



**BACKGROUND** // AUGUST 2015

# Pharmaceuticals in the environment - avoidance, reduction and monitoring

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# Pharmaceuticals in the environment – avoidance, reduction and monitoring

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## Core statements

- ▶ Residues of pharmaceuticals pollute our waters and soils. Their traces are found in groundwater and in some cases in drinking water. A risk for the environment has already been identified for a few pharmaceutical active substances. However, according to current knowledge, no risk for human health is indicated. In order to protect our waters and soils on a long-term basis and as well for reasons of preventative health protection the contamination of waters and soils needs to be reduced.
- ▶ For more than 10 years the Federal Environment Agency has been assessing the environmental risk of new human and veterinary pharmaceuticals within the marketing authorisation procedures. However, for many pharmaceuticals containing active substance which are on the market for a long time, no data are available to allow an assessment of the environmental risks. An effective reduction of the discharge of pharmaceuticals into the environment can only be achieved through a combination of measures at various levels (patient, doctor, pharmacist, water management, pharmaceutical industry). Mitigation measures imposed as part of the marketing authorisation alone are not sufficient.
- ▶ In addition to optimised wastewater treatment and the development of more environmentally friendly pharmaceuticals, conscious handling of pharmaceuticals and their correct disposal play a key role.
- ▶ The development of environmental quality standards for pharmaceuticals, especially for those occurring in environmentally relevant concentrations, is an effective measure to recognise the necessary actions to reduce contamination of waters and makes an important contribution to the water protection at national and European level.

## 1 Why does the Federal Environment Agency (UBA) deal with pharmaceuticals?

Pharmaceuticals are essential for human and animal health. The costs for good medical care and the sometimes uncritical handling of pharmaceuticals is the increasing pollution of the environment with residues of pharmaceuticals. These are often persistent and harmful for the environment. In order to protect our waters and soils in their functions as habitats and drinking water resources in the long term, the entry of pharmaceuticals into the environment must be

limited as far as possible. The aim of this background paper is to explain the facts and contexts of the topic of „pharmaceuticals in the environment“ and various different options for actions to reduce the environmental entry from the perspective of the UBA in an easily comprehensible manner.

### What are pharmaceuticals?

Pharmaceuticals are substances or preparations of substances which are intended to cure, alleviate, detect or prevent human or animal diseases. Pharmaceuticals in general consist of pharmaceutically active substances and excipients. They are used in human or animal bodies in various different pharmaceutical forms such as tablets, drops, solutions for injections, ointments, sprays or liquids. Some pharmaceutically active substances such as plant extracts have been used for thousands of years. Modern pharmaceuticals are developed in a targeted manner by means of pharmaceutical research and are industrially manufactured.

## 2 How do pharmaceuticals get into the environment?

### Pharmaceuticals in our everyday lives

Pharmaceuticals are one of the most important tools in medicine and are as good as ubiquitous in our lives. Almost everybody takes medications either when needed or on a regular basis. In 2011, each person with statutory health insurance received an average of nine packs with 520 defined daily doses (DDD) on prescription<sup>1</sup>. In addition to this there are medicines such as cold remedies and painkillers which are freely available from pharmacies. From a statistical perspective, the consumption of pharmaceuticals over the course of a human life increases drastically. For example, with an average of 56 DDD per year, males aged between 20 and 24 require the fewest medications. However, at an average of 649 DDD, males over the age of 60 consume almost twelve times that amount<sup>2</sup>. The consumption of pharmaceuticals is likely to increase further in the long term due to the demographic change in our society. In addition to humans, livestock and companion animals are also regularly treated with veterinary medicinal products in order to keep them healthy and productive. The majority of veterinary medicinal products are used in intensive farming, which would not be possible without pharmaceuticals in their current form.



Source: Fotolia #14053973 - Take some medicine © PictureArt

### Consumption volume

There is a wide range of authorised pharmaceutically active substances. On the German market alone approximately 2,300 different active substances for human pharmaceuticals are available, approximately half of which are potentially environmentally rele-

vant. Substances such as traditional herbal remedies, electrolytes, vitamins, peptides, amino acids and many other substances which occur naturally in the environment such as minerals are deemed not environmentally relevant as they are non-toxic or very rapidly degradable. A total of 8,120 t of the approximately 1,200 active substances in human pharmaceuticals which are possibly environmentally relevant were used in Germany in 2012<sup>3</sup>. This is an increase of almost 20 % in ten years compared to the 6,200 t consumed in 2002. Two thirds of this amount is made up of just 16 active substances (Fig. 1), the consumption of which is more than 80 t. The most commonly prescribed human pharmaceuticals are anti-inflammatory medicines, asthma medicines and psychotherapeutic medicines<sup>1</sup>.

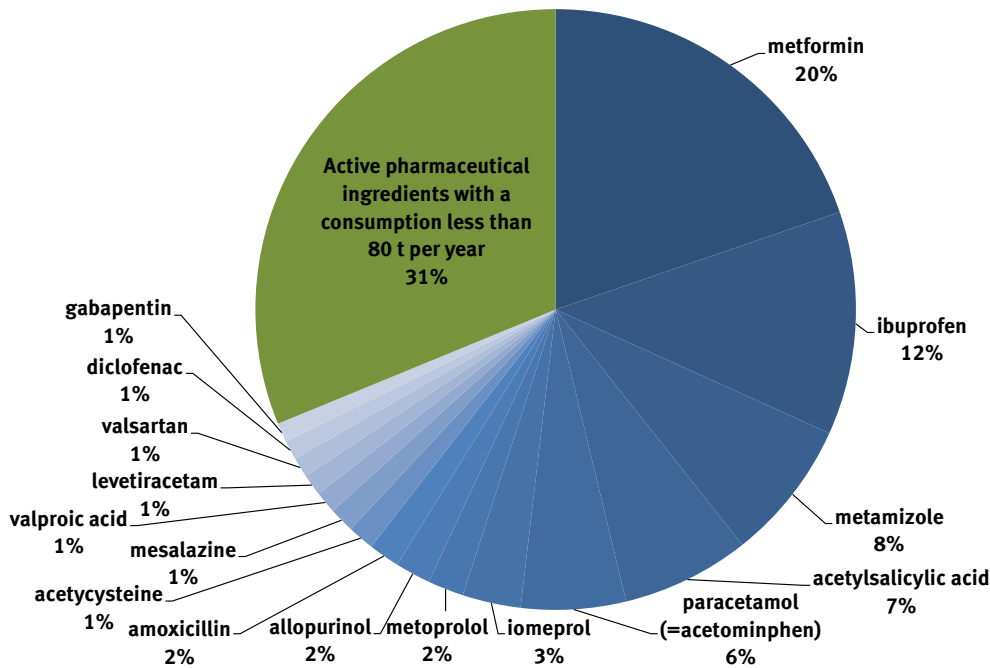
Significant groups of veterinary medicinal products are antibiotics and antiparasitics. In veterinary medicine, however, substances which affect the hormones, pharmaceuticals to treat inflammation and local therapeutic agents for the skin, udders and eyes are also used<sup>4</sup>. A total of more than 1,600 t of antibiotics is distributed to livestock farmers alone each year<sup>5</sup>. There are no current detailed consumption volumes available for all other veterinary medicinal products and for companion animals.

### Entry paths

Many tonnes of pharmaceuticals are used each day. A side effect difficult to avoid is their entry into the environment because pharmaceuticals mostly do not disappear after they pass through human or animal bodies. A large amount of these get into the environment without being changed and are still pharmaceutically active, others are excreted by humans or animals in form of metabolites. These residues are then converted and broken down in the environment. The transformation products formed in this process are often less or no longer pharmaceutically active but can have problematic environmental characteristics such as persistence or increased mobility. This can lead to them being more easily shifted, for example into the groundwater. Some transformation products might even be converted back into the pharmaceuti-

Fig. 1

**Overview of human pharmaceuticals with the highest consumption in 2012 and with relevance to the environment\***

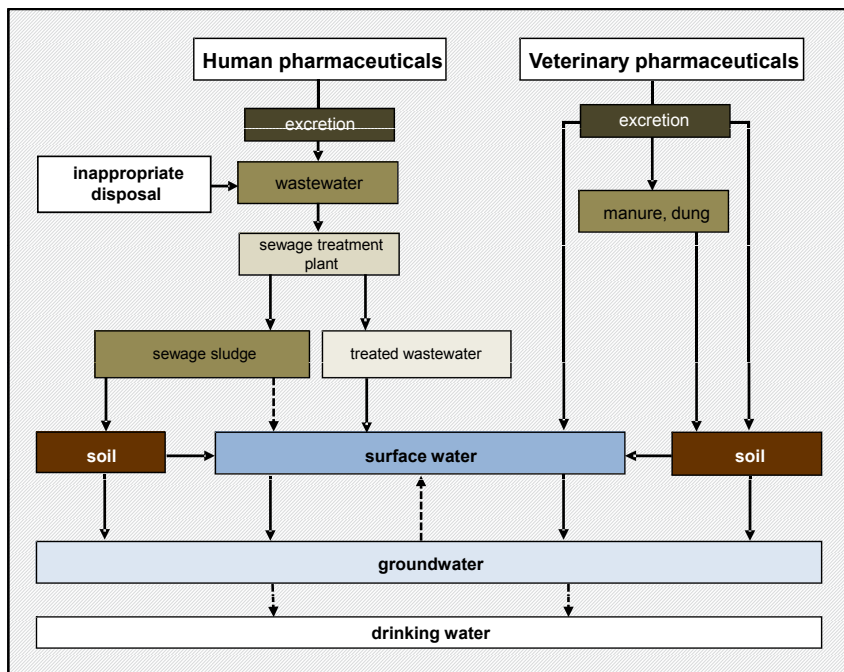


Source: IMS Health, 2013; compilation: UBA

\* excluded are traditional herbal remedies, electrolytes, vitamins, peptides, amino acids and certain natural substances

Fig. 2

**Main entry pathways of pharmaceuticals for human and veterinary use**



cally active original compound in the environment<sup>6</sup>. Human pharmaceuticals enter wastewater indirectly via human excretion. Also unused medicines which are incorrectly disposed of in drains and toilets find its way directly into wastewater<sup>7</sup>. Residues of phar-

maceuticals enter wastewater treatment plants via wastewater and the majority of them are removed. However, pharmaceuticals often pass through wastewater treatment plants without being removed. Those residues which have not been broken down then get

into the surface water via the wastewater treatment plant effluent. The main entry path for veterinary medicinal products is manure and dung of treated animals which is used as fertiliser on farm land (Fig. 2). Repeated application can lead to accumulation of those residues in soil. Veterinary medicinal products

from fertilised soils can also enter surface water and ground water via run-off at heavy rain fall events and leaching. In addition, direct entry onto pastures and into adjacent waters is caused by grazing livestock who have previously been treated with pharmaceuticals.

### 3 Are medicinal product residues in the environment a risk?

#### Medicinal product finds in the environment

Evidence of the first pharmaceutical in German waters was found rather by accident in the early 1990s. It was clofibric acid, a metabolite of the commonly prescribed lipid-lowering medicine clofibrate, which was identified in groundwater in Berlin by researchers looking for pesticide residues<sup>8</sup>. Since the „Berlin clofibric acid finding“, the topic of pharmaceuticals in the environment has increasingly been in the focus of science and the authorities.

Residues of pharmaceuticals are regularly measured within the scope of the water monitoring carried out by the federal states, and they can be found in surface waters almost everywhere. Although there is no systematic monitoring of pharmaceuticals in Germany yet, research projects and investigation programmes in the federal states, such as a literature study on behalf of the UBA<sup>9</sup>, already discovered more than 150 active substances in the various different environmental compartments. Substances of all significant pharmaceutical classes are found, and the following particularly commonly:

- ▶ iodised X-ray contrast media
- ▶ the anticonvulsant carbamazepine
- ▶ the analgesic/antiphlogistic diclofenac
- ▶ the antibiotic sulfamethoxazole
- ▶ lipid-lowering agents
- ▶ beta blockers
- ▶ synthetic hormones

A large number of pharmaceutically active substances are measured in surface waters in concentrations of 0.1 to 1.0 micrograms per litre ( $\mu\text{g/l}$ ). Many are found in lower and some in significantly higher concentrations, such as the X-ray contrast medium iomeprol with a maximum measured concentration of 20  $\mu\text{g/l}$  (Fig. 3). An evaluation of measurement programmes from the years 2009 to 2011 carried out by the

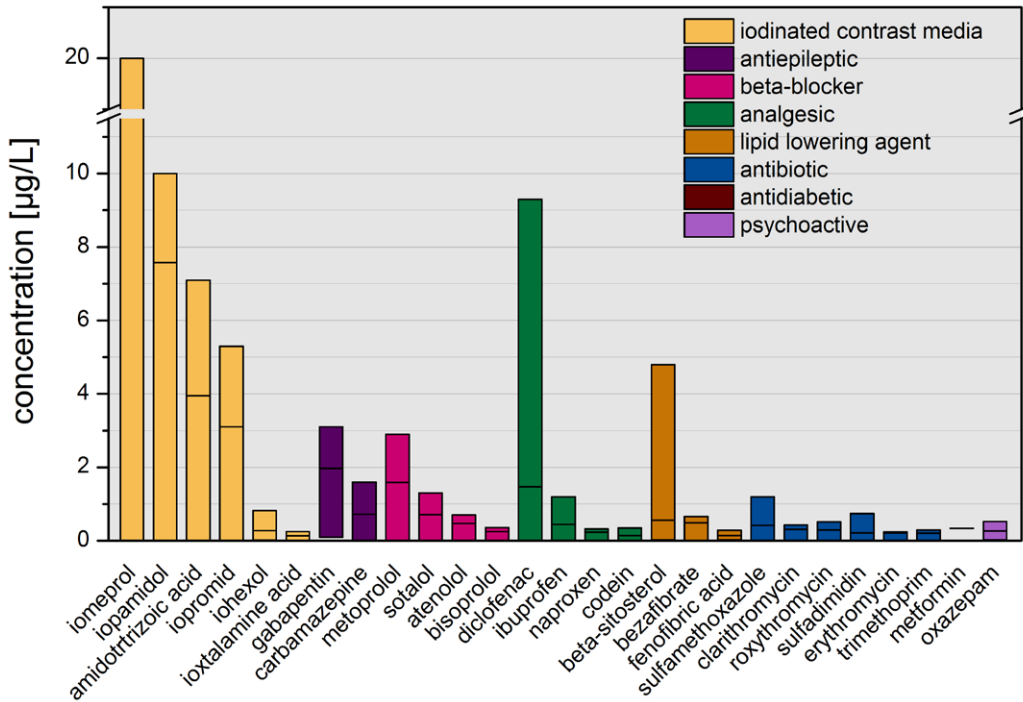
Federal Environment Agency shows that a total of 27 different pharmaceutically active substances from eight different therapeutic classes were measured in German surface water in concentrations above 0.1  $\mu\text{g/l}$ . In addition to X-ray contrast media, the commonly used painkiller diclofenac is also found at remarkably high concentrations (Fig. 3).



Source: Frank\_Fotolia\_29330273\_1

Fig. 3

**Pharmaceutically active substances detected in surface waters in concentrations above 0.1 µg/l**

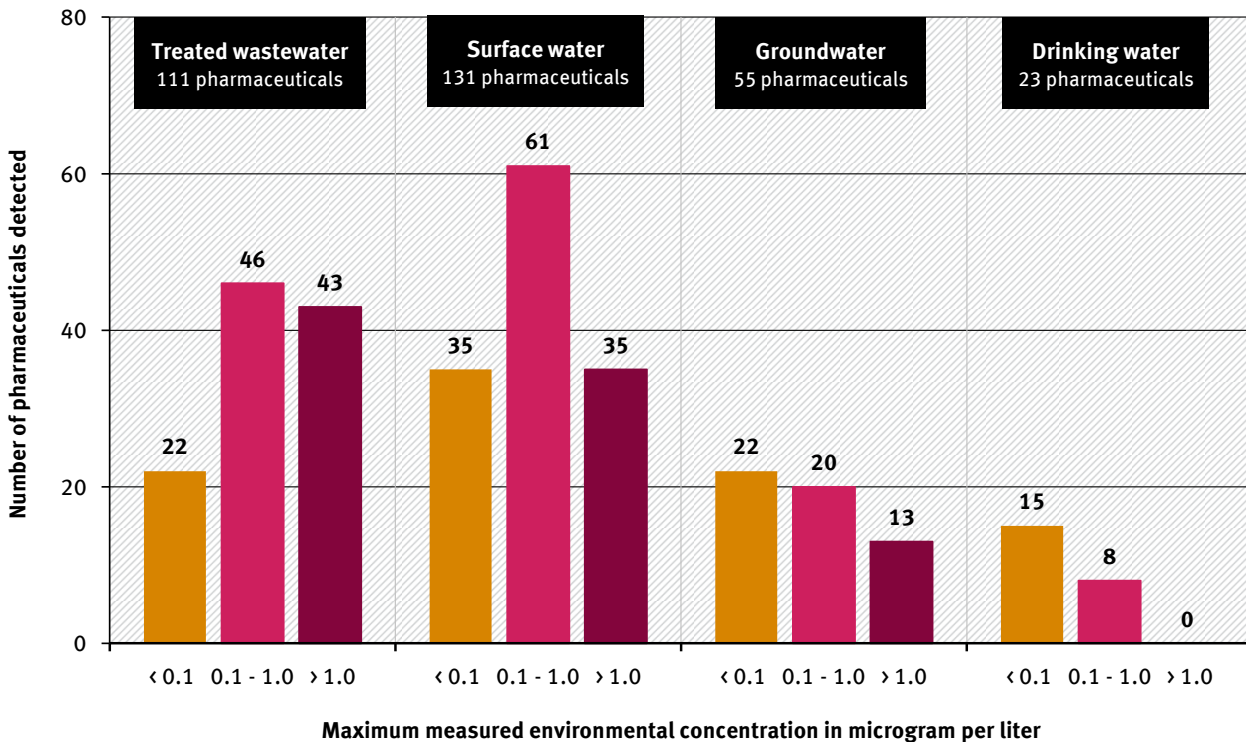


[Data: Bund/Länder Arbeitsgemeinschaft Wasser LAWA, compilation: UBA, 2013]

Box: The box shows minimal and maximal concentrations, line = max. mean value; Metformin: only one data point available

Fig. 4

**Number of measured pharmaceutically active substances in sewage treatment plants (STP effluent), surface waters, groundwater and drinking water; shown as concentration categories of the maximum measured concentration**



Source: Bergmann et al., 2011 – modified



Particularly high concentrations of human pharmaceuticals are measured in the effluents from wastewater treatment plants. As a consequence, surface waters which receive a high proportion of wastewater from communal wastewater treatment plants contain very high levels of pharmaceutical residues. Various different pharmaceuticals and their degradation products are also found in groundwater and on isolated occasions in drinking water (Fig. 4). In general, concentrations of pharmaceuticals decrease in the following order: Wastewater treatment plant effluent > surface waters > groundwater > drinking water.

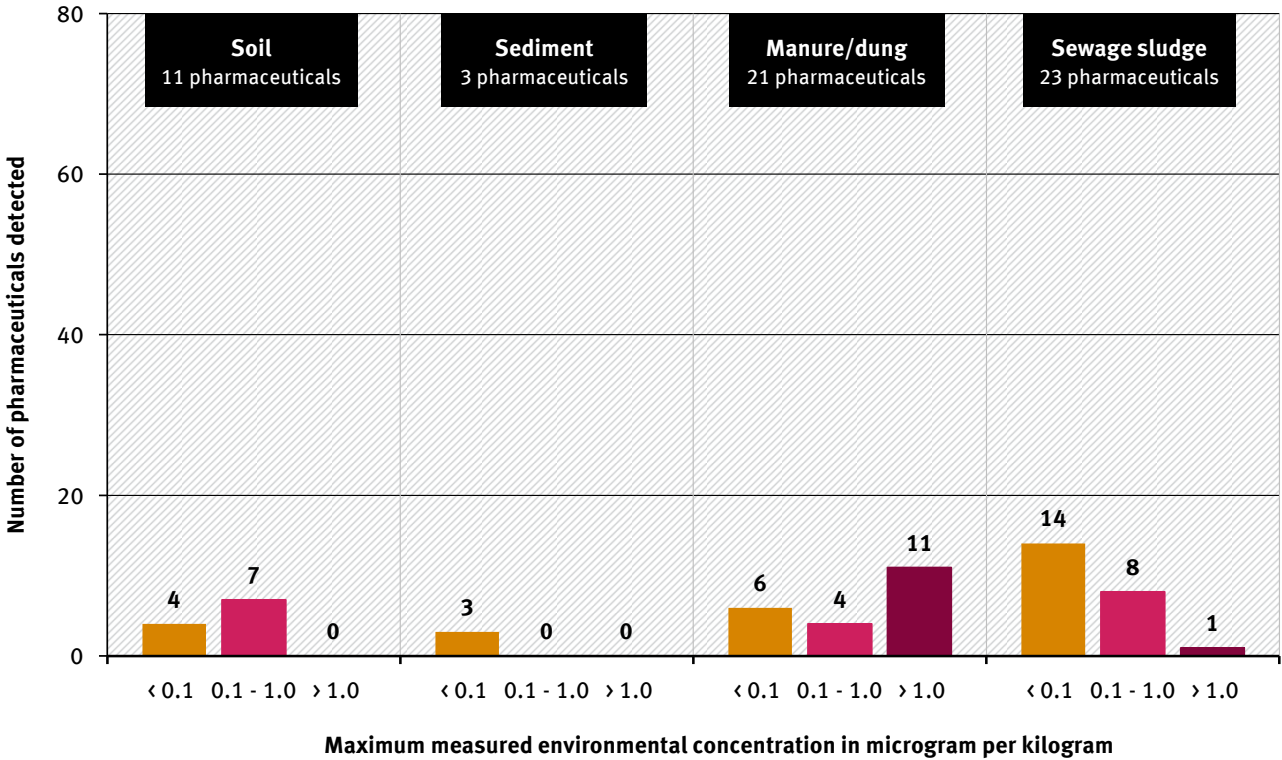
Sewage sludge from wastewater treatment also contains high concentrations of pharmaceutical residues. Bergman et al.<sup>9</sup> (2011) reported findings of 23 different pharmaceuticals (Fig. 5). Overall, the number of findings of pharmaceuticals in sewage sludge is significantly lower than in surface waters. The reason

for this is that only a small number of pharmaceuticals in sewage sludge have been investigated due to the comparatively work-intensive analytics. According to information from the Federal Statistical Office from 2012, approximately 800,000 tonnes of sewage sludge enter soils in Germany per year as fertiliser or for soil improvement<sup>10</sup>.

Residues from veterinary medicinal products are primarily to be found in dung and manure from treated livestock (Fig. 5). These get onto farm land as fertiliser where they can accumulate and be shifted into surface water, groundwater or even drinking water<sup>11</sup>. Measurements in groundwater close to livestock farms prove that where large amounts of agricultural fertiliser are regularly stored and spread onto fields, there are also residues of pharmaceuticals. The majority of these are antibiotics<sup>12, 13</sup>.

Fig. 5

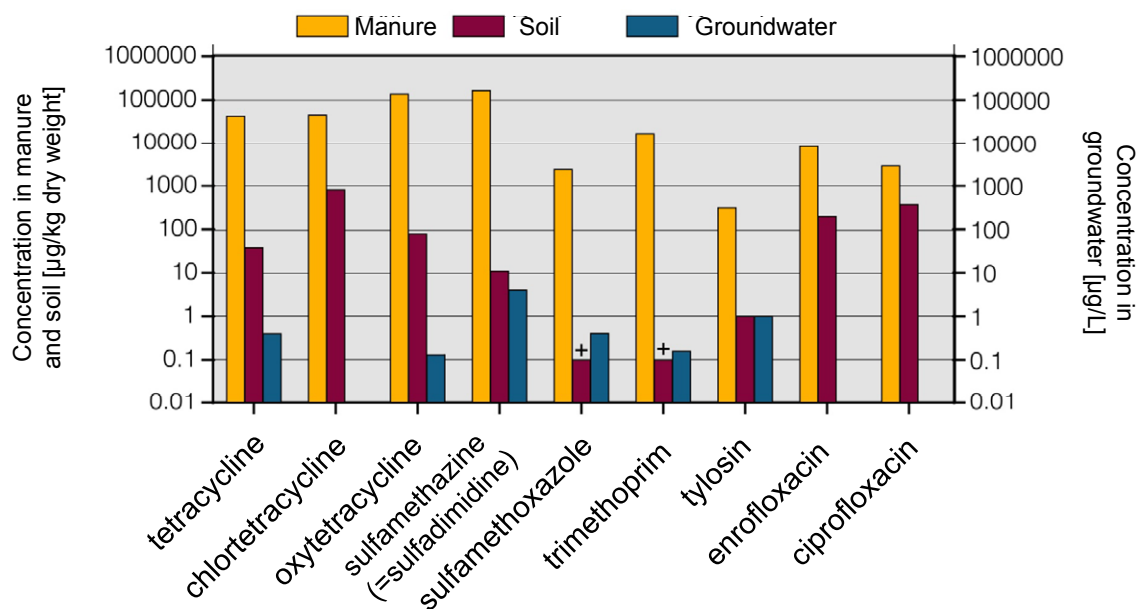
**Number of measured pharmaceutically active substances in soil, sediment, manure/dung and sludge, shown as concentration categories of the maximum measured concentration in mg/kg dry weight**



Source: Bergmann et al., 2011 – modified

Fig. 6

## Concentrations of antibiotics in soil, manure and groundwater (maximum concentrations)



+ readings < limit of detection of 0.1 µg/kg dry weight

[Data: Küster et al., 2013<sup>42</sup>; Hembrock-Heger, 2011<sup>43</sup>; Sattelberger et al., 2005<sup>44</sup> und Winckler, 2004<sup>45</sup>; compilation: UBA]

### Which pharmaceuticals are particularly relevant to the environment?

In order to assess the environmental risk of pharmaceuticals, not only data on consumption volumes need to be taken into account. Specific physico-chemical properties of the active substances e.g. water solubility, the metabolism in the body, the behaviour in the environment (degradation, shift) and the ecotoxicity of the substances must also be taken into account. Many properties important for the efficacy of a pharmaceutical might be problematic from an environmental perspective, such as high stability or good water solubility. Substances with so called PBT properties are classified as being of very high concern. Substances such as these:

- ▶ are stable in the environment and therefore difficult to be biodegraded (persistent),
- ▶ accumulate in organisms (bioaccumulating) and
- ▶ are poisonous to humans or environmental organisms, carcinogenic or affect the hormone system (toxic).

Due to their properties, PBT substances should not get into the environment. They would always pose a hazard regardless of their concentration and therefore

a marketing authorisation should not be granted. This applies generally to pharmaceuticals with PBT properties, too. To date, only very few pharmaceuticals are known to fall in this category. In case of pharmaceuticals for use in humans, a marketing authorisation is not ruled out despite the PBT properties for ethical reasons. From an environmental perspective, doctors should therefore prefer alternative and less problematic pharmaceuticals where possible. An open access environmental information and classification system for pharmaceuticals such as the one used in Sweden ([www.fass.se](http://www.fass.se)) could be an important tool for doctors in Germany, too.

### Specific risks of antibiotics

It is known that the excessive and inappropriate use of antibiotics can have consequences in terms of health risks. The problem of antibiotic residues in animal products such as in poultry is also subject of public discussions. It is less well known that antibiotics can also cause harmful effects in the environment. Antibiotics often have problematic intrinsic properties such as persistence. They are used in both human and veterinary pharmaceuticals to a substantial degree. In 2012 alone, approximately 1,600 t of antibiotics were provided to veterinarians<sup>5</sup>. The consumption of human antibiotics in the same year was approximately 630 t<sup>3</sup>. The majority of this amount enters waters and

soil via human or animal excretion either unchanged or as degradation products. It is known that certain antibiotics such as sulfonamides and tetracyclines can accumulate in soil. Scientists have shown that they also can be taken up by crops and consequently might get into the food chain<sup>9</sup>. Antibiotics are very frequently found in surface water and groundwater (Fig. 6) and have also been found in fish samples. Adverse environmental effects of antibiotics include, for example, the growth inhibition of plants and algae<sup>15, 16</sup>. As an alarming consequence of the increasing use of antibiotics in human and animal medicine an increasing development of resistant pathogenic bacteria has been observed. In order to contain hazardous antibiotic resistances persons in charge in the area of healthcare, animal husbandry and the food supply chain worked together to develop the German antibiotic resistance strategy (Deutsche Antibiotika-Resistenzstrategie, DART). This comprises a range of concrete measures and takes into account attempts to combat antibiotic resistance in humans and in animals. The pivotal aim of DART is the reduction and decrease of prevalence of antibiotic resistances<sup>17</sup>.

However, development of resistance is not only limited to human and veterinary medicines but can also occur in the environment<sup>18</sup>. In a research project, the UBA is currently evaluating whether antibiotic resistance in microorganisms is promoted to a greater extent at high concentrations of antibiotic residues as found in manure and sewage sludge. This would need to be taken into account in future environmental risk assessments.

### **Pharmaceuticals with endocrine effects**

Many pharmaceuticals with endocrine (in other words hormone-like) effects can also be of problem for the environment. In general this type of pharmaceuticals deliberately interferes with the hormone system. Medicines such as contraceptives, menopausal hormone therapy and treatment of hormone dependent cancer but also medicines to treat diseases of the thyroid gland and the nervous system aim at having an endocrine effect.

In factory farming, hormone preparations are used as a means for oestrus synchronisation in artificial insemination. Results from laboratory and field tests show that endocrine active substances also exert their often extensive effects such as disorders of reproduction also in organisms in the environment (Tab. 1).

This often occurs even at very low concentrations and presents a particular challenge to the research and assessment of potential environmental risks.

### **Which organisms are affected?**

Pharmaceuticals are generally biologically active substances with a specific effect which interfere in control mechanisms of organisms in a targeted manner. They can affect metabolism, shift the hormone balance or change the signal transmission from cell to cell, to give just a few examples of their possible effects. Since pharmaceuticals are developed intentionally to be highly stable to ensure a high level of efficacy and long shelf lives, their biological activity often ceases only partially or not at all when they get into the environment. Hence, they can also exert their specific effect on other organisms, known as non-



Source: fotolia. #45385058 - Forelle © Marcel Schauer

target organisms. The concentrations of pharmaceuticals measured in the environment are generally lower than the effect threshold for these substances. However, this does not apply to all substances. Critical areas where pharmaceutical residues enter the environment in relatively high concentrations are for surface waters primarily areas close to wastewater treatment plant effluents or intensively used pastures. These areas can present a risk to a large number of organisms. Different organisms in the environment can be affected depending on the specific effect of the pharmaceutical. For example, fish and snails are affected at very low concentrations of the contraceptive 17 $\alpha$ -ethinyl estradiol with drastic alterations of their reproductive organs such as the feminisation of male animals. As consequence of this endocrine effect these animals can no longer reproduce and the population is weakened. The growth of plants and

algae is inhibited by antibiotics and insects found in dung are adversely affected by antiparasitics which are used to treat livestock on pastures. Many examples exist where those adverse effects are demonstrated in laboratory studies. However, detrimental effects of pharmaceuticals were also observed in field studies and even under natural conditions (Tab. 1).

### Is human health at risk?

A few pharmaceuticals are also found in drinking water (Fig. 4). These include the painkillers diclofenac, ibuprofen and phenazone as well as the antibiotic sulfamethoxazole but also the above mentioned 17 $\alpha$ -ethinyl estradiol<sup>19</sup>. There are fractions of a microgram of these substances in one litre of water. These are concentrations which are orders of magnitude lower than the levels at which an effect on humans can be determined. The amounts found in 1 litre of drinking water are 100 to one million times lower than the recommended daily dose. In terms of

drinking water hygiene, these traces of pharmaceuticals are undesirable however they do not represent a specific health risk to humans on the basis of the current state of scientific knowledge<sup>20</sup>. In general, however, traces of pharmaceuticals in drinking water are disapproved by the consumer. In particular women and chronically ill persons express concerns about possible long-term consequences<sup>7</sup>. Moreover, traces of active substances, even if they are demonstrably not harmful, contradict the general principle of clean drinking water.

According to this principle drinking water should be free from impurities. The principle of minimisation requires to keep levels of impurities as low as possible with a justifiable degree of effort. At present no long-term risk can be deduced from a scientific perspective but precautionary measures and further observations in terms of the increasing demand for pharmaceuticals are necessary.

#### Effect threshold

Effect thresholds such as LOEC (Lowest Observed Effect Concentration: the lowest concentration at which an effect occurs in the test) are determined in standardised laboratory tests on model organisms such as algae, water fleas or fish. They are used to quantify the ecotoxicity of a substance. An effect threshold where no adverse effect occurs cannot be determined for all substances. There are substances such as carcinogenic substances or substances with PBT properties for which effects can occur even at very low concentrations. They are therefore assessed hazard based.

Tab. 1

## Effects of medicinal product active substances on organisms - examples from laboratory and field studies and the real environment

Active substance	Use	Non-target organism	Effect	Study	Reference
Deltamethrin	Veterinary medicinal product Antiparasitic	Chironomids	Killing of the larvae in sediment	Laboratory study	Akerblom et al., 2008 <sup>21</sup>
Diclofenac	Human pharmaceutical Analgesic	Rainbow trout	Damage to internal organs	Laboratory study	Triebeskorn et al., 2007 <sup>22</sup>
Diclofenac	Human pharmaceutical Analgesic	Vultures	Population decline	Environmental effect	Oakes et al., 2004 <sup>23</sup>
Enrofloxacin, Ciprofloxacin	Veterinary medicinal product Human pharmaceutical Antibiotic	Green algae, duckweed, cyanobacteria	Inhibition of growth	Laboratory study	Ebert et al., 2011 <sup>24</sup>
Ethinylestradiol	Human pharmaceutical Hormone	Fathead minnow	Population decline	Field test	Kidd et al., 2007 <sup>25</sup>
Ethinylestradiol	Human pharmaceutical Hormone	Fathead minnow	Inhibition of reproduction	Laboratory study	Länge et al., 2001 <sup>26</sup>
Ethinylestradiol	Human pharmaceutical Hormone	Carp	Female features in males	Environmental effect	Petrovic et al., 2002 <sup>27</sup>
Ethinylestradiol	Human pharmaceutical Hormone	Zebrafish	Alterations to the male gonads	Laboratory study	Nash et al., 2004 <sup>28</sup>
Fluoxetine	Human pharmaceutical Antidepressant	Leopard frog	Disorders of tadpole development	Laboratory study	Foster et al., 2010 <sup>29</sup>
Ivermectin	Veterinary medicinal product Antiparasitic drug	Dung beetles and dung flies	Killing of the eggs and larvae in dung	Laboratory and field test	Liebig et al., 2010 <sup>30</sup>
Ivermectin	Veterinary medicinal product Antiparasitic drug	Benthic meiofauna	Shift in species composition	Mesocosm study	Brinke et al., 2010 <sup>31</sup>
Oxazepam	Human pharmaceutical Antidepressant	Sea bass	Increase activity and changes to foraging behaviour	Laboratory study	Brodin et al., 2013 <sup>32</sup>
Propranolol	Human pharmaceutical Beta blockers	Japanese rice fish	Inhibition of growth	Laboratory study	Huggett et al., 2002 <sup>33</sup>
Propranolol	Human pharmaceutical Beta blockers	Mexican shrimps	Disorders of reproduction	Laboratory study	Huggett et al., 2002 <sup>33</sup>
Sulfamethoxazol	Human pharmaceutical Veterinary medicinal product Antibiotic	Rice plant Oat plant	Inhibition of germination	Laboratory study	Liu et al., 2009 <sup>15</sup>
Sulfadiazin	Human pharmaceutical Antibiotic	Maize plant	Killing of the plants	Greenhouse experiment	Michelini, 2012 <sup>16</sup>
Sulfadiazin	Human pharmaceutical Antibiotic	Soil bacteria	Alterations of the bacterial community	Mesocosm study	Hammesfahr et al., 2008 <sup>34</sup>

## 4 What are the legal provisions?

### Assessment of the environmental risks within the authorisation procedure of pharmaceuticals

Before placing a new pharmaceutical product on the market, possible effects on the environment are assessed by the competent authorities in addition to quality, efficacy and safety assessment. In Germany, the UBA has been responsible for the environmental risk assessment since 1998. Guidelines agreed within the EU are in place for the harmonised environmental risk assessment, for veterinary medicinal products since 1998 and for human pharmaceuticals since end 2006. The tasks of the UBA are in particular:

- ▶ Environmental risk assessment within the framework of national and centralised marketing authorisation procedures,
- ▶ Development and improvement of the scientific and legal bases for the assessment,
- ▶ Funding of research projects on the topic of „pharmaceuticals in the environment“ and
- ▶ Target group-specific informing about the environmental risks of pharmaceuticals.

The authorisation and placing onto the market of pharmaceuticals for use in humans and animals are regulated by the German Medicines Act (Arzneimittelgesetz, AMG). At EU level, European Directives 2001/82/EC<sup>35</sup> and 2001/83/EC (as amended)<sup>36</sup> and Regulation 726/2004/EC<sup>37</sup> set out the conditions for the authorisation of new human and veterinary pharmaceuticals. The EU legislation requires an environmental risks assessment of pharmaceuticals to be performed as part of new authorisation applications and risk mitigation measures to be provided if necessary. However, all products authorised before the introduction of the environmental assessment, pharmaceuticals known as old pharmaceuticals, are not subject to a subsequent environmental risk assessment. In contrast to veterinary medicinal products, for pharmaceuticals for use in humans a potential environmental risk is not considered in the benefit-risk assessment. The environmental risk is therefore not pivotal for the marketing authorisation of human pharmaceuticals. The European provisions laid out in the EC Directive were implemented in national law. Consequently, the German Medicines Act requires in the authorisation

dossier information on the mitigation of possible risks to the environment which could result from the storage, use or disposal of the medicinal product.

The Federal Environment Agency is the competent authority for the assessment and evaluation of submitted studies on behaviour and effects of pharmaceuticals in the environment. The environmental risk assessment is carried out in accordance with the guidelines of the European Medicines Agency (EMA). If the assessment gives cause for concern, the respective competent authorities (for human pharmaceuticals the Federal Institute for Drugs and Medical Devices – BfArM- and the Federal Office of Consumer Protection and Food Safety – BVL - for veterinary medicinal products) decide on obligations to protect the environment in agreement with the UBA. If it is not possible to establish any effective risk mitigation measures, the marketing authorisation of veterinary pharmaceuticals could be refused, whereas this option is not available for human pharmaceuticals. Within the risk assessment the Federal Environment Agency already identified serious environmental risks in many cases and corresponding obligations were issued. This applies to the therapeutic groups of anti-parasitics, hormones, cytostatics and antibiotics.

### Provisions to protect groundwater, drinking water and surface water

Water resources require particular protection not only as a habitat for aquatic organisms but also as a vital basis for human life. The principles of precaution and prevention therefore apply in particular for waters used for drinking water production<sup>38</sup>. The legal basis for the protection of our waters is the European Water Framework Directive (WFD), its Daughter Directive on priority substances in the field of water policy and the National Regulation on the Protection of Surface Waters (Verordnung zum Schutz der Oberflächengewässer, OGeWV). The German OGeWV regulates the classification and monitoring of the ecological and the chemical status of waters. For the assessment of the chemical parameters, environmental quality standards have been passed for 45 EU-wide priority substances and for 162 pollutants relevant in Germany (known as river basin-specific). If these standards are exceeded, specific measures must be taken to reduce

the entry of the respective substances. Pharmaceuticals are not yet on the lists. However, this should change with the next revision of the OGeV. The UBA cooperates with the federal states to set environmental quality standards for some pharmaceutically active substances classified as of particular concern.

Three substances with pharmacological effects have recently been discussed as part of the revision of the European Directive on Priority Substances: 17 $\alpha$ -ethinyl estradiol (EE2), 17 $\beta$ -estradiol (E2) and diclofenac<sup>39</sup>. While E2 and EE2 are a natural and a synthetic hormone, respectively, diclofenac is an analgesic used in large quantities and which is frequently measured at concentrations of several  $\mu\text{g}/\text{l}$  in

surface waters (Fig. 3). In 2013, all three pharmaceutically active substances had not yet been classified as priority substances but were included in a watch list, meaning that in future they will be more closely monitored across Europe. Listing as a priority substance would not compromise their therapeutic value but would take into account the potential adverse effects on fish and other organisms living in water. The establishment of environmental quality standards at a national and European level could be an important impetus for the long-term reduction of pharmaceutical contamination. If these substance-specific standards are exceeded concrete measures to reduce the contamination would become necessary<sup>24</sup>.

## 5 What concepts and mitigation strategies are available?

### Risk mitigation measures as part of authorisation

Competent authorities have only limited options for imposing conditions on human pharmaceuticals. A standard measure is the clear disposal advice on the package leaflet of a pharmaceutical for information on correct disposal.

For veterinary medicinal products, various different conditions in terms of use can also be issued in addition to the compulsory disposal advice on the package leaflet. These can concern the frequency of adminis-

tration, the time of administration or the handling of treated animals and their excretions. Such conditions are included in the summary of product characteristics for information of the consumer of the veterinary medicinal product (veterinarian, farmer, animal owners). For instance, a condition to protect dung fauna on pastures is not to allow animals treated with antiparasitics to graze on pasture for a certain time period after treatment. This measure protects dung insects from toxic antiparasitic residues which are excreted by treated animals.

### Measures beyond authorisation

Besides the marketing authorisation various measures exist at different levels to reduce the contamination of the environment with pharmaceuticals. Starting points for the reduction include pharmaceutical development itself, emission-reducing measures in water management and the responsible handling of pharmaceuticals by patients, pharmacists, doctors, veterinarians and animal owners (see also chapter 6 „What else needs to be done?“).

#### ► Pharmaceutical development

A particularly sustainable concept from an environmental point of view is to assess a pharmaceutical already at the start of its life cycle and not only at the end (end of pipe). Under the designation „Green Pharmacy“, various different approaches are being pursued to include environmental aspects in the process of



Source: fotolia. #52331748 - male cow veterinarian at farm takes analyzes © Jeno

the pharmaceutical development. Such approaches are aimed at the achievement of a better biodegradability of the pharmaceutical in the environment or at new routes of administration to enable a lower and more targeted dosing.

► Prescription and sale

An increased use of easily biodegradable pharmaceuticals could already be possible provided that information on the environmental behaviour of a pharmaceutical would be submitted. This would require the introduction of an environmental classification system based on the Swedish model.

In 2010, an expert discussion took place where ca. 50 experts in the fields of healthcare, pharmaceutical industry, water management, environmental organisations and consumer organisations discussed the „options to reduce the entry of human pharmaceuticals and their residues into untreated water and drinking water“. It was suggested to set up a ‚round table discussion‘ to clarify the respective options and conditions<sup>20</sup>. UBA is still advocating the set up of such a group. In addition, this expert discussion developed a catalogue of recommendations on issues of prescription and disposal, research and development, sanitary and environmental engineering and as well as in terms of assessment of safe drinking water and health which could be promoted by such a discussion group.

► Environmentally friendly animal husbandry

In animal husbandry, veterinary medicinal products should be used in a responsible and targeted manner. Representatives from agricultural and veterinary sciences and practice agree that the high use of veterinary medicinal products in agricultural livestock could be reduced considerably by means of targeted prophylaxis strategies to improve animal health in live stock. This includes improving animal husbandry and hygiene conditions, active animal health and operational management and qualification of the agricultural staff<sup>40</sup>. The focus should be especially on the reduction of the consumption of antibiotics and antiparasitics.

► Advanced wastewater treatment

Findings in surface waters show that wastewater treatment plants with three treatment processes are

not able to completely remove all residues of pharmaceuticals from wastewater. A relatively expensive but very effective method for elimination of even traces of pharmaceuticals and their degradation products is to equip wastewater treatment plants with an additional treatment process. Additional treatment processes are primarily ozonation or treatment with powdered activated carbon. An upgrading of the largest wastewater treatment plants already ensuring the treatment of 50 % of the wastewater amount in Germany would be cost effective and would result in the retainment of a large number of pharmaceuticals which currently pass through. Not only the contamination of waters with pharmaceuticals would be reduced significantly but also a large number of other contaminants of waters would be removed.

► Correct disposal of pharmaceuticals

Consumers can contribute in a simple and effective way to reducing the environmental pollution by pharmaceuticals by disposing of in a correct manner. Expired or unwanted pharmaceuticals must not be disposed of via toilets or drains under any circumstances. This is an additional and unnecessary entry into the environment via the wastewater. A representative survey showed that such disposal behaviour is relatively widespread<sup>7</sup> [[www.start-project.de](http://www.start-project.de)]. According to this



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survey, 16 % of respondents stated that they occasionally disposed of unwanted tablets via the toilet. Liquid pharmaceuticals are disposed occasionally via drain or toilet by up to 43 % of the respondents.

In Germany, there is currently no uniformly communicated take-back system for unwanted pharmaceuticals. The disposal of pharmaceutical residues via household waste is permitted as it is in general incinerated, thereby destroying the biologically active substances. However, it should be ensured that medicines disposed of via residual waste are not visible in the residual waste bin, for example by wrapping them

into newspaper. The aim of this measure is to prevent, for example, playing children from reaching medicines, accidentally mistaking them for sweets and swallowing them. In order to prevent improper access and to ensure medicines being sent to incineration, the Federal Environment Agency recommends their disposal of at household hazardous waste collection centres. Pharmacies also often accept back medicines even though they are not legally obliged to do so. The establishment of a nationwide, pharmacy-based return system, as it was in place until 2009, could contribute to the reduction of incorrect disposal of old medicines via wastewater.

## 6 What else needs to be done?

### ► Closing of data gaps

In the past few years, several research programmes sponsored by the EU investigated and confirmed the environmental relevance of pharmaceuticals (ERAPharm, KNAPPE, PILLS, PHARMAS, Poseidon). Despite the significant increase in research activity, the environmental risk can still not be estimated for a large number of pharmaceuticals. This applies in particular to those substances which were on the market before the introduction of the environmental risk assessment. For many of these substances known as old pharmaceuticals only few environmental data exist. Especially, data on long-term effects on environmental organisms are lacking. Those data are currently only collected for new marketing authorisations of pharmaceuticals. For many years the Federal Environment Agency has been advocating an old active substance programme which would systematically close these data gaps<sup>24</sup>. Currently, so called active substance monographs are under discussion where all environmentally relevant data are summarised and assessed. For the implementation of such a programme, both competent authorities and pharmaceutical industry are in demand.

### ► Post authorisation monitoring

To date, no further post-authorisation monitoring for pharmaceutical are performed concerning their behaviour in the environment or possible unintended environmental effects. However, it is considered necessary to monitor environmentally-relevant pharmaceuticals

in particular post authorisation. In addition to the obligation for state monitoring which arises e.g. from European and national regulations on the protection of surface waters, the obligation for pharmacovigilance as set out in the pharmaceutical legislation is a further option for the improvement of the environmental safety of pharmaceuticals. Hence, within the scope of pharmacovigilance the pharmaceutical industry could be obliged to investigate harmful effects on the environment with additional, targeted studies while a pharmaceutical is on the market. This is in principle possible for veterinary medicinal products but has not yet been established in concrete terms. An „environmental pharmacovigilance“ is not foreseen for human pharmaceuticals. Targeted monitoring of environmentally relevant pharmaceuticals could help to timely recognise focal points of pollution and ecological effects, to take measures and thereby increase the environmental safety of pharmaceuticals.

### ► Strengthening of communication and information

The problem of environmental pollution with pharmaceutical residues has hardly played any role in public perception to date<sup>7</sup>. Investigations have shown that an environmentally friendly handling of pharmaceuticals can be achieved by means of target group-oriented communication and information. Representatives of all areas which deal with pharmaceuticals (patients, doctors and pharmacists) should be addressed and sensitised to sustainable handling of pharmaceuticals. The prescription behaviour of doctors can play an important role in this. Their

awareness could be increased if they receive a respective additional training or if the problem is already addressed during their initial training<sup>41</sup>. Thus, in the long term willingness might develop to consider a reduction in the consumption of pharmaceuticals as solution, to look into it and eventually to practise it. Initial activities to establish a corresponding training module for health professionals are already in place in a project at Witten/Herdecke University funded by the UBA. The pharmaceutical industry should also fulfil their responsibility to a greater extent and

should use information campaigns to point out the potential environmental risks of an increasing pharmaceutical consumption and the options in terms of responsible handling. At present pharmaceuticals are strongly promoted, particularly on television, which encourages the population to handle pharmaceuticals in a rather careless manner. The goal should be qualitative changes in terms of environmental compatibility rather than a quantitative expansion of the supply with pharmaceuticals.

## 7 What can each individual do?

Through conscious, responsible behaviour, everybody can contribute to the reduction of the entry of pharmaceuticals into the environment. A few rules of thumb which should be taken into account:

- ▶ A balanced lifestyle with a healthy diet, sports and sufficient sleep can make many pharmaceuticals unnecessary
- ▶ Avoid pharmaceutical waste from the outset: check your medicine cabinet before visiting the doctor's to avoid double prescriptions; when you are at the doctor's ensure you get a custom-fit prescription; in the pharmacy ask for small packs.
- ▶ Avoid excessive self-medication. Use alternatives to pharmaceuticals such as home remedies, physiotherapy and relaxation exercises as far as possible and appropriate
- ▶ Ensure the correct dose: do not apply ointments too thickly; ask a doctor or pharmacist as a precaution
- ▶ Correct disposal of expired pharmaceuticals: not via drain or toilet

### Pharmacovigilance

Pharmacovigilance is the legally set out monitoring of pharmaceutical safety by doctors and veterinarians post-authorisation. It comprises the observation and recording of risks and adverse effects of a pharmaceutical during use in humans and animals, thereby increasing the safety of the pharmaceutical. To date, the monitoring of potential adverse effects on the environment (environmental pharmacovigilance) has only been set out legally for veterinary medicinal products.

## 8 Conclusion

Pharmaceuticals get into the environment after use where they can represent a risk to a large number of plants and animals. The environmental risks of pharmaceuticals are tested as part of the marketing authorisation procedure. There are still data gaps in terms of the environmental risk for old pharmaceuticals. These need to be closed. In order to reduce adverse effects on organisms in the environment and to decrease unnecessary pollution, a large number of measures are necessary. Each person can make their

own contribution by correctly disposing of and responsible use. Problematic pharmaceuticals should be monitored post authorisation and should be integrated into compulsory monitoring programmes.

In the future, an increased assessment should be performed to determine whether sustainability criteria are being met in the development, use and disposal of pharmaceuticals. This would benefit both the environment and as well as future generations.

# Glossary and list of abbreviations

Analgesics: painkiller

Antibiotics: substance to treat diseases caused by bacteria

Antiepileptics: substance to treat and prevent epileptic fits

Antiparasitics: substance against parasites such as lice, ticks, fleas and worms

Antiphlogistics: anti-inflammatory substance

Old pharmaceuticals: products authorised before the introduction of an environmental risk assessment and for which no subsequent environmental risk assessment is foreseen

Benthic meiofauna: community of medium-sized (0.3-1 mm) animal organisms living on the bottom layer of waters

Beta blockers: beta receptor blockers, substance to decrease blood pressure

Co-formulants: excipients which are used to manufacture pharmaceuticals but without any pharmacological activity of their own; these affect the shape, active substance release, stability and durability of pharmaceuticals

BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices), German competent authority for human pharmaceuticals

BVL: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (Federal Office of Consumer Protection and Food Safety), German competent authority for veterinary medicinal products

DDD: defined daily dose; assumed average maintenance dose per day for adults for the main indication of a pharmaceutical

Endocrine: affecting the hormone system; substances with hormone-like effects are also known as „endocrine disruptors“ if they cause harm.

Hazard-based assessment: takes into account the hazard on the basis of the inherent properties of a substance; in contrast to risk-based assessment which takes into account the ratio between exposure and effect of a substance. Pharmaceuticals without PBT properties are assessed risk-based.

Green Pharmacy: collective term for various different approaches for taking into account environmental aspects in the development of pharmaceuticals

Indication: a symptom or particular circumstance that indicates the advisability or necessity of a specific medical treatment or procedure

Sewage sludge: sludge which accrues during wastewater treatment; contains nutrients but also problematic substances such as heavy metals and organic pollutants

Contraceptive: substance to prevent pregnancy

Larva: intermediate form in the development from egg to adult animal

LAWA: Bund/Länder Arbeitsgemeinschaft Wasser (state water collective)

Lipid reducers: substance to prevent fat metabolism disorders

Maximum average value: highest average value of all state measuring points

Median value: also known as the central value; statistical figure which divides the data into two halves

Mesocosm: artificial, simplified model ecosystem e.g. artificial pond

Metabolite: degradation product from metabolic processes

Microgram:  $\mu\text{g}$ ; 0.001 mg

Milligram: mg; 0.001 g

Monitoring: systematic recording, observation and supervision

Non-target organisms: organisms which may unintentionally be harmed as a side effect of the use of chemicals

Surface waters: natural or artificial waters which are standing or flow such as rivers, brooks and lakes

OGewV: Oberflächengewässer-Verordnung (German surface water regulation)

Ecotoxicity: harmful effect of substances/chemicals on organisms in the environment

PBT substances: substances with concerning properties as a result of the combination of P = persistent (difficult to degrade or non-degradable and therefore persisting in the environment), B = bioaccumulating (accumulating in organisms) and T = toxic (poisonous to humans or environmental organisms or, for example, carcinogenic)

Pharmacovigilance: legally set out monitoring of pharmaceutical safety after authorisation

Population: group of the same species which are found in one location at the same time and form a reproductive community

Environmental pharmacovigilance: documented behaviour and effects of pharmaceuticals in the environment

WFD: European Water Framework Directive

RL: Richtlinie (Directive)

Pollutant: colloquial term for a substances or mixtures of substances found in the environment, the presence of which can have a negative impact on living organisms and ecosystems

Sediment: deposits of material for example on the bottom of waters

TM: Trockenmasse (dry mass)

Cytostatics: pharmaceuticals which inhibit cell growth or cell division and are used to treat cancer



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