharmaceutical ingredients can be found in soil, wastewater, surface water, sediments, groundwater, and even traces in drinking water. The report of the Office of Technology Assessment of the German Bundestag (TAB 2019) provides an overview.

3.2 Pharmaceuticals in water legislation

A legal obligation to reduce and avoid micropollutants such as active pharmaceutical ingredients could derive from the European Water Framework Directive 2000/60/EC (WFD) (EU 2000). Relevant are pollutants defined in point 4 of Annex VIII WFD², which the river basin authorities have to take into account in determining levels of pollution of surface waters according to Annex II WFD, which are relevant to the conditions and thus to related measures as well. The WFD subsidiary directives supplement these requirements: In accordance with Article 6 of Directive 2006/118/EC (EU 2006a), the substances are also to be taken into account in connection with groundwater protection in accordance with Point 4 Annex VIII WFD, and their inputs are to be prevented or limited accordingly. Article 8b of Directive 2013/39/EU (EU 2013) specifies the creation and regular updating of an EU-wide watch list for the identification of additional priority substances (see below), while Article 8c contains specific provisions for pharmaceutical substances (especially a strategic approach with appropriate measures).

The revised Groundwater Directive 2006/118/EG also specifies at least one method for monitoring substances for which little data is available and for which EU-wide quality standards or river basin-specific threshold values may have to be derived. In Germany, the relevant WFD regulations in the national groundwater and surface water ordinances (GwV or OGewV) should be made more specific with regard

² 4. Substances and preparations or their breakdown products whose carcinogenic or mutagenic properties or impairment of steroidogenic, thyroid, reproductive or other functions of the endocrine system in or through the water supply have been proven

to substances, especially for all river basin-specific substances. For several pollutants there are already valid environmental quality standards (EQS) at both European and national level. However, so far, EQS have not been established for active pharmaceutical ingredients either across the EU or nationally. The Federal Environment Agency has collected data from various sources and derived EQS proposals from them (UBA 2018a, see tab. 1).

(Swiss Federal Council 2020). The EQS proposed by the UBA are in a similar range, but are annual mean values.

At the EU level, there is now an updated watch list of substances relevant to surface waters, which are considered candidates for rating as priority substances and should therefore be included in monitoring programmes (EC 2020a). These also include

Substance name	EQS [$\mu\text{g/l}$]
17- α ethinyl estradiol	0.000035
17- β estradiol	0.0004
azithromycin	0.09
bezafibrate	2.3
carbamazepine	0.5
clarithromycin	0.13
diclofenac	0.05
erythromycin	0.2
ibuprofen	0.01
metoprolol	43
sulfamethoxazole	0.6

Table 1: Environmental quality standard (EQS): Suggestions for an annual mean value for individual active pharmaceutical ingredients (UBA 2018a)

The 2020 Swiss Water Protection Ordinance, which has been in force since April 1, 2020, has for the first time set limit values for three medicinal products for surface waters. The first value relates to short-term measurements; the second value is intended to assess long-term pollution and is calculated by determining the mean value over a period of two weeks: Azithromycin 0.18 $\mu\text{g/l}$ or 0.019 $\mu\text{g/l}$, clarithromycin 0.19 or 0.12 $\mu\text{g/l}$ and diclofenac 0.05 $\mu\text{g/l}$ long-term

the active pharmaceutical ingredients metaflumizone, venlafaxine (and its metabolite O-desmethylvenlafaxine), the antibiotics amoxicillin, ciprofloxacin, sulfamethoxazole and trimethoprim, as well as the antimycotics clotrimazole, fluconazole and miconazole. As part of the EU-wide common implementation strategy, a voluntary watch list procedure for groundwater protection was prepared in accordance with the current Groundwater Directive (EU

2006a). Relevant substances that were found more frequently in Germany and other participating Member States are sulfamethoxazole, erythromycin and sulfonamides in areas with intensive livestock farming.

At various measuring stations, the proposed EQS, in particular for the painkillers diclofenac and ibuprofen, are already being (sometimes substantially) exceeded. Isolated excess values were also found for the anti-epileptic carbamazepine, the antibiotic clarithromycin, the natural hormone 17- β -estradiol and its synthetic derivative 17- α -ethinyl estradiol (LAWA 2016, UBA 2018a).

For the antibiotic sulfamethoxazole, concentrations in the range of the proposed EQS were measured in municipal sewage treatment plants. In the event of low water flows and a high proportion of wastewater in bodies of water, it is therefore possible that the EQS proposal may be exceeded (LAWA 2016, UBA 2018a). Due to climate change, long periods of dryness are to be expected more frequently, like those which in the summers of 2018 and 2019, led to extremely low water levels in the major rivers as well. The EQS will then be exceeded more frequently.

In the opinion of the UBA, however, an exclusive fixation on EQS would not do justice to the overall problem of environmental pollution, since in addition to protection of aquatic ecosystems and drinking water supply, also seas, sediments and soils in general must be protected from further pollution (UBA 2018a).

In the Groundwater Ordinance (GwV) too, there is no threshold value for pharmaceuticals so far. In studies in 15 federal states in 2013, 16 active pharmaceutical ingredients were found in the groundwater with concentrations above 0.1 $\mu\text{g/l}$ (Bergmann et al. 2011, LAWA 2016). Discussions are under way to adopt the general threshold value of 0.1 $\mu\text{g/l}$ for

agricultural and non-agricultural pesticides as well as for active pharmaceutical ingredients and their metabolites, especially since no effectiveness thresholds can be established for many substances.

The Federal Environment Agency (UBA) has now derived health-related guide values (GOW) for drinking water for more than 30 active pharmaceutical ingredients and metabolites (UBA 2019a). For these substances, due to the mostly still incomplete toxicological data, maximum concentrations are derived at which no long-term health impact is to be expected.

3.3 Critical properties of active pharmaceutical ingredients

For the environment, long-lived (persistent) substances that are no longer removed after their release and that can accumulate in organisms or spread over a wide area are a central problem (BUND 2019a). When persistence combines with bioaccumulation and (eco)toxicity we can speak of PBT (persistent, bioaccumulating, toxic) substances, which now occupy a special position in the assessment of chemicals and as far as possible should not be used any more.

Substances that are very persistent and very bioaccumulating (vPvB substances) are also considered to be of particular concern. In combination with high mobility in the water cycle (PMT and vPvM substances), persistent substances are also very problematic (UBA 2018c). Carcinogenic, mutagenic and teratogenic substances (CMT substances) are also assessed very critically. This is especially true for certain cytotoxic drugs. Endocrine-active substances are especially relevant as well. Numerous hormones, particularly sex hormones and hormones for the thyroid gland, are widely used pharmaceutical agents that can affect environmental organisms such as fish and snails.

Even when the above property (combinations) are not present, most active pharmaceutical ingredients are physiologically highly active substances that can have a damaging effect on the environment and whose input must therefore be minimized. This applies to human and veterinary medicines. Of the latter, the best known example for environmental damage caused by pharmaceuticals is: Vultures were dying out in India and Pakistan. The vultures had eaten dead cows that had been treated with the anti-inflammatory agent diclofenac (Prakash et al. 2012). Diclofenac is also harmful to the liver, gills and kidneys of fish. Qiuguo Fu et al. found that this active ingredient is bio-transformed in amphipods to the even more toxic methyl ester (Fu et al. 2020). Other examples of observed harmful effects on the environment are effects on dung insects and fish caused by antiparasitic drugs and changes in the composition of microorganism communities in soils due to antibiotics (Fornfeld and Smalla 2018). Richmond, et al. showed in an Australian study that various active pharmaceutical ingredients accumulate in aquatic food networks, which can lead to high concentrations in some organisms (Richmond et al. 2018).

Sensitive species of invertebrate groups (e.g., mayflies, stone flies, caddis flies) in flowing waters disappear even at extremely low concentrations of micropollutants. Many pharmaceuticals are micropollutants that can be reduced through more extensive wastewater treatment (see Section 4.5.3, Trieb-skorn 2017). A reduction in micropollutants in water is necessary (BUND 2017, UBA 2018a).

3.4 Environmental risk assessment in the approval process

Since 2006 EU law has stipulated that the environmental impact of human and veterinary medicinal products must be assessed as part of the approval process. Only the active ingredients are evaluated, not the numerous formulation auxiliaries. The evaluation takes place in two tiers: First of all, it is determined whether, assuming that the active ingredient is not metabolized in the body and is not degraded further down the line, it exceeds a threshold value for exposure (phase 1). For human medications this threshold is for example 0.01 µg/l in surface water. Further studies on persistence and ecotoxicity are only required if this threshold is exceeded by the value obtained (phase 2). If the expected environmental concentration (PEC value) exceeds the threshold (PNEC value), there is a risk and mitigation measures are required. If there are indications that the substance can accumulate in living organisms (bioaccumulation), a PBT assessment is required with the aim of avoiding PBT substances as active substances as far as possible. The threshold value does not apply to antibiotics and hormones and a separate assessment is initiated for these (tailored risk assessment). In particular, more extensive ecotoxicological studies are required with fish. (e.g., blue-green algae tests for antibiotics or a full-life-cycle test with fish)

Assessment of the development of resistance in environmental media has so far played just as small a role with antibiotics as the question of whether the threshold value is not also unsuitable for other groups of active substances such as antiparasitics, antimycotics, cytostatics and neuropharmaceuticals (EMA 2018). There are also guidelines for environmental risk assessment for veterinary medical products (EMA 2006).

Groups of active substances with particular ecotoxicological relevance

Antibiotics Antibiotics are used to fight bacterial pathogens. That is why bacteria and bacterial communities (microbiomes) are particularly sensitive. Tests with cyanobacteria (blue-green algae) can be suitable for assessing the ecotoxicological potential (EMA 2018). The spread and emergence of antibiotic resistance in the environment represents a particular risk, which must therefore be included in the environmental risk assessment.

Antimycotics are effective against fungal diseases. The antimycotic clotrimazole is already toxic to algae at 350 µg/l (TAB 2019). It is thus not possible to apply the PEC threshold values in phase 1 of the environmental risk assessment.

Antiparasitics are effective, both internally and externally, against farm animals which are infested with parasites. Most of the parasites being combated are insects, which is why they have a pronounced insecticidal effect. Some active ingredients are also used as biocides or as insecticides in crop protection. An example of adverse effects in the environment is the effect of ivermectin against dung insects at very low concentrations (Liebig et al. 2010).

Hormones are used in human and veterinary medicine, such as in contraceptives. They act on aquatic organisms even at extremely low concentrations. For example, 17-β-ethinylestradiol (EE2) already causes feminization effects in some fish species at a concentration of 0.1 ng/l (Purdom et al. 1994). In laboratory tests, 0.2 ng/l EE2 led to a 100% loss of reproduction in one species of carp (Zha et al. 2008). Imposex occurs in snails – the development of genital organs that are opposite to the actual sex (SRU 2007). An assessment of the ecotoxicological potential is possible with fish using the "full lifecycle test". Gestagens are also reported to impair the development of amphibians in the nanogram range (Säfholm 2014). Not only sex hormones are of high ecotoxicological relevance but also, for example, thyroid hormones, which also influence larval development in amphibians. When evaluating hormones, it should be noted that numerous chemicals have (unintentionally) harmful effects on hormones. They are endocrine disruptors. The effects of chemicals with desired and undesired hormonal effects can cumulate in the environment or even reinforce each other.

Cytostatics such as 5-fluorouracil, cyclophosphamide or cis-platinum are used as chemotherapeutic agents in cancer therapy. Many active ingredients have a genotoxic effect. For some cytostatics, low effective concentrations of less than 1 µg/l have been reported (Filipic et al. 2013), for example in tests, that determine the genotoxic potential in fish (e.g., micronucleus test).

Neuropharmaceuticals are increasingly being prescribed – even in the face of the spread of neurodegenerative diseases (UBA 2018d). They can, for example, disrupt the reproduction or schooling behavior of fish, which massively reduces their survival chances. In the NEUROBOX project, test procedures are currently being developed that measure these ecological parameters (Kuckelkorn et al. 2020).

X-ray contrast media (organic chemicals containing iodine) are also not covered by the EMA's assessment procedure. As required, they are non-toxic, non-bioaccumulating and are excreted by the body very quickly. However, they are extremely persistent and highly mobile and cannot effectively be retained neither by sewage treatment plants nor bank filtration. They are thus a prime example of vPvM substances (very persistent, very mobile), which the Federal Environment Agency proposes to consider as substances of very high concern (SVHC) in accordance with the EU chemicals regulation REACH (UBA 2018c). The same as applies to X-ray contrast media also applies to contrast media in nuclear magnetic resonance imaging (MRI). Gadolinium chelates are also very persistent and mobile. The so-called gadolinium anomaly in the runoff of sewage treatment plants is now an indicator of the wastewater influence on surface and groundwater (Bayer. LfU 2020).

Finally, the EMA guidelines (EMA 2018) also ignore the fact that nanomaterials are gaining in importance in medicine, both as active ingredients and as carriers and drug delivery systems. The risks of nanomaterials for humans and the environment have not yet been adequately clarified. Not only the chemical composition but also the size, shape, charge, and other physicochemical properties of the nanoparticles determine their potential effects. For the evaluation of nanomaterials, more detailed information on the physical and chemical characteristics is required in order to be able to assess their behaviour in organisms as well as in the environment (Steinhäuser and Sayre 2017).

3.5 Combination effects

The neglect of combination effects in the approval procedure is also a clear deficit of the environmental risk assessment procedure. Medicinal products for human use reach the sewage treatment plants and then the receiving waters as a mixture of numerous

active substances, the effects of which can cumulate, increase or decrease. Even in the case of combination products with several active ingredients, the EMA guidelines ignore interactions. The risk tends to be underestimated. The research programme Pharmas, which examined several procedures with several active pharmaceutical ingredients in sewage treatment plants showed that the effects cumulate (TAB 2019). In the EU, there are several scientifically sound procedures for taking the cumulative effects of several substances into account (Altenburger et al. 2018, Kortenkamp et al. 2009). These should be applied.

3.6 The special case of antibiotic resistance

Recent studies have shown that the transfer of resistant bacteria from animals to humans is being observed. Findings of MRSA or ESBL in farm employees correlate with MRSA- or ESBL-positive findings in the animals. It seems remarkable that this correlation particularly affected pig feedlots, while the cattle and poultry farms examined were even in some cases MRSA-free or only slightly contaminated with ESBL (Dittmann et al. 2016). Recent studies by Greenpeace showed that of 15 pig manure samples tested, nine contained ESBL-forming pathogens and eleven colistin-resistant bacteria (Greenpeace 2020). Current studies by the Julius Kühn Institute (JKI) show that fresh and especially ready-cut salads wrapped in foil for sale are often not only contaminated with hygienically problematic, but also with antibiotic-resistant bacteria, which can be attributed to fertilization with manure (BfR and JKI 2018). Since the direct application of liquid manure to food crops is prohibited, this finding indicates that the bacteria are being taken up via the roots.

The exposure paths of antibiotic-resistant bacteria from human and veterinary medicine correspond with those of antibiotics. A very important additional emission path for resistant bacteria entering the

environment from animal husbandry is exhaust air from animal stalls, which is spread across the surrounding environment (Gärtner et al. 2016, von Salviati et al. 2015). Resistant bacteria can be inhaled when liquid manure and dung are spread on fields (Kabelitz et al. 2020). Surface waters in particular are contaminated via the sewage path. Sewage sludge, liquid manure and slurry potentially contaminate soil and subsequently groundwater and drinking water. The antibiotic levels in liquid manure and manure depend heavily on how the livestock are kept (Fromm 2013). The use of antibiotics is strictly limited in organic animal husbandry. An increase in antibiotic resistance in the soil due to the entry of antibiotics is the subject of discussion, but has not yet been conclusively clarified (Adler 2014). Antibiotic resistance can also originate in the environment: With some antibiotics, even very low concentrations – as they occur in the environment – are sufficient to exert selection pressure and contribute to the spread of resistance (Gullberg et al. 2011, Keen and Montforts 2012). It has also been proved that co-selection in the presence of biocides, pesticides such as glyphosate or heavy metals such as copper and zinc can lead to antibiotic resistance in the environment (van Bruggen et al. 2018, Westphal-Settele et al. 2018). Finally, in the environment, antibiotic resistance can be exchanged among different bacteria by means of horizontal gene transfer.

An overview of antibiotics and antibiotic resistance in the environment can be found in Schröder et al. (2020).

A special case became known in 2018: An additive with viable bacteria that produce riboflavin (vitamin B2) was added to many feeds. These bacteria were

endowed with four types of resistance to antibiotics. Three of them were introduced into the genetic material of the bacteria with the help of genetic engineering. According to the European Food Safety Authority (EFSA), feed containing this additive poses a risk to consumers, users and the environment (FEEDAP 2018). The affected feeds – which had already been on the market since 2014 – had to be withdrawn from the market by mid-2019. It is not known whether there are other similar cases.

Antibiotic-resistant genes can also enter the environment through genetically modified organisms (GMOs). Resistant genes are often used in genetic engineering as marker genes in order to be able to easily identify GMOs. For example, the synthetic ampicillin-resistant gene (β -lactam, bla) from genetically modified bacteria was detected in Chinese rivers (Chen et al. 2012).

4. Where to begin?

Consequences and measures for preventing or minimizing harmful effects of pharmaceuticals on the environment

The aim of a pharmaceutical strategy must be to reduce the entry of active pharmaceutical substances into the environment as much as possible so that negative effects on the environment or human health are avoided. For this, the entire life cycle from development through production to application and elimination or disposal must be considered. This is also emphasized in a statement by several non-governmental organizations (Changing Markets Foundation et al. 2018). On March 11 2019, the EU Commission finally published its “European Union Strategic Approach to Pharmaceuticals in the Environment,” with various proposals and declarations of intent to reduce the environmental impact of pharmaceuticals (EC 2019). Unfortunately, most of the proposed measures are not very specific and are limited to considerations, determination of further research needs and appeals to the parties involved. In particular, there is still a lack of legislative measures to reduce the effects of pharmaceuticals on the environment (BUND et al. 2019c, PAN 2019). A chance was wasted.

In a roadmap for a European Pharmaceutical Strategy (“EU Pharmaceutical Strategy – Timely Access for Patients to Affordable Medication”) published in June 2020, the European Commission emphasized that improvements in connection with the environmental risks of medicinal products are necessary in order to achieve the objectives of the European “Green Deal”, namely the zero pollution goal for a non-toxic environment. In doing so, it emphasized the challenges of antibiotic resistance (EC 2020b).

The medically indicated use of medication and the freedom of therapy for doctors in human and veterinary medicine must of course be guaranteed to the necessary extent for the measures listed below.

4.1. Research and development

4.1.1 Collecting data and data transparency

All ecological and human toxicological data available from manufacturers and importers and obtained from third parties, as well as on the persistence and behaviour in the environment of drugs or their active ingredients and, if applicable, metabolites, should be made available to a central body (e.g., in Germany, the Federal Environment Agency) for evaluation purposes and made publicly available. Pharmaceuticals approved before 2006 that have not been subjected to an environmental risk assessment (so-called “old drugs”) must be included. The Federal Environment Agency (UBA) favours the introduction of a so-called monograph/master-file system for active pharmaceutical ingredients as a replacement for the previous product-based assessment. This system in the form of a transparent and publicly accessible dataset should be implemented at the European level for new active ingredients, but also for so-called “old” active ingredients without an environmental risk assessment. The UBA hopes that this will result in more consistent and up-to-date assessment in terms of saving resources, protecting animal welfare, and improving the availability of environmental data on substance assessment, which are currently largely not publicly available (UBA 2018a).

Transparent compilation of the findings yielded by monitoring of pharmaceuticals in the environment is equally important, in order to be able to recognize which pharmaceutical residues pose a potential danger to environmental media and drinking water and whether specific measures are necessary. This dataset should also include the occurrence of antibiotic resistance. UBA has already created an important basis for this in a compilation to SAICM (UBA 2016).

4.1.2 Research funding

Knowledge of the occurrence and effects of pharmaceuticals in the environment is still fragmentary, so that there is a considerable need for research.

The development of less polluting drugs or forms of application that can, for example, be better retained in sewage treatment plants and therefore not find their way into the water supply, must be promoted more strongly (“green pharmacy”). This applies in particular to alternatives to active substances that are persistent in the environment and can become a problem for the drinking water supply (PMT substances). As part of a project funded by the German Federal Environmental Foundation, two antibiotics were developed and submitted for patents. The project showed that pharmaceutical effectiveness can be maintained even with improved environmental friendliness (Leder et al. 2015, 2018, Kümmerer 2019). However, further development to market maturity seems to be failing due to the apparently insufficient profit prospects for the pharmaceutical industry. In general almost no antibiotic research is being carried out by manufacturers. Of 239 newly approved drugs in the last decade, only nine were antibiotics – all of them from already known classes of active ingredients (VDI 2020). Phage therapy – an alternative for treating bacterial infections – is hardly being developed any further.

Active pharmaceutical ingredients should not be persistent, but should be sufficiently stable to be able to achieve their effects in the organism. Green pharmacy research is the responsibility of manufacturers and the state. In order to promote appropriate levels of development of active ingredients by industry, there is already the EU-wide possibility of extending patent protection for particularly environmentally friendly alternatives as compensation for the increased research and development costs (TAB 2019).

Hardly any new antibiotics have come onto the market for several years. It is to be feared that with increasing resistance in the foreseeable future, in many cases, effective treatments will no longer be available. The German government recently initiated the establishment of an international platform for the investigation and development of novel antibiotics and the associated antimicrobial resistance (AMR), which was already decided upon at the G20 conference. The research initiative, which is to receive funding of €500 million for a period of 10 years, is primarily intended to develop recommendations on how the need for new therapies and diagnostics for bacterial infections can be met. The priority here is the development of new types of antibiotics to combat increasingly resistant pathogens (Federal Government 2017).

Occurrence, development and spread of antibiotic resistance are only partially understood. Specific research to identify the associated risks and how to avoid them is required.

Ecotoxicological research on the effects of drugs is also an important focus. Medicines often have very specific modes of action. It is therefore necessary to develop test strategies for drug groups that take this into account.

There is still little knowledge of how drugs interact with each other. Increased research on suitable methods for taking account of combination effects is thus important.

It is not feasible to include several thousand active substances in monitoring. Consequently, the development of a flexible but nevertheless comprehensive concept for the monitoring of pharmaceuticals in the environment has priority. One focus here is the soil. There is still a lack of reliable scientific findings that would make the derivation of environmental quality standards for the soil possible.

Demands and recommendations of BUND/FoE Germany

- *Creation of a publicly accessible dataset on toxicological and ecological properties of pharmaceutical substances, for example by means of a monography system.*
- *Creation of a publicly accessible dataset on the incidence of active pharmaceutical ingredients in the environment (including antibiotic resistances).*
- *Research programmes to develop drugs that are less harmful to the environment ("green pharmacy").*
- *Development of new, environmentally friendly antibiotics to avoid therapeutic gaps in view of the increasing spread of resistance.*
- *Research programme on the spread and development of antibiotic resistance in the environment.*
- *Research on the ecotoxicology of drugs, taking into account specific mechanisms of action and combination effects.*
- *Research on the conception of monitoring programmes in the environment and their implementation.*

4.2 Legal requirements

4.2.1 Approval procedures for medicinal products

Many drugs that were approved before 2006 have never been tested for their environmental impact. Such "old drugs" must be subjected to a retroactive environmental review and, if necessary and possible, withdrawn from the market. On the basis of the monograph system (see Section 4.1.1), priorities for a step-by-step review of environmental risks can be determined.

In the case of veterinary medications, environmental risks are included in the risk-benefit analysis. This can lead to the refusal of approval, which in rare cases actually does happen. In some cases, the risk

can also be minimized by placing conditions on use. This option does not exist for medicinal products for human use, since environmental risks are not taken into account in the risk-benefit analysis. As a result, the environmental risk assessment remains largely without consequences. Even if the protection of human health is the dominant issue, environmentally dangerous human medication should only be authorized with attached conditions if there is a significant therapeutic benefit and no more environmentally friendly alternatives are available. The approval of more environmentally friendly drugs should replace environmentally harmful medicines on the market in the medium term.

Approvals of antibiotics as veterinary medicinal products that are particularly relevant as reserve antibiotics (e.g., colistin or polymyxin E) or broad-spectrum antibiotics as human medicinal products should be revoked in accordance with Art. 37 (3) of the EU Veterinary Medicines Regulation 2019/6.

The system of pharmacovigilance (recording of side effects and risks after approval) should be expanded and developed with regard to environmental effects. Regular monitoring of the effects on the environment of drugs that have already been approved on the basis of current scientific knowledge makes it possible to reduce any environmental risk identified through additional requirements and, if necessary, withdrawal of approval.

In general, manufacturers have to assume more extensive responsibility for their products (extended producer responsibility). This means, for example, taking over the costs of post-registration monitoring or other obligations associated with the authorization. Such costs should not be passed on to the general public or to those insured by the health insurance companies.

Risk reduction measures to protect the environment should be required for drug approval, for example:

If a risk is identified by the environmental risk assessment, manageable mitigation measures must be formulated and implemented. However, there are currently very few effective and proportionate risk reduction requirements for medicinal products for human use.

The evaluation guidelines for veterinary and human medicinal products must be further developed. This includes a separate assessment of active ingredients with PBT/vPvB properties and PMT/vPvM properties. The entry of such substances into the environment must be prevented as completely as possible or, in individual cases, should only be possible under strict conditions.

The combined effects of several active ingredients are completely ignored in the assessment guidelines. Active pharmaceutical ingredients almost never appear individually in the environment but act together on the organisms living in water and soil. For this reason, the additive effects according to Kortenkamp (2009) should be taken into account, at least with combination products. An additive approach is also suitable for groups of active substances (e.g., sartans or beta-blockers as antihypertensive agents). In any case, in accordance with the precautionary principle, a critical review should be carried out of whether the specified safety factors are conservative enough to take account of the joint occurrence of a large number of active substances.

When antibiotics are approved, assessment methods for possible antibiotic resistance must be developed and made mandatory (UBA 2018b). One possibility is to determine the concentrations of antibiotics at which the formation of resistance is induced (MSC – minimum selectable concentration according to Bengtson) (Bengtson and Larsson 2016, Khan et al 2017, Lundström et al 2016).

Special assessment procedures (tailored risk assessment) replacing the standard procedure for determining environmental risks are also required for hor-

mones, antiparasitics, antimycotics, cytostatics, neuropharmaceuticals and nanomedical preparations.

X-ray contrast media and MRI contrast media are generally considered to be non-toxic and inert, but they are very persistent and overcome all barriers in wastewater treatment and drinking water extraction. Their use should therefore be bound by conditions (see Section 4.5.2) or avoided if degradable alternatives are available.

Feed additives with pharmacological effects (cocciostats) should only be permitted to be added to feed if an infestation is medically indicated. Consequently, they must be subjected to the pharmaceutical approval procedure.

4.2.2 Water and environmental law

If active pharmaceutical ingredients are found widespread in high concentrations in surface waters, they are to be regarded as dangerous substances according to Directive 2013/39/EU (EU 2013). Europe-wide or nationally (according to OGeV), environmental quality standards (EQS) should be derived for such active substances or their metabolites. The EQS are to be monitored by means of monitoring and action plans developed in order to minimize concentrations. For active substances relevant to drinking water, health-related guide values (GOW) must be derived and monitored.

Furthermore, systematic concepts for monitoring the spread of antibiotic resistance in the environment are to be developed, e.g., as part of the monitoring of bathing water in accordance with Directive 2006/7/EC (EU 2006b) and also for soil monitoring.

Demands and recommendations of BUND/FoE Germany

- *Stepwise environmental review of old drugs that were approved before 2006.*
- *Introduction of risk-benefit assessment for human medicinal products with the possibility of refusal of approval for environmental reasons.*
- *Pharmacovigilance should be expanded with regard to environmental risks (extended producer responsibility).*
- *Development of effective and practicable risk reduction measures for human medicines, in order to reduce risk.*
- *The assessment guidelines must take into account that medicinal substances are released into the environment in mixtures and include the additive combined effects in the assessment.*
- *Further development of the evaluation guidelines, in particular: PBT and PMT substances may only be approved in rare exceptional cases if no other treatment alternatives are available; active ingredient groups with particular ecological relevance (e.g., hormones and antiparasitics) must be subject to a specific assessment (tailored risk assessment); the development of resistance must be included in environmental risk assessment when evaluating antibiotics.*
- *Pharmacologically active feed additives are to be approved as medicinal products*
- *Development of environmental quality standards for active pharmaceutical ingredients and their systematic monitoring.*
- *Monitoring of antibiotic resistances in soils, surface waters and bathing waters.*

4.3. Production

Wastewater from production facilities for pharmaceuticals is an important input point source of active substances (Anliker et al. 2020). Transparent minimum standards must be guaranteed along the entire pharmaceutical supply chain, including environmental protection requirements. This can be done, for example, by introducing environmental criteria within the framework of Good Manufacturing Practice (GMP). Effective protection of the environment from the entry of production residues or waste must also be taken into account. GMP requirements also apply in countries outside the EU such as India and China, where the majority of pharmaceutical manufacturing takes place today. For example, production facilities in India have recently fallen into disrepute because more and more antibiotic-resistant bacteria have been found in receiving surface waters (Baars et al. 2017). In the case of production sites in Europe, the requirements of the Industrial Emissions Directive 2010/75/EU (EU 2010) apply. Here, best available techniques (BAT) must be specified and implemented. A BREF (Best Available Techniques Reference Document) document for pharmaceutical production must be developed. Demanding standards for the discharge of wastewater must also be developed and included in the wastewater ordinance. Adjustments of the Indirect Discharge Ordinance may also be necessary.

Demands and recommendations of BUND/FoE Germany

- *The federal government should take the initiative in revising the requirements for good manufacturing practice (GMP) to include environmental requirements. This must then also be enforced internationally in manufacturing countries outside the EU.*
- *At EU and national level, according to the Industrial Emissions Directive and the Waste Water Ordinance, state-of-the-art requirements are required for pharmaceutical production.*

4.4 Proper use

4.4.1 Human medicine

Promotion of the sparing use of pharmaceuticals, as well as education and awareness-raising campaigns about pharmaceuticals and their effects on the environment are necessary. Apparently, many drugs are still not taken or not taken for long enough, and leftovers are often not disposed of properly. If antibiotics are medically indicated, there is a risk of premature discontinuation and the associated build-up of resistance. The medically unnecessary prescription of antibiotics for viral diseases is particularly problematic. Antibiotics are often given as a precaution without diagnosing the exact cause of the infection. The development and application of rapid diagnostic tests to differentiate between viral and bacterial infections would be important here (VDI 2020). Neighbouring European countries such as the Netherlands have significantly more effective control over the prescription and dispensing of antibiotics and can serve as a model.

A particular problem is that numerous non-prescription drugs – including environmentally relevant ones such as diclofenac and ibuprofen – are heavily advertised, which leads to a significant increase in drug consumption. Human medicinal products with known environmental risks should therefore always require a prescription.

Advertising of pharmaceutical products should generally be avoided. Patients with symptoms should obtain advice from a pharmacist or a doctor before buying and taking any medication. In principle, this also applies to online trading in non-prescription drugs.

Expert advice from doctors, pharmacists and health insurers requires that they are aware of the potential risks of individual preparations. This can be achieved by means of information for doctors or provided on the package insert. An exemplary approach could be the Swedish environmental classification system, which covers persistence, bioaccumulation and

(eco) toxicity of the drugs and communicates potential environmental hazards in this simple way (TAB 2019).

On this basis, doctors, pharmacists and health insurers can advise patients on which medication should be given preference for environmental reasons, if there are no medical reasons against it. For example, the Berlin Water Supplier (Berliner Wasserbetriebe) successfully advised doctors to prescribe the blood pressure lowering drug valsartan less, after concentrations of valsartanic acid above the GOW value were measured in the drinking water of the Berlin-Tegel waterworks (DKG 2017, Schimmelpfennig and Dünnbier 2019). In this case, however, switching to other sartans with a similar hazard profile cannot be considered as success, since the effects of the sartans probably cumulate. In addition, the change in prescribing practice was not primarily made in order to protect drinking water. In 2018, valsartan preparations contaminated with the carcinogenic dimethylnitrosamine were withdrawn from the market. Due to delivery bottlenecks and increased co-payments, doctors began to prescribe other active ingredients, e.g., candesartan (Schimmelpfennig and Dünnbier 2020). Health insurance companies should agree to reimburse the costs for environmentally friendly alternatives even if they are more expensive than environmentally harmful products.

It is important to provide doctors and pharmacists with comprehensive training on the issue of the environmental risks of pharmaceuticals so that they can include this in the advice they provide to patients (HCWH 2014, UBA 2017e).

Public health could promote and act as frontrunner in green sourcing medicines with a lower environmental impact.

4.4.2 Veterinary medicine

Those people working in agriculture and veterinary medicine should be specifically informed and educated on the subject of veterinary drugs and the

environment. The task of veterinarians must include advising farmers on how to reduce the use of medicines and minimize their emission into the environment. In particular, it must be ensured that antibiotics are not administered “preventively” to all animals on a farm, but that sick animals are separated. In two leaflets, the UBA has put together information on how veterinarians and farmers can each make a contribution to reducing emissions into the environment (UBA 2017c, 2017d). With regard to antibiotics, the German Antibiotic Resistance Strategy DART should be adjusted and explain which measures can be used to protect the environment against the spread of resistances.

Veterinarians have the right to manufacture, mix, store and sell prescription drugs themselves. This so-called “dispensing right” should be abolished, as it contributes to a significant increase in the use of medication.

So far, only estimates of the consumption of veterinary drugs in feedlots are available. Farmers should be required to document the veterinary drugs used with their stock, in particular hormones (for oestrus synchronization) and antibiotics, as well as the co-selectors zinc and copper used in animal feed over each particular slurry production period.

Further measures to reduce the entry of veterinary medicinal products by the veterinary profession and agriculture include preventive measures to improve animal health, improvements in feeding and stable hygiene, measures in fertilizer storage, processing and application as well as agricultural practice (UBA 2017a, 2017b, 2018a). In addition, the targeted observation of possible side effects (eco-pharmacovigilance) can help to avoid harmful environmental impact and reduce consumption.

In aquaculture, almost all veterinary medications find their way into water bodies, either directly or indirectly. That is why animal husbandry conditions should take account of ecological aspects and the

use of veterinary drugs should be documented and monitored. BUND/FoE Germany rejects open aquaculture systems, as they heavily pollute the waters (BUND 2013).

4.4.3 Overarching measures in agriculture

The main entry path for veterinary pharmaceuticals into the environment is the spreading of farm slurry and manure into the soil. Thus, compliance with the rules for needs-based fertilization helps to reduce the entry of veterinary drugs and other micropollutants into soils. With regard to bodies of water – not only for pesticides but also for veterinary drugs – the widening of shoreline strips and the designation of water protection zones could help.

The use of sewage sludge in agriculture is already restricted. However, there are still transition periods until 2029 or 2032 for small sewage treatment plants. The spreading of sewage sludge on or in soils will also be permitted in the future with fewer than 50,000 population equivalents (see Section 3.1). Sewage sludge contains some nutrients such as phosphorus, but it is a pollutant sink in wastewater treatment, which contains a large number of chemical residues that cannot be completely analysed and is also hygienically questionable. Consequently, in Switzerland agricultural recycling has been abolished and the sewage sludge is subjected to phosphorus recycling. A UBA study showed that phosphorus recycling significantly reduces or completely eliminates pharmaceuticals (UBA 2019b). In addition to the requirements of the Sewage Sludge Ordinance (BMJV 2017), sewage sludge should only be introduced into the soil if it meets the requirements of the quality and test provisions for sewage sludge of the Gesellschaft für Qualitätssicherung Landbauliche Abfallverwertung mbH (Society for Quality Assurance Agricultural Waste Treatment) (QLA 2017). In particular, it must successfully pass through the screening of pharmacologically active substances mentioned in the requirements and the test for estrogens.

The grazing of animals on open pastures can help to reduce the consumption of pharmaceuticals, especially antibiotics, although parasite infestation that requires treatment can also occur outdoors. In such cases, only antiparasitic agents that do not permanently damage the ecologically important dung fauna should be used. Promoting the grazing of animals on open pastures is also important for keeping landscapes open for nature conservation reasons.

Today's industrial animal production is inconceivable without the intensive use of veterinary medicinal products and should be refused, not only for the concern of animal welfare (BUND 2019b).

An essential starting point for reducing the consumption of veterinary medicinal products is improving and monitoring the conditions under which animals are kept (HCWH 2017) – a requirement which, also for reasons of animal welfare, cannot be postponed any longer. The alignment of the housing conditions with the movement needs and the natural group behaviour of animals as well as improved stall hygiene contribute significantly to avoiding medication. A binding transformation of livestock farming to better animal welfare, more environmental protection and fewer veterinary drugs is thus essential. For example, in February 2020 the so-called Borchert Commission submitted a specific proposal on how animal and environmental protection issues can be implemented in animal husbandry by 2040 (Competence Network 2020). Although the use of veterinary medicinal products is not directly addressed in the report, the measures are suitable for reducing medication in animal husbandry.

Ecological animal husbandry also contributes to reducing the environmental pollution of water and soil through substantial restrictions on the use of veterinary drugs and in particular antibiotics, since animals are only given antibiotics in exceptional cases when they are kept ecologically. Germany, however, is still a long way from the goal of the federal government's national sustainability strategy of achieving 20% organic agricultural land with the

current level of around 9% (BMEL 2020). This also applies to ecological animal husbandry.

Demands and recommendations of BUND/FoE Germany

- *Prescription requirement for all human medicinal products with environmental risks.*
- *General advertising ban for non-prescription human medicines.*
- *Doctors give precedence to prescribing and pharmacists to selling environmentally friendly drugs based on an environmental classification system.*
- *The public health system serves as a frontrunner in the use of environmentally friendly drugs.*
- *Veterinarians and farmers receive targeted on-the-job training with regard to suitable measures for reducing the environmental impact of pharmaceuticals.*
- *The dispensing right of veterinarians is abolished.*
- *Farmers are obliged to document the consumption of veterinary medicinal products.*
- *The rules for appropriate fertilization must be observed. Shore margins and extended water protection zones reduce the entry of pharmaceuticals into waters.*
- *Entry of active substance residues from drugs into agricultural soils through the application of sewage sludge must be avoided. Agricultural sewage sludge must meet the quality and test regulations of the Society for Quality Assurance Agricultural Waste Treatment. Phosphorus from sewage sludge is always recycled.*
- *Support of grazing animal husbandry.*
- *The animal welfare-friendly husbandry of farm animals reduces the need for veterinary drugs, especially antibiotics. Consequently, compulsory transformation of animal husbandry to providing better animal welfare, more environmental protection and less medication is necessary.*
- *Organic animal husbandry is promoted because it has a significantly lower demand for veterinary pharmaceuticals.*

4.5 Waste and sewage

4.5.1 Drug residues and disposal

Many patients do not use up their medications completely or store them beyond the expiry date. This is often due to the fact that the packaging sizes are not adapted to actual needs. In the case of liquid drugs in particular, consumers then improperly dispose of unused drug residues via the toilet or sink. It is estimated that this is the cause of around 10% of wastewater pollution. Medicinal residues are always waste and do not belong in the wastewater!

The disposal of pharmaceutical residues as waste is not regulated uniformly in Germany but is left to the individual regional authorities. As a result, consumers are often unsure about correct disposal procedures. There is a real patchwork of different disposal systems: Disposal in municipal waste, with transporter for dangerous goods, in pharmacies or recycling centers (Zeschmar-Lahl and Friege 2018).

If municipal waste is incinerated, this is an appropriate method of disposal because the medicines are also incinerated. However – with a decreasing tendency – approximately 25% of municipal waste in Germany is not incinerated but mechanically and biologically treated before being disposed of, which does not lead to a complete elimination of the active substances. This treatment usually also produces wastewater that contains pharmaceuticals.

The establishment of nationwide collection and return systems would thus prevent inappropriate disposal of residual drugs in households. In order to make such a regulation successful, public awareness needs to be raised (HCWH 2017). It makes sense to reinstall the return of pharmaceuticals in pharmacies across the board and make it mandatory by law (Zeschmar-Lahl and Friege 2018). A solution has to be found so that medicines purchased online can also be disposed of in this way.

The inclusion of the necessary disposal information on the outer drug packaging in addition to the standard disposal information on the instruction leaflet

seems sensible but is currently rejected at the European level. The package inserts must be formulated in a way that is understandable for consumers and, in the case of export drugs, formulated in at least one additional world language.

4.5.2 Improvement of decentralized wastewater treatment ("hotspots")

If the raw sewage in the inlet flow into a sewage treatment plant has an above-average proportion of pharmaceutical residues, it should be checked whether indirect dischargers with a high consumption of pharmaceuticals are responsible. In these cases it can make sense to subject partial flow from, for instance, a hospital to decentralized treatment before it is discharged into the sewer system. Such pretreatment can also help reduce exposure to disinfectants and pathogens.

Almost 20% of the active pharmaceutical ingredients contained in municipal wastewater come from health care facilities and around 80% from households. However, the proportion of X-ray contrast media, certain antibiotics, and cytostatics that are discharged by hospitals is above average.

If medication that has been administered is quickly excreted by the patient, it makes sense to collect this excretion separately. Setting up separate toilets or collecting excretions directly from the patient using urine bags is appropriate for this.

Pilot studies show that collection systems for direct use with patients such as urine bags are both efficient and practical for X-ray contrast media. It makes sense to collect the urine for at least 24 hours in order to trap most of the active substances. Up to 30–40% of the X-ray contrast agent is excreted in the first visit to the toilet after an X-ray examination (TAB 2019).

As a general rule, X-ray contrast media should not enter the sewage system or wastewater, but should be removed separately, because such substances are only very incompletely removed even at the fourth

stage of wastewater treatment (see Section 4.5.3). X-ray contrast media are used in roughly equal parts in hospitals and radiology practices using X-rays, which is why both types of healthcare facility must be covered by regulation.

What applies to X-ray contrast media also applies to contrast media in magnetic resonance imaging (MRI). Gadolinium chelates are also excreted very quickly and are not broken down in sewage treatment plants. Used urine bags must be disposed of as waste, i.e. incinerated (UBA 2018a). Collection by means of urine bags is already common practice for radiopharmaceuticals.

In addition, health facilities should be obliged to document their use of medication (as well as the use of other micropollutants such as disinfectants) and their environmentally friendly disposal. The aim must be to use drugs sparingly but in a targeted manner. It should also be checked whether an environmentally friendly drug can be given preferred use if it fulfils the same medical purpose. An environmental audit according to EMAS could serve to achieve these goals.

Training medical staff in health facilities on the environmentally friendly use of pharmaceuticals can help to raise awareness of the problem. This also applies to the caring staff in facilities for the elderly with high levels of medication.

4.5.3 Central wastewater treatment – sewage treatment plants

In Germany, municipal wastewater in sewage treatment plants usually has three purification stages: a mechanical, a biological and a third stage, which is used to eliminate phosphorus and nitrate nitrogen. Many active pharmaceutical ingredients are only partially removed in this way. For this reason, the introduction of a fourth purification stage is being discussed, which, in addition to pharmaceuticals, would also eliminate other micropollutants. Research studies have shown that not only the concentration of several pollutants is reduced – the cleaning performance of the 4th level is reported as being about 70% – but

the toxicological and ecotoxicological effects of the wastewater discharge are also significantly reduced (Triebkorn 2017). In the Mannheim sewage treatment plant, for example, the estrogenic activity of the treated wastewater was reduced by 85% without this being explained by chemical analyses of individual substances (UBA 2018a). Switzerland is already systematically installing the 4th purification stage in large wastewater treatment plants.

The wastewater is further purified either by adsorption on activated carbon or by oxidative treatment with UV/ozone or by membrane filtration. In view of the large number of chemically completely different active ingredients, the three processes are very effective for some active ingredients, but less so for others. A combination of processes delivers the best results. In the opinion of the UBA, nanomembrane filtration is the most effective way of retaining antibiotic-resistant bacteria. The UBA also refers to the high level of efficiency of the introduction of a fourth cleaning stage, due to the broad spectrum of micropollutants which can be reduced effectively by this measure. Their practical feasibility has been demonstrated by the expansion of sewage treatment plants in, for instance, North Rhine-Westphalia and Baden-Württemberg. The discussion of the implementation of the polluter pays principle, i.e. the question of the financing of these measures, seems to be having an inhibiting effect (UBA 2018a).

The annexes of the federal wastewater ordinance – beyond the question of their application in sewage treatment plants in the pharmaceutical industry – should be examined in connection with the possible inclusion of restrictions on pharmaceuticals in municipal wastewater treatment (BUND 2017).

Consideration should also be given to whether the pollution of wastewater by micropollutants such as pharmaceuticals can be taken into account in an “enhanced” effluent discharge fee and thus contribute to the financing of more extensive wastewater treatment (TAB 2019).

With regard to pollution through effluents from sewage treatment plants and subsequent pollution of water with pathogenic bacteria – in particular antibiotic-resistant bacteria – it should be emphasized that the Wastewater Ordinance does not place any requirements on the microbial contamination of wastewater. It is not without reason that the Biological Agents Ordinance classifies the profession of sewage works operator as a non-targeted activity with a high level of exposure to pathogens. Section 41 para 1 of the German Protection against Infection Act (IfSG) specifies that: “Those obliged to dispose of sewage have to see to it that the sewage is disposed of in a way that does not give rise to any hazards to human health due to pathogens” (BMJ 2000). This legal provision must be implemented urgently.

Demands and recommendations of BUND/FoE Germany

- *Medication residuals shall not be flushed away in the toilet or sink.*
- *A standard system for disposal of medication residuals through pharmacists must be (re)installed.*
- *Instructions on the drug packaging must inform consumers about proper disposal.*
- *Specific wastewater flows with particularly high drug contamination (from health facilities) must be identified. At such hotspots, it should be checked whether decentralized treatment of specific flows would bring improvements and where this is the case these should be made mandatory.*
- *Excretions from patients treated with X-ray or MRI contrast agents should be collected separately, e.g., in urine bags, and incinerated.*
- *The use of medication in healthcare facilities must be documented. Environmentally friendly active ingredients should be preferred. An EMAS audit may lead to continuous improvements.*
- *The staff of health and care facilities must be trained in the sparing use of drugs.*
- *The fourth purification stage should gradually be introduced in municipal sewage treatment plants in the categories 3 to 5 (from 5,000 PE) if there are ecological or health reasons. A reform of the effluent discharge fee could help financing.*
- *Microbiological requirements on effluents of sewage treatment plants should be included in the Wastewater Ordinance in accordance with the requirements of the Protection against Infection Act.*

4.6 Public relations

There is a low level of information and awareness of the effects of pharmaceutical residues in the environment in the general public, but also in specialist circles such as the health sector. Promote of the sparing use of pharmaceuticals is necessary as well as education and awareness-raising campaigns about pharmaceuticals and their effects on the environment (HCWH 2017).

For this it is necessary that the relevant content is integrated into the training and further education of medical staff, caring professions and pharmacists. In the case of the general public there is a need for state-financed, professionally neutral public awareness campaigns.

4.6.1 Human medicine

Drug consumption has increased considerably in the general public in recent years. In particular, this involves non-prescription drugs, which are also heavily advertised. Strengthening health protection is a task for society as a whole. All precautionary and preventive measures, including sports and nutrition, have an indirect effect on drug requirements. The health insurance companies and politics also have the task of strengthening awareness among consumers that not every minor indisposition needs to be treated with medication. Confidence in the body's self-healing powers for simple illnesses must be strengthened.

Many medicines are taken without any medical need. An analysis of which factors are responsible for the increase in drug consumption (apart from the increase in the average age) could help to develop a strategy for better health management (UBA 2018a).

Numerous drugs are only available in packaging sizes that exceed the needs of the patient. This leads to excessive costs and also to avoidable, additional drug waste.

A not inconsiderable proportion of unused medication is disposed of via the sewage system. In order

to remedy this deficiency, awareness and training campaigns have also been launched recently for doctors and pharmacists. This work must be significantly intensified in the future (BUND 2017). More information on the correct disposal of drug residues is a necessary and comparatively cost-effective reduction measure. To achieve this, comprehensive and targeted information should continue to be provided in nationwide campaigns, with the participation of the pharmaceutical industry. Appropriate disposal information on the external packaging of drugs in addition to the standard disposal information on the package insert is still sensible, even if this is currently rejected at European level (UBA 2018a).

In Germany, responsibility for waste disposal lies with the municipalities and districts. The recommendations for disposal differ according to the regional disposal structure. As part of the RiSKWa funding measure, a map of Germany has been drawn up that shows the public the existing recommendations at city/district level (available at: www.arzneimittelsorgung.de, BMBF 2016). In the medium term, a uniform system of disposal via pharmacies should make communication easier (see Section 4.5.1).

4.6.2 Veterinary medicine

Further education and information for those working in agriculture and veterinary medicine should be made available to help reduce the consumption of veterinary medication (UBA 2017b, 2017c, 2017d).

This particularly applies to the administration of antibiotics and the resulting antibiotic resistance, which has decreased in the past but is still somewhat higher than in human medicine. This is possible, for example through a reduction in germ pressure and better stable hygiene, reporting of environmental damage via eco-pharmacovigilance, proper application and pretreatment of fertilizer (longer storage and fermentation of manure usually reduces the concentration of drug residues). Overarching initiatives such as the German Antibiotic Resistance Strategy DART can also help to raise awareness of antibiotics and resistance to them (UBA 2018b).

It is also necessary for the operators of fish farms and other aquacultures to disseminate information on the effects of medicinal products on water in order to raise awareness. Stocking density is also a substantial factor in relation to drug consumption. Finally, beekeepers too should be informed about how to protect bees from the Varroa mite in an environmentally friendly manner.

Demands and recommendations of BUND/FoE Germany

- *Health prevention and care must be expanded.*
- *Integration of the topic of pharmaceuticals in the environment in the training and further education of medical staff, associated professions and pharmacists.*
- *State-financed and professionally neutral information campaigns for citizens about pharmaceuticals in the environment.*
- *The health insurance companies and politicians should raise awareness that drugs should only be administered/taken if they are medically necessary.*
- *Manufacturers and pharmacists should offer packaging sizes adapted to requirements.*
- *Consumers must be informed through campaigns and warnings that drug residues must not be disposed of down the toilet. The regional disposal structure must be better communicated to consumers. In the medium term, standard disposal procedures for drug residues by pharmacies should be aimed for.*
- *Farmers should be trained in measures they can adopt to reduce the use of veterinary medicinal products. In particular, they must be made aware that antibiotics should not be used as a precautionary measure.*
- *Fish farmers and aquaculture operators, whose use of pharmaceuticals often ends up in the water, should also be trained about the effects on the environment.*

4.7 Financing

Extended producer responsibility should apply to the pharmaceutical industry, i.e. manufacturers should be responsible for the entire life cycle of drugs. This requirement arises from the polluter pays principle. It is true that pharmaceutical manufacturers are not solely responsible for all cost-effective measures to reduce drug consumption. For example, more extensive wastewater treatment (4th stage of wastewater purification) is not required solely because of the presence of active pharmaceutical ingredients.

Financial participation of polluters in the cost of reductions was called for by, among others, the Environment Ministers' Conference and the Federal Council of Germany. Both would like manufacturers and importers of drugs and active pharmaceutical ingredients to be appropriately involved in the costs of the mitigation measures (UBA 2018a). Other examples of appropriate funding by manufacturers and importers are information and education services, the costs of organic pharmacovigilance and monitoring programs.

Establishment of a fund or a drug levy should be discussed as a financing model, as Gawel et al. (2017) proposed.

Demands and recommendations of BUND/FoE Germany

- *According to the polluter-pays principle, pharmaceutical manufacturers have extended product responsibility for the life cycle of pharmaceuticals. Thus, they should make a major contribution to financing the measures mentioned above. Suitable financing models must be developed.*

5. Conclusion

Medications are a widely underestimated environmental problem. The pollution of waters and soils by drugs and their metabolites, especially by antibiotics and antibiotic-resistant pathogens, has reached a serious level. An overall strategy is needed with measures that will lead to a significant reduction in environmental pollution.

The measures mentioned in Chapter 4 differ in terms of their relevance and how quickly they can be implemented. Many groups bear the responsibility for finding an effective strategy for reducing the pollution of the environment by pharmaceuticals: first and foremost, according to the polluter pays principle, the manufacturers and importers, but also doctors, pharmacists, politicians, the water industry and, last but not least, the consumers. It is apparent that a bundle of measures with different responsible parties is required in every case. A “medicines-in-the-environment strategy” can only lead to success if effective measures are adopted for all stages of the medicinal product life cycle outlined above. Future generations will thank us if a healthy ecological state of our waters and soils can be restored through significantly reduced input of pharmaceuticals and unpolluted drinking water is also available in the future.

6. Glossary

AMR	Antimicrobial resistance
BfR	German Federal Institute for Risk Assessment
BVL	Federal Office of Consumer Protection and Food Safety
DART	German Antibiotic Resistance Strategy
Dispensing right	The right to manufacture, mix, store and dispense pharmaceutical substances requiring a prescription
EFSA	European Food Safety Agency
EMA	European Medicines Agency
ESBL	Extended-spectrum beta-lactamase (Beta(β)-lactamases with an extended spectrum) = enzymes which can break the structures of antibiotics containing β -lactam
EU	European Union
GMP	Good Manufacturing Practice (of pharmaceuticals)
GOW	Health related guide values (for drinking water)
GwV	Groundwater Ordinance (Grundwasserverordnung)
HCWH	Health Care without Harm
JKI	Julius Kühn-Institut (Federal Research Centre for Cultivated Plants)
LAWA	German Working Group on water issues of the Federal States and the Federal Environment Ministry
MRE	Multi-drug resistant pathogenic bacteria
MRSA	Methicillin-resistant Staphylococcus aureus (MRSA)
NRZ	National Reference Centre for Surveillance of Nosokomial Infections
Old drugs	Medicinal products with authorization prior to 2006
OGewV	Ordinance on the Protection of Surface Waters (Oberflächengewässerverordnung)
PAN	Pesticide Action Network
PBT	Persistent, bioaccumulative, toxic
Pharmacovigilance	Observation of side effects of drugs after authorisation
PMT	Persistent, mobile, toxic
RiSKWa	Risk Management of New Pollutants and Pathogens in the Water cycle
RKI	Robert Koch Institute
SAICM	Strategic Approach to an International Chemicals Management
UBA	German Federal Environment Agency
UN	United Nations
EQS	Environmental quality standard
vPvB	Very persistent and very bioaccumulative
vPvM	Very persistent and very mobile
WFD	European Water Framework Directive
WHO	World Health Organization

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Imprint

Published by:

*Bund für Umwelt
und Naturschutz
Deutschland e. V. (BUND),
Friends of the Earth Germany,
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Grommelt, in collaboration with
the BUND working groups
"Health", "Environmental
Chemicals and Toxicology",
and "Water".*

*We are grateful for contribu-
tions made by the working
groups "AK Boden/Altlasten"
(Soil/Contaminated Sites)
and "AK Landwirtschaft" (Agri-
culture).*

Responsibility under press law:

Petra Kirberger

Production:

Natur & Umwelt GmbH

1st edition, November 2020