SRU German Advisory Council on the Environment

Pharmaceuticals in the Environment

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1 Introduction

1. The use of pharmaceuticals is an essential component of modern medicine, and one which makes a significant contribution to the high standards of health in the Federal Republic of Germany. The development of active ingredients in human medicines in particular has increased rapidly in recent decades, with an emphasis on the search for new pharmaceutical effects, in addition to the problems of side-effects and safety issues. The active ingredients in pharmaceuticals are among the most extensively studied substances in terms of their absorption and distribution in cells and the generation of biological effects on mammals.

2. By contrast, far less attention has been devoted to the consequences of discharging pharmaceuticals into the environment. The early Seventies saw the publication of the first ever study examining the discharge of active pharmaceutical ingredients into the environment (STOCK and REUPERT 2006). However, it was not until the discovery of clofibric acid in Berlin surface waters in 1994 that research into this substance risk was stepped up significantly (STAN et al. 1994). Traces of around 120 pharmaceuticals have since been detected in the environment. Although the low concentration in waterbodies does not imply a health risk, the fact that these are used for water supply purposes in some regions is nevertheless problematic. Even after purification, pharmaceuticals remain as trace substances in drinking water, which subsequently falls short of required purity standards.

3. For many of the active ingredients in use over a number of years, there has been little research into their long-term effects on the environment, and for this reason we often lack appropriate methods with which to perform a substance risk assessment. Our inadequate knowledge of the environmental risks associated with pharmaceutical discharges of active ingredients which have been marketed for many years is all the more astonishing given the extensive data available on their clinical effects, particularly when one considers that the research effort required in order to overcome this information deficit would be comparatively minimal. Some of the active pharmaceutical ingredients discharged into the environment have a harmful effect on organisms and other environmental consequences which should be given greater importance when weighing up the benefits/risks of using these active ingredients, or when devising measures to minimise their discharge into the environment. Active ingredients discharged into the environment in effective concentrations as point sources include analgesics, contraceptive hormones and antibiotics.

4. Since the discovery of the growth-inhibiting effects of penicillin on bacteria and the development of a broad range of antibiotics, most bacterial infections are no longer fatal. However, it has now been proven beyond doubt that cases of bacterial resistance are increasing sharply due to the intensive and widespread use of antibiotics. These findings pose a potentially serious problem for human health. Many multiresistant strains of human pathogens are found and dispersed in effluent, not only from hospitals but also in sewage sludge. The use of antibiotics in the treatment of livestock also encourages the spread of resistant bacteria which can pose a health risk for humans, particularly in the event of direct contact. Active ingredients are also excreted and spread on the soil as organic fertilisers. Given the widespread use of antibiotics to treat humans and animals and the fact that the development of new antibiotics cannot keep pace, measures need to be taken to address the problem of multiresistant bacterial strains.

5. Apart from the very low concentrations often found in environmental media, it is the sheer number of highly different active pharmaceutical ingredients which pose a particular challenge to the assessment of environmental risks. In the licensing process, an environmental risk assessment is only carried out for the new product being registered; there is no opportunity for comparison with structurally identical or related preparations which are already licensed. This information deficit cannot be rectified under existing regulations, yet all pharmaceuticals with a comparable effect share the same potential environmental consequences, and therefore, confining assessment to the newly registered active ingredients will distort the risk perception.

For an adequate assessment of the environmental consequences of pharmaceutical use, including active ingredients which have been licensed for some time, we need a differentiated analysis of the problem. Some pharmaceutical products are synthetic in the narrowest sense of the word, i.e. they do not occur in nature in a similar structure. They often demonstrate a high degree of effect specificity – for example, by influencing physical functions that may be restricted to humans and a few selected animal species. Furthermore, the concentrations of active ingredients discharged into the environment are often too low to trigger these specific effect mechanisms in organisms. The environmental risk can therefore be expected to be minimal. Nevertheless, our knowledge of the effects in mammals cannot be transferred to the environment without further clarification using well-established laboratory ecotoxicity tests.

The environmental relevance of some synthetic active pharmaceutical ingredients, which are used in large quantities such as ibuprofen (used in the treatment of pain and inflammation), remains largely unknown. Suitable information is urgently needed in order to facilitate an environmental risk assessment.

Meanwhile, other active pharmaceutical ingredients, such as cardioactive glycosides, taxanes, podophyllotoxins and antibiotics, are predominantly nature-identical, which

could indicate that they are less problematic for ecosystems because adaptation mechanisms are available, or because they are readily degradable. Nevertheless, the environmental relevance of discharging these nature-identical structures into environmental media where they do not occur naturally, or only in much lower concentrations, remains uncertain.

6. Due to their broad application profile, human medicines are released more or less continuously from multiple sources and enter the sewage system. Some are able to enter surface waters largely unhindered, because they cannot be sufficiently eliminated during their passage through the sewage treatment plant. The environmental relevance of contraceptive hormones is a particular case in point. Other examples include active ingredients from the group of analgesics, antibiotics, radiographic contrast media and anticonvulsives. The drugs detected in the environment are not necessarily consistent with the most widely prescribed active ingredients within a treatment group. The number of pharmaceuticals detected to date in waterbodies is also much lower than the number of frequently used drugs. The spectrum of pharmaceuticals absorbed in sewage sludge is relatively low, because many drugs transported into sewage remain in the water phase. Current findings suggest that population-relevant effects in the ecosystem occur primarily in areas where relatively high concentrations of substances enter the environment – for example, in the immediate vicinity of sewage treatment plant outfalls or in agricultural land regularly treated with contaminated organic fertilisers.

7. It is already apparent that certain regions would benefit from a reduction in discharges of active ingredients for preventive reasons. As techniques to determine water and soil quality become increasingly sensitive, scientists are now in a better position to document the distribution of active pharmaceutical ingredients in the environment. Soil pollution via the use of organic fertilisers contaminated with pharmaceuticals used in the treatment of animals occurs periodically at varying intervals. However, there is a lack of suitable data available to allow us to assess the environmental consequences of such discharges. In the interests of soil conservation, therefore, it is a matter of identifying which measures may be used to effectively minimise the discharge of active pharmaceutical ingredients via organic fertilisers and at a reasonable cost.

2 Properties of pharmaceuticals

Definitions of pharmaceuticals

8. Pharmaceuticals are traditionally used to ameliorate disease symptoms and promote healing. As medical technology has become more advanced, another application area is the detection of disease (e.g. via the use of radiographic contrast media). Once the causes have been clarified, in some cases it is even possible to preventively administer drugs which will prevent the disease from developing or minimise its severity. Pharmaceuticals are therefore used in sick or healthy individuals to influence physical functions or mental states. Because humans and some highly developed animals share very similar basic physical functions, many pharmaceuticals are also used to treat pets, livestock and animals in zoos. The main shared application areas between humans and animals include drugs for the treatment of pain and inflammation, as well as antibiotics. Because some diseases only affect certain species of animal but not humans, some pharmaceuticals have only been tested – and are only licensed – for use on animals, such as parasiticides for the treatment of hoofed animals. Some pharmaceuticals which are not licensed for human use due to the unfavourable risk/benefit ratio may nevertheless be used in animals. In terms of environmental problems, the two aforementioned application areas clearly differ in terms of the discharge paths of active ingredients, the principal sources of pollution, and the temporal development of contamination (cf. no. 27 ff.). In livestock farming, pharmaceuticals are not only used to treat infected individual animals, but are also used prophylactically to keep the entire stock healthy and as feed additives, although the latter is subject to increasing restrictions. The statutory regulations to guarantee the safe use of drugs must distinguish between the following three areas in terms of the special benefit/risk considerations:

- Use in humans,
- Use in sick animals or where illness is imminent, and
- Use as a feed additive in animal husbandry with the possibility of discharge in food

(cf. Chapter 5).

The distribution and use of pharmaceuticals is subject to licensing with precise specification of the intended use (indication). There are currently more than 3,000 active ingredients licensed as pharmaceuticals which are marketed in more than 9,000 preparations. The German Pharmaceuticals Act (AMG) sets out the requirements governing the evaluation of pharmaceutical effects and the consideration of benefits/risks. In the Federal Republic of Germany, prescription-only drugs may only be sold to patients and doctors by pharmacies, and for this reason, it is possible to ascertain the total quantity of active ingredients sold for this sector. However, a number of freely accessible preparations are increasingly becoming available from retailers or via the Internet for self-medication. Such quantities are not included in the pharmacy records. Additionally, there are substance overlaps with a number of freely accessible food supplements which are likewise omitted from the records.

Classification of pharmaceuticals

9. Licensed pharmaceuticals are a very heterogeneous group which includes both synthetically produced molecules, plant and bacteria extracts, metal oxides, metal-organic compounds, blood constituents as well as virus constituents. Some, such as blood preparations, are very short-lived in organisms and in the environment, while others, such as metals, are non-degradable. An overview of pharmaceuticals is based on classification, which also reflects the various patterns in the development history of pharmaceuticals. The oldest synthetic pharmaceuticals still in use, such as acetylsalicylic acid, are classified according to the pharmaceutical effect profile, from which the indication is derived. Pharmaceuticals classified according to their intended application include products to alleviate pain (analgesics) such as acetylsalicylic acid and paracetamol, drugs for the treatment of non-bacterial inflammation (antiphlogistics), products to treat convulsions (antieleptics), drugs for the treatment of high blood pressure (antihypertensives), and products for the treatment of high blood sugar levels (antidiabetics). Many of the long-established active pharmaceutical ingredients (such as acetylsalicylic acid and paracetamol) have a well-known clinical profile and benefit/risk profile, yet their effect mechanism remains unspecifically broad or is still unknown.

10. More recently developed pharmaceutical ingredients were characterised on the basis of their cellular attack mechanisms, from which the principal indication is then likewise derived. These include, for example, drugs which attack the adrenoceptor (receptors in the sympathetically innervated tissue, which respond physiologically to the natural transmitter substances adrenaline and noradrinaline), subtype ß2, which are used as stimulators to eliminate increased levels of resistance of the respiratory tract in asthma or to suppress contractions in pregnancy (so-called ß2 mimetics or ß2 adrenoceptor antagonists). As agents which inhibit the adrenoceptor, subtype ß1, they are used to treat high blood pressure or to prevent angina attacks (so-called ß1 blockers or ß1 adrenoceptor antagonists). Minor modifications to the molecular structure can often make the difference between a promoting or inhibiting influence on physical functions. Another example is the folic acid antagonist methotrexate, which depending on its concentration can either inhibit (tumour) cell growth or exhibit an anti-inflammatory effect, because the mobility and function of white blood cells (leucocytes) is restricted by methotrexate. There is therefore a very varied indication between higher and lower concentrations with the same effect mechanism.

11. Recently, researchers have modelled the structure/effect relationship of existing pharmaceuticals and used this to design new active ingredients. This includes drugs which act on the immune system, those which act on serotonin reabsorption, those which act on fatty acid metabolism, and those which act on tension-dependent ion channels. Active pharmaceutical ingredients developed in this tradition are often classified on the basis of their structural features, such as statins, fibrates, and chinolones.

Effect qualities of pharmaceuticals

12. It can generally be said that the interaction of more recently developed pharmaceuticals with specific target structures in cells and tissues is widely known, and that their effect mechanisms are comparatively specific and disease-based in terms of their pharmaceutical effect profile. Some of the effect principles are generally applicable to all organisms, while others are specific to certain species, and in some cases even to specific diseases. When considering the pharmaceutical effect profile with unwanted side-effects, therefore, it is necessary to distinguish between specific effects, i.e. those linked to the desired mechanism, and non-specific effects, i.e. those which cannot be predicted by mechanistic means.

The use of pharmaceuticals may therefore have enormous relevance for ecosystems, depending on the quantities discharged via sewage and waste and the persistence of the active pharmaceutical ingredients and their by-products in environmental media. Here too, when weighing up the benefits and risks during safety testing, it is important to distinguish between forecastable and unforecastable effects. The endpoints of unforecastable effects can only be determined via screening analyses. Once a pharmaceutical effect profile has been established, the leading clinically successful substances are usually further modified, often leading to a higher level of effectiveness for subsequent active ingredients. Hence, structurally related active pharmaceutical ingredients with a largely similar clinical profile may deviate by up to several hundredfold in the clinical dosage required. Examples of a substantial increase in the efficiency of active pharmaceutical ingredients include the latest benzodiazepines compared with their earlier counterparts, the latest histamine type-2 receptor blockers (gastric acid secretion inhibitors) or H^+/K^+ ATPase inhibitors, proton pump inhibitors (gastric acid secretion inhibitors). While this may be linked to a reduction in non-specific and unwanted side-effects, it also becomes more difficult to obtain chemico-analytical evidence of a biologically effective structure in bodily fluids or in environmental media.

Structures of pharmaceuticals

13. Some active pharmaceutical ingredients are obtained from natural sources such as plants or bacterial cultures, and some of them undergo only slight semi-synthetic modification, benefiting from the fact that a number of outstanding biologically active ingredients with highly complex molecular structures are found in nature. Examples of such substances include cardioactive

glycosides, podophyllotoxins or taxanes which are used as inhibitors for (tumour) cell growth, and antibiotics which have become indispensable as bacterial growth inhibitors. While it was once common in antibacterial treatment to distinguish between active ingredients isolated from bacterial cultures (antibiotics in the conventional sense of the word) and active ingredients that are derived entirely synthetically (antibacterial chemotherapy drugs such as sulphonamides), this distinction has since been largely waived. When producing antibiotics from cultures, the technological masterstroke lies primarily in the isolation and concentration of the active ingredients, without producing any substance types which are not already known in nature.

14. When assessing environmental relevance, the use of antibiotics in particular poses a special constellation. The underlying effect principle is reflected in the competition between bacterial strains for growth in the natural environment. The desired therapeutic effect of killing or inhibiting the growth of a microorganism in order to keep the macroorganism (human or animal) alive may be linked to effects in the environment. Such effects, in conjunction with exposure, represent the actual environmental risk. The use of antibiotics creates pathogens which are resistant to active ingredients, which may in turn upset the sensitive balance of pathogens in the waste path, e.g. in the bacterial purification stage of sewage treatment plants, and which may secondarily lead to problem infections among humans and animals. In intensive care wards, there have already been reported cases of multiresistant pathogens for which no effective treatment options are available. Despite a very varied spectrum of antibacterially effective pharmaceuticals with highly specific mechanisms, the problem of multiresistant human pathogens is becoming ever more pressing, for example in the treatment of tuberculosis.

Peculiarities of finished preparations

15. Formulations that are mixed by the pharmacist are now a rarity, and tend to be limited to the preparation of dermatological products or the mixing of ready-to-use tumour inhibitor solutions. The most common medicines today are finished products, which in addition to the actual active ingredient itself also comprise a large number of fillers, auxiliary substances and markers which make the product easier to handle, safe to use, identifiable and suitable for storage. In purely quantitative terms, the active pharmaceutical ingredient is generally the least significant portion of the finished preparation. Pharmaceutical technology is sophisticated, and the auxiliary substances licensed for pharmaceutical production are listed in the European Pharmacopoeia, or the German Pharmacopoeia (DAB) section thereof.

The confusingly large number of finished products made from a common active pharmaceutical ingredient is partly attributable to a range of different individual doses or varying forms of administration. However, it may also arise when the patent protection for a particular active ingredient expires, and pharmaceutical companies seize the opportunity to market an additional variant. In such cases, the licensing check will depend solely on furnishing proof of the product's pharmaco-technological quality, since evidence of the effectiveness and safety of this active ingredient has already been submitted. It is not the mandate of the licensing process to assess the demand for a broader market supply. Often, this can sensitively impact the safety testing for environmentally relevant endpoints, since in such cases it becomes virtually impossible to obtain an overview of the quantities actually sold and ingested.

It would be impossible to retrospectively call for the missing environmental test data for preparations already licensed, because no one pharmaceutical company has overall responsibility and can therefore be held accountable. This situation applies to many of the so-called "old substances" already on the market in 1978 prior to the entry into force of the Pharmaceuticals Act, the licensing of which required a different range of data than that stipulated for new licenses. The overall data situation of the most common (in volume terms) active pharmaceutical ingredients is extremely heterogeneous in terms of environmentally relevant data, and the supervisory authorities have insufficient powers to selectively request retrospective information.

3 Pharmaceutical consumption

3.1 Human medicines

16. In Germany there are around 9,450 pharmaceutical preparations with around 3,000 different active ingredients licensed for use in humans (BPI et al. 2006), with annual sales of active pharmaceutical ingredients totalling around 31,000 tonnes. Of the 3,000 or so active ingredients, 111 are classified as potentially environmentally relevant (HUSCHEK and KRENGEL 2003) on the basis of the quantities sold and the exclusion criteria of the EMEA (European Medicines Agency) for environmental risk assessment. Below we list the consumption quantities and percentile excretion rates of the principal representatives of these 111 active ingredients (Table 1). The antiphlogistic ibuprofen is the most widely used active ingredient in quantity terms. However, following ingestion of this medicine, only approximately 1 % of the dosage is excreted in an unaltered state. Almost nothing is known about the environmental relevance of the remaining 99 % of the active ingredient which enters the environment in a modified form. Other active ingredients with annual consumption levels in excess of 50 tonnes include the analgesic metamizole, the antibiotic sulphamethoxazole, the antieleptic carbamazepine and the antiphlogistic diclofenac, as well as the antihypertensive metoprolol.

A risk assessment on the basis of annual consumption quantities soon reaches its interpretational limits. For example, metoprolol represents more than 20 structurally related active pharmaceutical ingredients with similar effect mechanisms. The effective therapeutic dose varies by a factor of 5 to 10. For this group, the proportion of active ingredients excreted in an unaltered state following ingestion ranges between 20 and 90 %. As such, the environmental relevance of active pharmaceutical ingredients can only be reliably assessed on the basis of suitable categorisation.

17. Antibiotics are an important group of active ingredients in terms of their possible effects on the ecosystem (see below) and annual consumption quantities. In Europe, approximately two-thirds of the antibiotic volume is used in human medicine (FEDESA 2001). Around 75 % of the active ingredients used are excreted intact, i.e. as an effective parent substance (HUSCHEK and KRENGEL 2003; KÜMMERER and HENNINGER 2003).

Table1

Consumption quantities of active ingredients in human medicines in Germany, 2001

Active pharmaceutical ingredient or indication group*	**CAS registry no.**	**Annual consumption quantity in kg**	**Percentage of dose that is excreted unaltered**
Analgesics (pain relief)			
Metamizole	68-89-0	64,400	0 (metabolites only)
Phenazone	60-80-0	24,850	5
Propyphenazone	479-92-5	24,180	2
Codeine	76-57-3	9,700	70
Morphine	57-27-2	880	10
Antirheumatics and antiphlogistics (for the treatment of rheumatic diseases)			
Ibuprofen	15687-27-1	344,880	1
Diclofenac	15307-86-5	85,800	70
Indometacine	53-86-1	3,700	30
Ketoprofene	22071-15-4	1,613	10
Piroxicam	36322-90-4	724	5
Meclofenamic acid	644-62-2	unknown	unknown
Antitussives and expectorants (for the treatment of coughs, colds, bronchitis etc.)			
Ambroxol	18683-91-5	14,470	6
Codeine	76-57-3	See above	See above
Dihydrocodeine	125-28-0	1,245	40
Hydrocodone	125-29-1	8	40

Bronchospasmolytics and antiasthmatics (for the treatment of chronic bronchitis and asthma)			
Salbutamol	18559-94-9	414	80
Terbutaline	23031-25-6	118	60
Fenoterol	13392-18-2	72	50
Clenbuterol	37148-27-9	1	90
Antibiotics (for the treatment of bacterial infections), (penicillins not included due to their rapid degradability)			
Sulphamethoxazole	723-46-6	53,600	33
Doxycycline	564-25-0	24,180	2
Ciprofloxacin	85721-33-1	17,973	45
Clindamycin	18323-44-9	16,100	30
Trimethoprim	738-70-5	11,426	80
Roxythromycin	80214-83-1	9,550	60
Clarithromycin	81103-11-9	7,159	35
Norfloxacin	70458-96-7	4,724	70
Ofloxacin	82419-36-1	2,280	95
Oxytetracycline	79-57-2	2,020	Not known
Tetracycline	60-54-8	1,530	Not known
Spiramycin	8025-81-8	300	25
Chloramphenicol	56-75-7	202	10
Chlorotetracycline	57-62-5	99	Not known
Antihypertensives (betareceptor blockers, for the treatment of high blood pressure)			
Metoprolol	37350-58-6	93,000	10
Sotalol	3930-20-9	26,600	90
Atenolol	29122-68-7	13,500	90
Propranolol	525-66-6	3,900	5
Bisoprolol	66722-44-9	2,914	50
Antieleptics (for the treatment of epilepsy)			
Carbamazepine	298-46-4	87,600	30

Psychopharmaceuticals (for the treatment of emotional disorders)			
Diazepam	439-14-5	1,107	30
Cytostatics (inhibit cell growth, for the treatment of leukaemia, cancer and tumours)			
Cyclophosphamide	50-18-0	385	7
Ifosphamide	3778-73-2	170	50
Hormones (including contraceptives)			
17α-ethinyloestradiol	57-63-6	50	85
We have selected those active pharmaceutical ingredients and ingredient groups which are considered particularly environmentally relevant by virtue of their consumption quantities and inherent properties (such as persistence and effect specificity) CAS Registry No. – Chemical Abstracts Service – International reference standard for chemical substances			
SRU/Statement no. 12–2007/Tab. 1; data source: HUSCHEK and KRENGEL 2003			

3.2 Veterinary medicines and feed additives

18. Around 27 million pigs, 1.1 billion chickens, 13 million cattle and 2.6 million sheep, as well as other animal species in less significant quantities, are currently kept in Germany (Federal Statistical Office 2005b). Aquaculture also produces around 40,000 tonnes of fish – in 2004 the total figure was 41,645 tonnes, including 21,600 tonnes of rainbow trout and 16,000 tonnes of carp. The majority of fish production occurs in aquaculture farms with a total pond surface area of around 40,000 ha. Only a very minor role is played by technical fish-farming systems (ponds with closed water cycle, annual production in 2003: 509 tonnes) and marine aquaculture (BMVEL 2005). Large numbers of animals are also kept as pets or hobbies (around 7.5 million cats and 5.3 million dogs), (IVH 2006). In terms of the use of pharmaceuticals, pets are very different from farmed animals as they are not kept in large numbers and the risk of infection is therefore lower. Furthermore, they generally have a considerably lower body weight, which means that smaller quantities of active ingredients are used. The responsible use of pharmaceuticals is indispensable to preserve the health of both livestock and pets.

19. On the basis of panel surveys derived from a random sample of 750 veterinary practices spread representatively across the Federal Republic of Germany, the *Bundesverband für Tiergesundheit* (German Association for Animal Health, BVT) estimated the quantities of veterinary medicines consumed in Germany in 2003 (cf. Table 2), (SCHNEIDEREIT 2004). The survey only included pharmaceuticals purchased by vets, so these figures exclude sales via public pharmacies, although the study suggests that these only account for a minimal proportion of the total volume traded. Antiinfectives (all antibacterial substances) headed the list in terms of quantity with 668.8 tonnes, accounting for 70 % of the total mass (cf. table 2). By comparison, the consumption of antibiotics in human medicine is estimated at around 500 tonnes per annum (2003), according to HUSCHEK and KRENGEL. 98 % of the active antibiotic ingredients in veterinary medicine are used to treat pigs and poultry, while the remaining 2 % is spread among other species. Tetracyclines are the most important group of active ingredients in volume terms, followed by sulphonamides and aminoglycosides (THIELE-BRUHN et al. 2003; UNGEMACH 2000).

20. Antibiotics are prescribed to animals for a variety of reasons: For the treatment of sick animals, and as a prophylactic to protect against disease. Other uses, although subject to increasing restrictions in recent years, include promoting growth and improving the utilisation of food. In 1997 to 1999 there were already signs of a discernible decline in the use of antibiotics as performance enhancers in Europe, presumably due to the gradual phasing out of this form of use. Since 1 January 2006, antibiotics have no longer been authorised as feed additives in the European Union (EU) (cf. No. 92).

However, it is very noticeable that the use of antibiotics in the EU for therapeutic purposes increased by 12 % in 1999 compared with the year 1997, despite there being no significant increase in livestock numbers over the same period (FEDESA 2001). A similar development has also been observed in Denmark, where the phasing-out of antibiotics in feedstuffs was linked to an increase in medical usage (KJELDSEN 2002). It is not currently

possible to assess the development in Germany, firstly because it is impossible to clearly allocate the overall consumption of antibiotics to specific purposes; and secondly, because the addition of antibiotics to feedstuffs was legal up until 31 December 2005.

21. The annual quantities of substances used to treat parasitic infections in the gastro-intestinal tract (endoparasiticides) are considerably lower than the consumption figures for antibiotics (cf. Table 2). Active ingredient groups which have increased significantly compared with an earlier study for the year 1998 include those used to treat parasites in the gastro-intestinal tract, generally worms, as well as parasites on the skin or coat (such as lice) (endectoparasiticides). These active ingredients have a broad effect specificity and are not metabolised by the organism, both properties with a high degree of environmental relevance. Consumption quantities of non-steroidal antiphlogistics (synthetic antirheumatics; substances which have both an anti-inflammatory and pain-relieving action), which include acetylsalicylic acid, approximately doubled in 2003 compared with 1998 levels. Overall, however, the use of active ingredients showed only a minimal increase over the same period (SCHNEIDEREIT 2004).

Table 2

Consumption of veterinary medicines in Germany, 2003

Group of active ingredients	Quantity used (t)
Antiinfectives (antibiotics)	668.8
Endoparasiticides	31.3
Endectoparasiticides	1.6
Ectoparasiticides	13.5
– Of which livestock	9.4
– Of which pets	4.1
Hormones	0.67
Cardiac drugs (ACE inhibitors,cardiac glycosides etc.)	0.28
Non-steroidal antiphlogistics	4.5

SRU/Statement no. 12–2007/Tab. 2; data source: SCHNEIDEREIT 2004

22. A study conducted by the Federal Environmental Agency (UBA) on the use of pharmaceuticals in intensive farming drew rather different conclusions. Unfortunately, this preliminary study only managed to survey 60 vets, and extrapolation of the results for the whole of Germany cannot therefore be considered reliable. This study estimated the annual consumption of antibiotics at approximately 2,127 tonnes, based on a survey of prescriptions issued during the period April 2000 to July 2001. The figure for parasiticides, at 21.7 tonnes (the survey covered 14 groups of active ingredients), is lower than the result obtained by the BVT. Of the other active ingredients covered, acetylsalicylic acid heads the league with 147.4 tonnes.

23. A survey of pharmaceutical consumption in livestock farming for the period from June 1998 to June 1999 conducted on behalf of the state of Brandenburg likewise included a survey of vets, but only recorded the quantities of active ingredients derived from veterinary production orders (pharmaceuticals administered with feed). The study disregarded the administration of medicines via drinking water or injections. The evaluation revealed that antibiotics accounted for the lion's share of active ingredients with 6.62 tonnes (69.9 %), followed by zinc oxide with 2.78 tonnes (29.4 %) as a feed additive. The single active ingredient used in the greatest quantities was chlorotetracyline with 3.26 tonnes (LUA 2002). Like the BVT study, this study likewise indicated the overall dominance of prescriptions for pigs.

24. A high proportion of the veterinary medicines sold in Germany are used in livestock farming for food production purposes. The study by HUSCHEK and KRENGEL (2003) on behalf of the Federal Environmental Agency (UBA) measured the quantities of veterinary medicines used for selected animal groups, and derived data for their use in household pets, in commercial fish farming (= breeding and farming for food production purposes) and in the breeding of ornamental fish. The study concluded that the most important active ingredients, in quantity terms, used to treat small animals in the year 2000 were isopropyl alcohol (1.2 tonnes), cefalexine (1 tonne), glycerol (0.6 t), povidone iodine (0.5 t) and metamizole sodium (0.39 t). The dominant pharmaceutical spectrum (in volume terms) in this field alone indicates that the treatment of wounds is a priority area.

25. A data survey examining the use of medicines in commercial fish production was carried out on behalf of the state of Baden-Wuerttemberg in 2001. The data collated in this survey was extrapolated to produce consumption quantities for the whole of Germany (HUSCHEK und KRENGEL 2003). In Germany, only two medicines are currently licensed for use in commercial fish farming. However, in case of an emergency, fish may be treated with medicine which is licensed for use in a different animal intended for human consumption. This practice is now well-established, since licensing is not very profitable, given the low quantities of commercial fish production in Germany. Overall, the total volume of active ingredient used is 391.13 kg,

which applies exclusively to trout production. Carp production is a special case and virtually no pharmaceutical products are used (HUSCHEK and KRENGEL 2003). Carp tend to be kept in extensive aquaculture with a low population density. They are also far less sensitive than trout, and because they are peaceful fish, they are much less susceptible to injuries requiring treatment. However, not all other authors agree that no antibiotics are used in carp production. Some claim that young carp in particular are treated with active ingredients (personal disclosure by Dr. Iris Fuchs, Veterinary Advisor to the Upper Franconian Government, Bayreuth, 30 March 2006).

To date, the only figures available are for antibiotics administered with feed, which therefore enters watercourses directly (cf. Table 3). There is no data on substances applied externally for the treatment of parasites or infections (so-called bath treatments), for example. As such, we are unable to comment on the quantities of active ingredients used in such treatments.

Table 3

Calculated quantities of pharmaceuticals consumed in fish farming in Germany (2001)

Active substance	Quantity (kg)
Trimethoprim	48.92
Sulphonamides	244.51
Amoxicillin	48.85
Chlorotetracycline	37.95
Erythromycin	7.18
Florphenicol	3.21
Enrofloxacin	0.51

SRU/Statement no. 12–2007/Tab. 3; data source: HUSCHEK and KRENGEL 2003

26. HUSCHEK and KRENGEL (2003) likewise prepared rough estimates of the use of pharmaceuticals in the breeding of ornamental fish. The most significant active substances in volume terms, after sodium chloride with 55 t, are the antibiotics nifurpirinol (3 t), oxytetracycline (1.6 t), sulphonamides (1.1 t) and chloramphenicol (1 t). The authors point out that in this application area, large quantities of active substance are acquired illegally. There is also a particularly high risk of incorrect dosage, unsuitable treatment cycles and misapplication, as reflected in the different treatment recommendations found in the relevant literature. This data suggests that considerably higher quantities of pharmaceuticals are used in the farming of ornamental fish than in commercial fish production, although the accuracy of consumption estimates is questionable, due to the difficulty of assessing this particular market (personal disclosure by Dr. Iris Fuchs, Veterinary Advisor to the Upper Franconian Government, Bayreuth, 30 March 2006).

4 Pollution situation

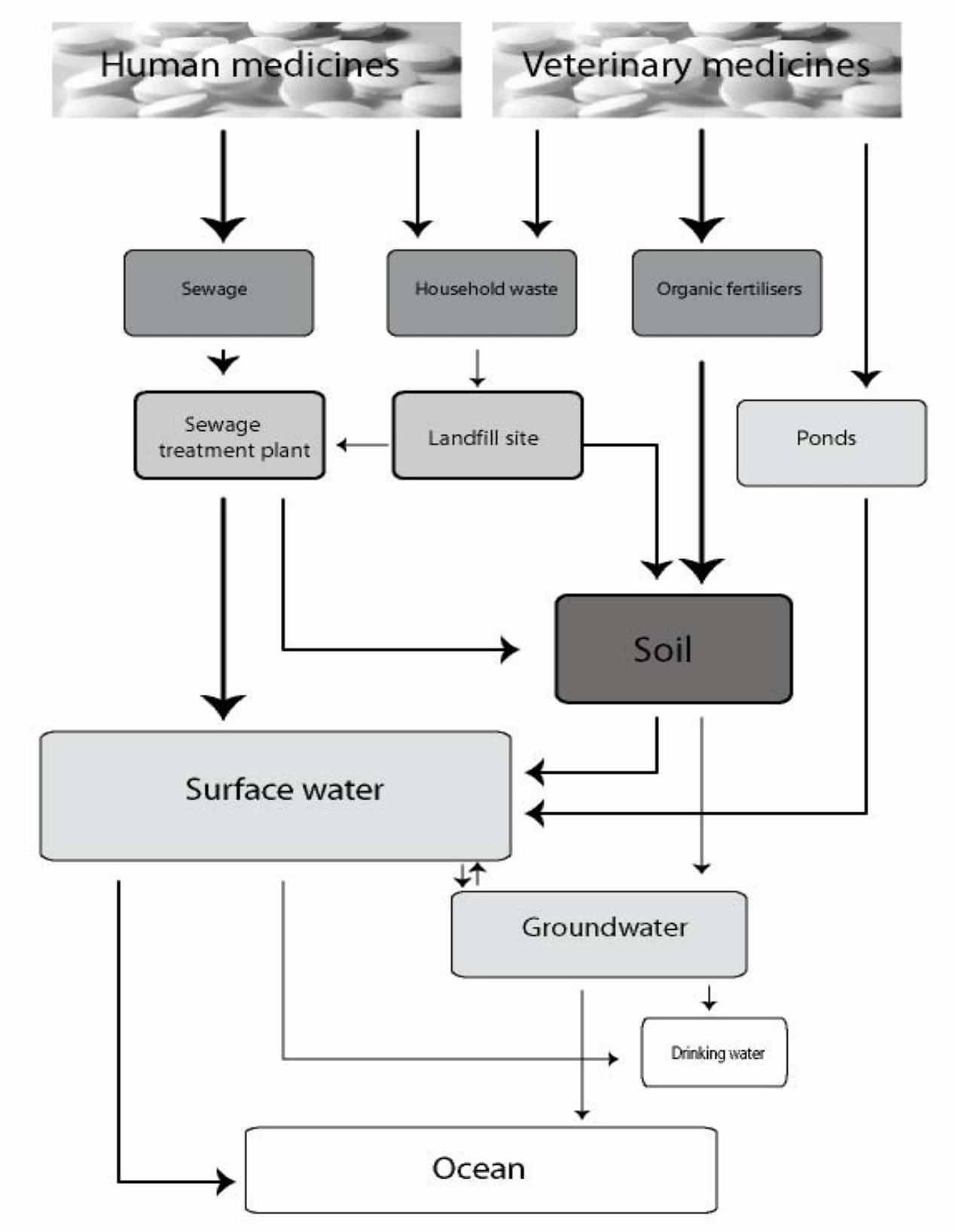
4.1 Discharges into the environment

27. As a result of the statutory provisions on good manufacturing practice, coupled with significant improvements in sewage treatment, and the high cost of selected active ingredients, which means that the loss of even small quantities is expensive, emissions of pharmaceuticals during the production process are negligible. Accidents are the only case likely to lead to the release of large quantities of active pharmaceutical ingredients or their intermediate products. Industrial point sources therefore play only a minor role in the discharge of pharmaceuticals into the environment.

The main discharge of both veterinary and human medicines occurs as a result of proper usage – in the treatment, detection and prevention of diseases – whereby the active ingredients enter the waterbodies or soils diffusely. Medicines may either be applied externally (topically) to the patient or ingested into the body. A substantial portion of externally applied medicine enters the environment unaltered via the sewage system. As a result of metabolic processes ingested medicine may remain unaltered at a molecular level through to complete mineralisation. Metabolism of medicines has often led to unwanted side-effects in humans, and therefore, in the search for safe treatments, care has been taken to ensure that medicines are metabolised as little as possible. For example, radiographic contrast media which are unstable in the body have been known to cause problems in patients due to iodine splitting, and are therefore increasingly being replaced by more stable alternatives which are excreted quickly and unaltered from the body (LfW 2004; LUA 2002; RÖNNEFAHRT et al. 2002). The need for diagnosis using radiographic contrast media has since been superseded by other imaging procedures which cause less radiation pollution (ultrasound, MRT, PET).

Figure 1

The principal discharge routes for pharmaceuticals into the environment



SRU/Statement no. 12–2007/Fig. 1

4.1.1 Human medicines

28. The principal discharge of human medicines occurs within the context of proper usage. The active ingredients enter the sewage treatment plant as effluent, and are then transported into the surface water depending on the degree of elimination (degradation and sorption) (cf. Figure 1). Effluent from hospitals is of particular relevance in this context, since it may contain particularly concentrated quantities of active ingredients (cf. also KÜMMERER 2004a). Moreover, a significant quantity of untreated sewage containing active ingredients enters groundwater and surface waters via leaking sewers and rainwater overflow (IRMER et al. 2006). Active pharmaceutical ingredients may also be discharged into the environment via the application of sewage sludge in agriculture.

29. In Germany, pharmaceutical residues are classified as waste subject to monitoring, and are the responsibility of the local waste management authority. Pharmaceuticals that are collected separately should be incinerated (Bayerisches Landesamt für Umweltschutz 2004). Disposal together with household waste is admissible, but this could lead to incidents and environmental discharges. In all cases, disposal via household waste that is destined for incineration is preferable to disposal via the sewage system. The advantage of selective collection via pharmacies and special waste collection points is that pharmaceutical residues can be reliably destroyed via incineration. Surveys indicate that a considerable portion of the total volume of medicine sold in Germany is still disposed of via household waste and via the toilet (ISOE 2006). Waste cytotoxic and cytostatic pharmaceuticals arising primarily in hospitals require special monitoring and must be disposed of separately. The *Länderarbeitsgemeinschaft Abfall* (Working Group of the Federal States on Waste) has published guidelines on the correct disposal of waste from the healthcare system, which also contain recommendations on the handling of waste pharmaceuticals (LAGA 2002). As the landfilling of untreated household waste has been prohibited since 1 June 2005, pharmaceutical residues that are disposed of in household waste end up either in waste incineration plants (around 54 % of all discarded domestic waste) or in mechanical-biological or mechanical-physical treatment plants (cf. also Statistisches Bundesamt 2005a). There have been no studies to investigate what happens to pharmaceuticals in mechanical-biological treatment plants; depending on the nature of the packaging and the pharmaceutical product, as well as the technology used, they may either enter the high-calorific or medium-calorific waste fraction intended for incineration (e.g. tablet packaging), or the fraction intended for landfilling (e.g. glass bottles), or the effluent from the mechanical-biological treatment plant.

Active pharmaceutical ingredients have been found in untreated landfill leachate in concentrations of a similar magnitude to those found in sewage treatment plant inlets, while some active ingredients were found in significantly higher concentrations (according to data from BLAC 2003). Old sedimentation and household waste landfills without leachate collection may therefore represent locally significant sources of pharmaceutical discharges into the environment.

4.1.2 Veterinary medicines and feed additives

30. The bulk of veterinary medicines are used in agricultural animal feed (BLAC 2003). As such, the principal discharge route is via animal excretion products, which in turn are applied to the fields in the form of organic fertilisers (slurry, solid manure). During storage or treatment (composting, fermentation) of the organic fertilisers, active ingredients may be degraded or absorbed by organic substance. Key influencing factors include the duration of storage, temperature, incidence of light, pH value, complex formation capacity and sorption behaviour (KTBL 2005). For example, the tetracycline concentration in solid chicken manure after three months' storage was reduced to between 0 and 40 % of the original concentration (in terms of C content). In similar experiments with pig slurry, significantly longer degradation periods were ascertained for tetracyclines (half-life up to 105 days), while sulphadiazine was found to be far less persistent (WINCKLER et al. 2004). Depending on the active ingredient and the storage conditions, therefore, the storage or treatment of organic fertilisers may reduce environmental discharges to a certain extent. However, this is still a matter of some controversy, in view of the limited number of studies available on this topic (THIELE-BRUHN 2004). In the past, there was no standardised method for analysing the degradation behaviour of pharmaceuticals in organic fertilisers. Exposure assessment methods for the discharge of pharmaceuticals via organic fertilisers are currently being drawn up on behalf of the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) (UFORDAT, project FKZ 20267435) and will be incorporated into the EMEA guidelines; it is hoped that this will facilitate a uniform assessment of exposure. In pasture farming, the excreted active pharmaceutical ingredients – especially highly effective parasiticides – enter the soils directly, and are absorbed or degraded depending on their inherent properties. The non-degradable portion and metabolites may subsequently be transported into surface waters as a result of erosion, or may pass through the soil and enter the groundwater. Other discharge routes, which are less significant in quantitative terms, include sewage discharge from farms and the airborne transport of dust from animal sheds.

31. A number of studies have now proven that plants absorb active ingredients from soils fertilised with slurry containing antibiotics. For example, winter wheat cultivated on open ground was found to contain traces of chlorotetracycline (GROTE et al. 2006). Other results from greenhouse studies have likewise indicated active

ingredients being absorbed by maize, cabbage and onions (KUMAR et al. 2005). However, it is not currently possible to accurately assess the quantities of pharmaceutical residues from soils absorbed by plants due to the limited number of studies on this topic.

32. In aquaculture, the breeding and keeping of commercial and ornamental fish produces more direct discharges of pharmaceuticals and feed additives than conventional agriculture; these enter the fish pond together with the feed, or via the excreted faeces of the fish. With the exception of closed systems, they are subsequently transported into surface waters via the outfall. In sea-based fish farms, active pharmaceutical ingredients are transported directly into the ecosystem. Experts estimate that around 70 to 80 % of the active ingredients used in fish farming enter the environment in this way (SAMUELSEN et al. 1992). However, Germany only has a handful of such facilities (LOZAN et al. 1996). In technical facilities or aquariums, the active ingredients used may likewise enter the surface water via the effluent.

4.2 Documentation and behaviour in the environment

33. The behaviour of active pharmaceutical ingredients in the environment depends on their inherent properties. The transportation and degradation pathways of only a handful of active ingredients are currently known, and even less is known about the environmental behaviour of their decomposition products or metabolites.

To date, around 120 active pharmaceutical ingredients have been documented in the environment. This comparatively small number is due to the fact that many active ingredients are used in relatively small quantities, their detection (if they can be detected at all) entails time-consuming analysis, or they are very short-lived. The active ingredients detected in the environment are all "old" pharmaceuticals which did not require an environmental risk assessment at the time of licensing (cf. no. 114) (RÖNNEFAHRT et al. 2002).

4.2.1 In aquatic systems

34. Numerous studies on the aquatic environment document the existence of active pharmaceutical ingredients in surface waters. In most cases, sections of the aquatic environment were analysed for the existence of selected substances. By contrast, in 1998 and 2003 the Bund-Länder Ausschuss Chemikaliensicherheit (Federal/Land Task Force on Chemical Safety, BLAC) commissioned and published a series of comprehensive studies analysing the principal media (BLAC 1998; 2003). The most recent analysis programme aimed to obtain a representative overview of the pollution situation and to clarify the substance flow of such active ingredients into the environment. Over the course of the one-year project, samples from effluent, surface waters, groundwater and landfill leachate were analysed for up to 39 different active ingredients originating from human medicines, veterinary medicines as well as pharmacologically active feed additives. The results of the study verify that almost the entire range of active ingredients are found in local authority sewage and associated sewage sludge. The highest concentrations (in the µg/l range) were detected in effluent, but large numbers of active ingredients were also found in surface waters. Peak levels in excess of 1 µg/l were ascertained for carbamazepine, iopamidol (radiographic contrast medium containing iodine) and metoprolol. The maximum diclofenac level found was 0.47 µg/l (90 % percentile = 0.14 µg/l). The BLAC study found no traces of 17α-ethinyloestradiol. By contrast, a study by ADLER et al. found 17α-ethinyloestradiol (conjugated and free form) in 30 and 50 % respectively (2 analysis series) of the 39 Bavarian surface water samples analysed (ADLER et al. 2001). Maximum concentrations of 2.5 and 3 ng/l were measured, although the median was less than 0.1 ng/l (detection was possible in 51 % and 30 % of cases). The detection of 17α-ethinyloestradiol in this study is attributable to the more sensitive analysis technology used, with a determination limit of 0.1 ng/l, ten times lower than the equipment used in the BLAC study.

Only just over one-third of these pharmaceutical substances were detected in the groundwater analysed on behalf of BLAC (cf. Table 4).

35. Traces of pharmaceuticals have since been detected in both seawater and drinking water. Active pharmaceutical ingredients found in the North Sea include propyphenazone, carbamazepine, clofibric acid and ibuprofen and its metabolites hydroxyl- and carboxy-ibuprofen. The measured concentrations were in the region of a few ng/l. As would be expected, detection occurred in the immediate vicinity of estuaries and coastlines, while in the central North Sea, detection was around the determination limit. The concentration conditions of the active ingredients detected provide an important insight into the transportation and degradation of these substances (WEIGEL 2003). The concentrations measured in drinking water were generally less than 100 ng/l; maximum levels of 70 to 86 ng/l were detected for clofibric acid, iopamidol and ipromide (TERNES 2001b; 2001a).

36. There is currently no data available on the discharge of active pharmaceutical ingredients into Germany's surface waters from fish farms. An Austrian study found traces of the antibiotic oxytetracyline in the sediment of the trout farm four months after having been administered once only (SILIGATO et al. 2004). This discharge pathway could therefore pose a risk to waters and should be investigated.

Table 4

Maximum pharmaceutical concentrations in bank filtrate, surface waters and sewage treatment plant effluent

Pharmaceutical	**Groundwater** Bank filtrate total		**Surface waters (SW)** All representative SW		**Effluent** Sewage plant outflows total	
	Concentration [µg/l]					
	Max	**90 perc.**	**Max**	**90 perc.**	**Max**	**90 perc.**
Amidotrizoic acid	1.4	0.39	0.95	0.62	15.8	10.4
Atenolol	<DL	<DL	0.07	0.02	1.8	0.79
Bezafibrate	0.11	0.014	0.35	0.14	4.8	1.43
Bisoprolol	0.11	<DL	0.085	<DL	2	0.27
Carbamazepine	1	0.23	1.81	0.27	22	3.5
Chloramphenicol	<DL	<DL	<DL	<DL	0.07	<DL
Clarithromycin	<DL	<DL	0.95	0.01	1.8	0.5
Clenbuterol	<DL	<DL	0.06	<DL	0.1	<DL
Clofibric acid	1.9	0.37	0.185	0.04	3.3	0.51
Cyclophosphamide	<DL	<DL	0.1	<DL	0.15	<DL
Dehydrated erythromycin	<DL	<DL	0.46	0.065	6	0.62
Diazepam	<DL	<DL	0.033	<DL	0.1	<DL
Diclofenac	0.43	0.053	0.47	0.14	10	4.04
Dimethylaminophenazone	8.84	0.01	0.079	<DL	0.17	<DL
Estradiol	<DL	<DL	<DL	<DL	0.022	0.001
Oestrone	<DL	<DL	0.001	<DL	0.165	0.021
Ethinyloestradiol	<DL	<DL	<DL	<DL	0.009	<DL
Ibuprofen	<DL	<DL	0.092	0.01	3.7	0.43
Indometacin	<DL	<DL	0.032	<DL	0.3	0.185
Iomeprol	0.16	<DL	0.53	0.29	10	2.65
Iopamidol	1.4	0.11	1	0.55	9.4	4.82
Iopromide	0.04	<DL	0.45	0.27	7.4	2.74
Ketoprofen	<DL	<DL	0.033	<DL	0.24	0.096
Metoprolol	0.03	<DL	1.8	0.09	9.12	2.01
Naproxen	<DL	<DL	0.11	0.02	0.94	0.24
Phenazone	0.19	0.157	0.84	0.09	0.9	0.27
Propranolol	<DL	<DL	0.22	<DL	0.65	0.23
Propyphenazone	0.12	0.1	0.065	0.04	0.99	0.25
Roxithromycin	<DL	<DL	0.06	0.016	1.7	0.84
Salbutamol	<DL	<DL	0.05	<DL	0.16	0.023
Sotalol	0.37	<DL	0.95	0.11	6.5	2.76
Sulphadimidine	<DL	<DL	0.145	0.005	0.24	0.025
Sulphamethoxazol	0.079	0.07	0.377	0.11	4.7	0.85
Terbutaline	<DL	<DL	0.03	<DL	0.6	<DL
Trimethoprim	<DL	<DL	0.17	0.035	1.5	0.23

DL = Detection level
Max = Maximum level
90 perc = 90 percentile (forms the upper limit of the representative value range and can therefore be used to delimit pollutants).

SRU/Statement no. 12-2007/Table 4; data source: BLAC 2003

37. There is currently very little data available on the persistence and degradation behaviour of active pharmaceutical ingredients in aquatic systems. Most studies have established the elimination of such substances in sewage treatment plants. The degree of elimination in the mechanical and biological purification stages of the sewage treatment plant differs very significantly from one active ingredient to another. Studies indicate that the concentration of some substances decreases during the sewage purification process. For example, ibuprofen was 57 to 60 % eliminated in a pilot sewage purification plant (ZWIENER and FRIMMEL 2004). Some studies of sewage treatment plants have even indicated maximum elimination rates of between 96 and 99 % for this active ingredient (BUSER et al. 1999). Substance flow analyses for antibiotics produced similar results. For example, elimination rates for the fluorochinolones ciprofloxacin and norfloxacin ranged between 80 and 90 %. However, a not insignificant portion of these antibiotics was transferred into the sewage sludge, which indicated high content levels of between 2 and 3 mg/kg (GIGER et al. 2003).

38. By contrast, the study commissioned by BLAC indicated virtually no significant differences between the sewage treatment plant inlets and outfalls for many of the pharmaceutical concentrations measured such as carbamazepine, clofibric acid, diclofenac and metoprolol – in other words, there was no evidence of any significant degradation or sorption of the active ingredients during the sewage purification process. Clofibric acid and diclofenac are known to be persistent substances with elimination rates of just 2 to 6 % in the pilot sewage purification plant (ZWIENER and FRIMMEL 2004).

After passing through the sewage treatment plant, the remaining active pharmaceutical ingredients and their metabolites which have not been degraded, adsorbed or absorbed enter the surface waters, from where they may be transported into the ocean or may pass through soil into the groundwater. Clofibric acid is one active substance which has been detected both in groundwater and in the waters of the North Sea (BUSER et al. 1998; HEBERER et al. 1997). In areas where groundwater abstraction points are located in the immediate vicinity of contaminated surface waters (such as Berlin), active substance concentrations are found to be significantly higher than elsewhere. For example, at one such abstraction point, HEBERER et al. (1997) measured maximum clofibric acid levels of 7.3 µg/l, compared with levels normally in the ng range.

39. The transport behaviour of active substances from surface water into the groundwater is influenced by a whole range of factors. The chemico-physical properties of the substance such as polarity and sorption behaviour play a key role; so too does the type of sediment and rock it passes through. In laboratory experiments, MERSMANN (2003) found that transport behaviour is dependent on pH value, the content of organic substance, water saturation and aerobic properties. As such, the active substances carbamazepine and propyphenazone exhibit a low level of degradation and a relatively high mobility. Clofibric acid is likewise very persistent and exhibits a low sorption capacity, while ibuprofen concentration levels in water are reduced, presumably as a result of microbial degradation.

4.2.2 In soils

40. It is far more difficult to detect pharmaceuticals in soils than in aqueous media, since many substances are absorbed or adsorbed by organic particles and must first be separated from them using complex extraction processes. Due to the dominance of antibiotics among the active pharmaceutical ingredients used in livestock farming, the detection of pharmaceuticals in agricultural soils is primarily confined to this group of substances. This type of soil contamination particularly affects regions with a high density of cattle and areas with single-species farms. In the data from a number of studies compiled by HAMSCHER et al. (2004), tetracycline exhibited the highest levels, with concentrations of up to 300 µg/kg in the soil (cf. Table 5). Concentrations of other antibiotic substances were significantly lower, and of the sulphonamides group, sulphamethazine was the only substance found to exceed the detection limit (cf. Table 5). Peak levels were found in dried slurry residues (350 µg/kg of tetracycline and 1,440 µg/kg of chlorotetracycline) (HAMSCHER et al. 2004) and in soil dust samples (1,200 µg/kg) taken from the immediate vicinity of animal sheds (THIELE-BRUHN 2004).

41. Antibiotics have also been found in soils fertilised with sewage sludge. For example, GOLET et al. (2002) detected the two fluorochinolones ciprofloxacin and norfloxacin in concentrations of up to 0.3 mg/kg, with active ingredients being detected up to 20 months after the soil had been treated, indicating a very high level of persistence.

42. A substantial proportion of the imported antibiotics are bonded to the soil matrix, and cannot subsequently be desorbed via simple extraction. The sorption of active pharmaceutical ingredients in soils is decisively influenced by their physico-chemical properties as well as by the properties of the soil (soil type, content and composition of organic substance and clay minerals, pH value) (THIELE-BRUHN 2004). The joint project by the Deutsche Forschungsgemeinschaft (German Research Association, DFG) "Veterinary medicines in soils: Fundamental principles of risk assessment" (scheduled to run until 2008) will investigate in greater depth the identification, quantification and modelling of the principal response, transportation, bonding, ageing and effect mechanisms of two active pharmaceutical substances (sulphadiazine and difloxacine) (TU Berlin, no year).

Table 5

Maximum concentration levels of various antibiotics measured in agricultural (top) soils fertilised with conventional organic fertilisers

Active substance	Samples	Maximum concentration levels [µg/kg]
Tetracyclines		
- Oxytetracycline	1	<10
- Tetracycline	60	310
- Chlorotetracycline	14	30
Sulphonamides		
- Sulphamethazine	14	11
- Sulphadiazine	14	<1
- Sulfathiazol	14	<1
- Sulphamerazine	14	<1
- Sulphamethoxypyridazine	14	<1
- Sulphamethoxazol	14	<1
- Sulphadimethoxine	14	<1
- Tylosin	14	<1
- Salinomycin	2	<1.6
- Tiamulin	2	0.7
Source: HAMSCHER et al. 2004		

Laboratory studies to investigate the behaviour of antibiotics in soils indicate degradation via abiotic processes, which include adsorption on surfaces, complexing, diffusion and sequestration, as well as photo-degradation. At the same time, however, active substances may also be protected from biotic degradation (the latter is evidently less significant) by sorption, contributing to their environmental persistence (THIELE-BRUHN 2004).

Unlike the tetracyclines, which have low water solubility and a high protein affinity, and which were found to be very persistent and not very mobile in various monitoring studies (they are absorbed/adsorbed to a large extent by soil particles and were therefore only detected in the upper soil layers), sulphonamides have also been detected in groundwater. This would suggest that this group of veterinary medicines is transported from the agricultural soil into the groundwater. Tetracyclines, by contrast, may accumulate in soil as a result of the repeated application of organic fertilisers, but exhibit only limited bio-availability due to the high level of sorption (KTBL 2005, page 52).

4.3 Risks to the environment

4.3.1 Effects on aquatic ecosystems

43. Although pharmaceuticals rank among the most widely studied substances in terms of their effects on mammals, to date proportionately little has been known about their ecotoxicity potential, particularly with regard to the long-term consequences of their presence in the environment. The debate currently centres around antibiotics, partly in view of the possible formation of antibiotic resistance (section 4.4.2) and hormone active substances which exhibit an oestrogenic and anti-androgenic effect, as well as other effects such as the induction of vitellogenin (an egg yolk precursor protein expressed in the livers of fish). However, other groups of active ingredients such as cytostatics (cytotoxic or cell growth-inhibiting substances), antiphlogistics and (in the case of veterinary medicines) parasiticides also represent a potential environmental risk, due to the high quantities consumed in some cases, combined with their inherent properties. Generally speaking, the active ingredient concentrations

ascertained from acute toxicity tests for aquatic organisms are significantly higher than the substance concentrations measured in the environment (BLAC 2003; FENT et al. 2006). For example, the maximum concentration of fluoxetine – a serotonin reabsorption inhibitor with an antidepressive effect – measured in surface water is 12 ng/l, while standardised ecotoxicity tests suggested that effects were only detectable in the µg/l range (BROOKS et al. 2003).

Below, six different active ingredients or active ingredient groups – clofibric acid, carbamazepine, diclofenac, ibuprofen, 17α-ethinyloestradiol and antibiotics – are used as examples to illustrate the ecotoxic effect of pharmaceuticals.

Clofbric acid

44. Clofibric acid is the active metabolite of the three active pharmaceutical ingredients ethyl-clofibrate, etofibrate and etofyllinclofibrate which are members of the lipid-lowering family (cholesterol reducers). It is one of the most widely investigated active pharmaceutical ingredients in terms of its behaviour in aquatic systems and, despite a decline in the quantities of parent substance used, is considered a marker substance for the discharge of pharmaceuticals into the environment. Back in the early 1990s, clofibric acid was detected in surface waters and in groundwater (STAN et al. 1994; STAN and LINKERHÄGNER 1992). The available studies indicate minimal acute ecotoxicity of this active ingredient metabolite. The effective concentrations (EC_{50} levels) in tests for acute toxicity range between 12.5 mg/l (*Lemna minor* = lesser duckweed) and 126 mg/l (fish embryo test). The fact that active pharmaceutical ingredients such as clofibric acid have a low level of toxicity is hardly surprising, since during the systematic search for therapeutic effects, low toxicity in mammals was one of the reasons it was chosen, and its effect mechanism exhibits a high level of specificity for mammals. The effective concentrations for chronic toxicity of clofibric acid are similarly low (cf. Table 6), with the exception of a study which tested administered clofibrates. In this instance, the EC_{10} (concentration at which an effect occurs in 10 % of test animals) derived from a reproduction test on water fleas (*Daphnia magna*) was 0.0084 mg/l (cf. Table 7). The actual environmental relevance of this substance is due to its poor biodegradability and the high mobility of clofibric acid.

Table 6

(Sub-) acute effect of clofibric acid, carbamazepine, diclofenac, ibuprofen, 17α-ethinyloestradiol and antibiotics in standardised ecotoxicity tests

Trophic level/ test organism	Active substance (group)	Effective concentration [mg/l]	Test parameter (test duration)/ Defined endpoint	Bibliography
Bacteria				
Luminescent bacteria (Vibrio fischeri)	Clofibric acid	91.8	EC50 (30 min)/ luminescence	FERRARI et al. 2003
Luminescent bacteria (Vibrio fischeri)	Carbamazepine	81	EC50 (30 min)/ luminescence	FERRARI et al. 2003
Luminescent bacteria (Vibrio fischeri)	Diclofenac	11.4	EC50 (30 min)/ luminescence	FERRARI et al. 2003
Luminescent bacteria (Vibrio fischeri)	Ibuprofen	12.3	EC50 (5 min)/ luminescence	HUSCHEK und KRENGEL 2003
Luminescent bacteria (Vibrio fischeri)	17α-ethinyloestradiol	212	EC50 (30 min)/ luminescence	KOPF 1997
Luminescent bacteria (Vibrio fischeri)	Antibiotics: Tetracycline Streptomycin	0.026 8.2	EC50/ luminescence	BACKHAUS und GRIMME 1999

Microalgae: Green algae *(Desmodesmus subspicatus)*	Clofibric acid	115	EC_{50} (3 days)/ growth	CLEUVERS 2003
Green algae (Desmodesmus subspicatus)	Carbamazepine	74	EC50 (3 days)/ growth	CLEUVERS 2003
Green algae (Desmodesmus subspicatus)	Ibuprofen	315	EC50 (3 days)/ growth	CLEUVERS 2003
Green algae (Pseudokirchne-riella subcapitata)	Diclofenac	16.3	EC50 (3 days)/ growth	FERRARI et al. 2003
Green algae (Desmodesmus subspicatus)	17α-ethinyloestradiol	0.84	EC50 (3 days)/ growth	KOPF 1997
Cyanobacterion (Microcystis aeruginosa)	Antibiotics: Ciprofloxacin	0.005	EC50	HUSCHEK und KRENGEL 2003
Aquatic plants: Lesser duckweed *(Lemna minor)*	Clofibric acid	12.5	EC_{50} (7 days)/ growth	CLEUVERS 2003
Lesser duckweed (Lemna minor)	Carbamazepine	25.5	EC50 (7 days)/ growth	CLEUVERS 2003
	Diclofenac	--		
Lesser duckweed (Lemna minor)	Ibuprofen	4.0	EC50 (7 days)/ growth	POMATI et al. 2004
Lesser duckweed (Lemna minor)	Antibiotics: Tetracycline	1.1	EC50 (7 days)/ growth	POMATI et al. 2004
Crustaceans: Water flea *(Daphnia magna)*	Clofibric acid	72	EC_{50} (48 h)/ Mobility	CLEUVERS 2003
Water flea (Daphnia magna)	Carbamazepin	100	EC50 (48 h)/ Mobility	CLEUVERS 2003
Water flea (Daphnia magna)	Diclofenac	68	EC50 (48 h)/ Mobility	CLEUVERS 2003
Water flea (Daphnia magna)	Ibuprofen	108	EC50 (48 h)/ Mobility	CLEUVERS 2003
Water flea (Daphnia magna)	17α-ethinyloestradiol	6,4	EC50 (48 h)	SCHWEINFURTH et al. 1997
Water flea (Daphnia magna)	Antibiotics: 9 diff. active substances**	4.6-1,000	EC50 (48 h)/ Mobility	WOLLENBERGER et al. 2000

Fish: Embryos	Clofibric acid	126	EC_{50} (48 h)/ Pulse rate	HANISCH et al. 2004
Zebrafish *(Danio rerio)*	Carbamazepine	35.4	LC_{50} (96 h)	LIEBIG 2005
	Diclofenac	--		
Bluegill *(Lepomis macrochirus)*	Ibuprofen	173	LC_{50} (96 h)	WEBB 2004
Rainbow trout *(Oncorhynchus mykiss)*	17α-ethinyloestradiol	1.6	LC_{50} (96 h)	SCHWEINFURTH et al. 1997
Bluegill *(Lepomis macrochirus)*	Antibiotics: Bacitracin	173	LC_{50} (96 h)	HUSCHEK und KRENGEL 2003
EC_{50} = Concentration at which an effect occurs in 50 % of the test animals LC_{50} = Concentration which leads to mortality in 50 % of the animals ** Metronidazole, oxalic acid, olaquindox, oxytetracycline, streptomycin, sulphadiazine, tetracycline, tiamulin and tylosin -- No data available				
SRU/Statement no. 12-2007/Table 6				

Carbamazepine

45. Carbamazepine is an antieleptic, and another active pharmaceutical ingredient which enters the environment in large quantities. The substance has a moderately acute toxic effect on microalgae *(Desmodesmus subspicatus,* EC_{50} = 74 mg/l), crustaceans *(Daphnia magna,* EC_{50} = 100 mg/l) and fish *(Danio rerio,* EC_{50} = 35.4 mg/l) (cf. Table 6). In contrast to short-term tests, the effect concentrations for chronic exposure are significantly lower. For example, in *Daphnia magna* an adverse effect on reproduction was ascertained at a concentration of just 1.26 mg/l (cf. Table 7). The larval hatch rate of midges *(Chironomus riparius)* was reduced from a concentration of just 0.14 mg/kg carbamazepine in the sediment. Studies on water fleas *(Ceriodaphnia dubia)* exhibit a modified reproduction rate at a similarly low exposure level of 0.1 mg/l in the water (FERRARI et al. 2003) (cf. Table 7).

Diclofenac

46. Diclofenac is an analgesic with anti-inflammatory properties which inhibits prostaglandin synthesis in particular. One indication of the potential environmentally hazardous effects of residues or contamination with this active ingredient is the fact that vulture populations in India and Pakistan have declined by up to 95 %. These very significant population decreases are attributed to the consumption of cattle and goats previously treated with diclofenac which subsequently died, either as a result of an accidents or due to disease. It is assumed that the absorption of active ingredients in scavengers leads to malfunction of the kidneys (GREEN et al. 2004; OAKS et al. 2004). Like the active substances already mentioned, the acute toxicity level, tested on aquatic organisms, is low to moderate. The EC_{50} for *Daphnia magna* is 68 mg/l (cf. Table 6). In the luminescent bacteria test and for green algae, EC_{50} levels of 11.4 and 16.3 mg/l respectively were ascertained. By contrast, chronic exposure of fish led to adverse effects even at much lower concentrations. For example, in rainbow trout, histopathological changes in the liver and kidneys were ascertained at a concentration of 5 µg/l (cf. Table 7). Moreover, the fish examined exhibited an accumulation of diclofenac in all organs and tissue (kidneys, gills, liver and muscle tissue). The highest bioconcentration factor (2,732) was ascertained for the liver.

Ibuprofen

47. Ibuprofen is the most widely used active ingredient in human medicine in terms of quantity. Based on the available data, a moderately acute toxic effect on test organisms in standard ecotoxicity tests is assumed. The ascertained effective concentrations (EC_{50} levels) range between 12.3 mg/l in the luminescent bacteria test and 315 mg/l for the green algae *Desmodesmus subspicatus,* whereby the effect may vary significantly between different species (cf. Table 6). For example, the EC_{50} level for diatomaceae (*Skeletonema costatum)* at 7.1 mg/l is considerably lower than for green algae (*Desmodesmus subspicatus)* (Knoll Pharmaceuticals and BASF 1995). Indications suggest that ibuprofen has a remarkable bioaccumulation potential. The BLAC has classified the substance as toxic for aquatic organisms, since longer-term exposure could induce harmful effects in the waterbody (BLAC 2003). The chronic effect of ibuprofen is evidently still largely unknown.

Table 7

Chronic and sub-chronic effect of clofibric acid, carbamazepine, diclofenac, ibuprofen, 17α-ethinyloestradiol and antibiotics in ecotoxicity tests

Trophic level/ test organism	Active substance (group)	Effective concentration [mg/l]	Test parameter (test duration)/ defined endpoint	Bibliography
Crustaceans: Water flea *(Daphnia magna)*	Clofibric acid (clofibrate)	0.0084	EC_{10} (21 days)/ Reproduction	KOPF 1997
Water flea *(Daphnia magna)*	Carbamazepine	1.26	LOEC (21 days)/ Reproduction	LIEBIG 2005
Water flea *(Ceriodaphnia dubia)*	Diclofenac	2	LOEC (7 days)/ Reproduction	FERRARI et al. 2003
--	Ibuprofen	--	--	--
Water flea *(Daphnia magna)*	17α-ethinyloestradiol	0.105	EC50 (21 days)/ Reproduction	KOPF 1997
Water flea *(Ceriodaphnia dubia)* Water flea *(Ceriodaphnia dubia)*	Antibiotics: Ofloxacine Sulfamethoxazole	10 0.20	NOEC (7 days)/ Reproduction NOEC (7 days)/ Reproduction	FERRARI et al. 2003 FERRARI et al. 2003
Fish:	Clofibric acid	70	NOEC (10 days)/ Mortality	FERRARI et al. 2003
Zebrafish *(Danio rerio)*	Carbamazepine	25	NOEC (10 days)/ Mortality	FERRARI et al. 2003
Rainbow trout *(Oncorhynchus mykiss)*	Diclofenac	0.005	LOEC (28 days)/ Organ changes	SCHWAIGER et al. 2004
--	Ibuprofen	--	--	--
Zebrafish *(Danio rerio)*	17α-ethinyloestradiol	0.00001	LOAEC (14 days)/ Vitellogenin induction	VERSONNEN and JANSSEN 2004
Zebrafish *(Danio rerio)* Zebrafish *(Danio rerio)*	Antibiotics: Ofloxacine Sulfamethoxazol	>16 > 8	NOEC (10 days)/ Reproduction NOEC (10 days)/ Reproduction	FERRARI et al. 2003 FERRARI et al. 2003

NOEC = No Observed Effect Concentration
LOEC = Lowest Observed Effect Concentration
LOAEC = Lowest Observed Adverse Effect Concentration
EC_{50} = Concentration at which an effect occurs in 50 % of test animals
EC_{10} = Concentration at which an effect occurs in 10 % of test animals
No data available

SRU/Statement no. 12–2007/Tab. 7

17α-ethinyloestradiol

48. In recent years, the possible effects of xenobiotics on the hormonal system have featured prominently in the debate surrounding substance risks. Active pharmaceutical ingredients also include hormones, especially steroid hormones and hormone-like substances (e.g. 17α-ethinyloestradiol, methyltestosterone). The best-known active ingredient, and one which has been particularly well studied in terms of its environmental effects, is 17α-ethinyloestradiol, which is the principal active component of oral contraceptives and is therefore comparatively widely used. Although 17α-ethinylestradiol is used in relatively small quantities compared with other active substances (annual

consumption quantity approx. 50 kg), it has a very high oestrogenic potential and a relatively long active period of effectiveness. 17α-ethinyloestradiol has considerable structural similarity to the female sex hormone 17β-oestradiol and acts on the physiological receptor and its signal transduction mechanisms.

49. In various laboratory tests, 17α-ethinyloestradiol exhibited a low to moderate acute ecotoxicity potential. Effective concentrations ranged between 0.84 mg/l for the green algae *Scendedesmus subspicatus* and 212 mg/l in the luminescent bacertia test (cf. Table 6). An LC_{50} level of 1.6 mg/l was ascertained in rainbow trout *(Oncorhynchus mykiss)*. By contrast, the concentrations at which changes to aquatic organisms were observed under chronic exposure were considerably lower. For example, a full life cycle test on the fathead minnow *(Pimephales promelas)* revealed histopathological changes in the livers and kidneys of larvae and juvenile animals from a concentration of just 0.01 µg/l, over an exposure period of four weeks (SCHWEINFURTH et al. 1997). VERSONNEN and JANSSEN (2004) observed effects on the zebrafish (*Danio rerio*) at similar concentrations (cf. Table 7). After just 14 days' exposure, a vitellogenin induction was ascertained in male and female animals, and the GSI (gonadosomatic index – ratio of gonad mass to total body mass) was also reduced in the latter. In a multi-generational study of the same species, 210 days' exposure to 5 ng/l of 17α-ethinyloestradiol disrupted egg production in the young (F1 generation), which failed to produce any viable eggs, and the testes (sex organs) of all males exhibited abnormalities (NASH et al. 2004) (cf. Table 7). Effects were also observed in invertebrates at similarly low exposure concentrations. The LOEC levels ascertained in long-term studies (6 months) of the giant ramshorn snail *(Marisa cornuarietis)* ranged between 1 ng/l (decline in fertility) and 250 ng/l (induction of imposex = females additionally form parts of the male reproductive system) (SCHULTE-OEHLMANN et al. 2004).

Antibiotics

50. Active antibiotic substances may cause adverse effects in the microorganism populations of surface waters and their sediments, as well as having a lasting disruptive effect on the purification function of sewage treatment plants. Inhibiting the activity of sewage sludge bacteria may significantly impair the degradation of organic substances and hence adversely affect the sewage plant's purifying function (ALEXY et al. 2004). In model sewage treatment plants, evidence was found of a decrease in bacterial density and changes in composition as a result of exposure to antibiotic concentrations occurring in hospital effluent (KÜMMERER et al. 2000; STANISLAWSKA 1979). Studies of nitrifying bacteria provide further indications of the effect of antibiotics in sewage vis-à-vis the purification function. Nitrification is an important stage in sewage treatment and is used to eliminate ammonia. Antibiotic concentrations occurring in the environment are lower than the minimum inhibitory concentrations measured in the laboratory. However, the length of incubation plays a key role. For example, in a comparison with short-term tests (2 to 4 days), the active substance concentrations which demonstrated an effect following an incubation period of more than five days were reduced by a factor of ten.

The extent to which active antibiotic ingredients in sewage encourage the increased formation of resistance in sewage treatment plants is still largely unclear. There has been a lack of suitable studies in this connection to date (ALEXY et al. 2004).

51. In order to facilitate a better assessment of the risk of antibiotic occurrence in surface waters, *inter alia*, standardised ecotoxicity tests were conducted with marine bacteria. Like the nitrifying bacteria, it was found that concentrations occurring in the environment had no effect on bacteria in the acute test, but that effects were observed with long-term exposure (FROEHNER et al. 2000; BACKHAUS und GRIMME 1999).

52. Negative effects on higher organisms in the ecosystem as a result of exposure to antibiotics are less probable, due to the fact that the active substances generally have a high level of specificity, but not impossible (cf. also KÜMMERER 2004b). By contrast, microalgae are influenced by antibiotics at varying levels of intensity. For example, blue-green algae (cyanobacteria) were found to be particularly sensitive to many active antibiotic substances, because they are closely related to bacteria. For example, the EC_{50} for ciprofloxacin ascertained in *Microcystis aeruginosa* was 5 µg/l (cf. Table 6). Studies by LANZKY and HALLINGSORENSEN (1997) likewise found that the green algae *Chlorella sp.* and *Selenastrum capricornutum* were impaired as a result of metronidazole. Hence, the possibility of algae populations being affected by active antibacterial substances in surface waters cannot be excluded. In this respect, it should be noted that even a minimal decline in the algae population – which represents an important food source for higher organisms – can disrupt the balance of aquatic ecosystems (ALEXY et al. 2004).

53. There are some indications that antibiotics cause negative effects in zooplankton. For example, tiamulin and other active substances were found to be reproduction-toxic for water fleas *(daphnia magna),* while bacitracin reduced the hatch and survival rate of the brine shrimp *Artemia salina* (BRAMBILLA et al. 1994; WOLLENBERGER et al. 2000). Effects in fish were only found, if at all, at very high exposure concentrations, such as those which may occur in acquacultures (ALEXY et al. 2004; HUSCHEK and KRENGEL 2003).

54. The extent to which antibiotics can influence biotic communities in waterbody sediment is still unknown. At very high concentrations of active substances, changes in bacterial composition and the support of fungal growth

have been observed (ALEXY et al. 2004). There are some indications that in fish ponds, or rather in the sediment beneath sea-based fish farms, effects on bacterial activity are likely. In this connection, studies which indicated a high level of persistency for certain antibiotics in the sediment are a cause for concern (HEKTOEN et al. 1995). Meanwhile, other studies indicate reduced antibiotic activity for selected active substances as a result of bonding to sediment particles (ALEXY et al. 2004). An effect on higher organisms or those living in the soil is less likely, as indicated *inter alia* by studies by BAGUER et al. (2000) on various invertebrates (benthic invertebrates).

Evaluation of available data

55. The above comments on the effects of various active pharmaceutical ingredients or substance groups give some indication of the difficulty of performing ecotoxicity assessments of such substances.

Although data regarding the acute effect of key active ingredients is available which may provide indications of possible ecotoxic effects, these results are generally confined to non-specific narcotic effects and do not permit any conclusions to be drawn with regard to possible chronic effects (SCHÄFERS 2003). This is backed up by the large difference ascertained between active concentrations in acute and chronic tests. Studies are now available on the long-term effects of selected active ingredients, but only a few of them cover important population-relevant endpoints. This information deficit, particularly vis-à-vis chronic effects, means that work is still needed to clarify whether the environmental concentrations detected trigger population-relevant changes in the ecosystem.

56. Another reason why it is difficult to relate the results of laboratory studies to the actual environmental situation is the absence of a summative approach to substances with similar effect mechanisms. To date, only very few studies have examined mixed exposure to active pharmaceutical ingredients. The work by CLEUVERS (2003) proved that combined exposure to clofibric acid and carbamazepine in *Daphnia magna* (water flea) has a more powerful effect than a mere additive effect. Exposure to a single active ingredient led to a 1 % and 16 % reduction in mobility respectively in daphnia, while combined exposure with the same substance concentration produced a 95 % reduction in mobility. This suggests that combined exposure may even lead to overadditive effects.

57. Generally speaking, it is difficult to draw conclusions from data obtained in test models regarding possible changes to the environment. On the other hand, it is virtually impossible to trace the effects ascertained in aquatic systems to individual pollutants, given the very low concentrations of individual components and the high number of active pharmaceutical ingredients, other environmental chemicals and natural compounds with a similar effect potential also present in the water, making accurate isolation of a single factor very difficult. Apart from a few selected hot spots of pollutant contamination, it is not normally possible to make a causal connection between a certain incidence of exposure and environmental effects. On the other hand, for selected effect mechanisms, such as those linked to receptors, it is reasonable to assume that with mixtures of active ingredients and natural substances, the environmental effects will be compounded, and that the summated effect should therefore be considered.

58. The studies on fish exposed to effluent from sewage treatment plants are a well-known example of this. Induction of vitellogenin production and the formulation of female sex cells was detected in males (LfW no year; HARRIES et al. 1996; PAWLOWSKI et al. 2003). These effects are seen as indications of oestrogenic substances in sewage treatment plant effluent. However, these studies were unable to determine the extent to which naturally excreted steroid hormones, synthetically produced hormones such as 17α-ethinyloestradiol or other xeno-oestrogens (e.g. nonylphenols) in sewage were responsible for the observed effects in fish. Natural human hormones are in any case responsible for a significant portion of the oestrogenic activity detected in sewage treatment plant outfalls (DESBROW et al. 1998). Nevertheless, full laboratory life cycle tests on fish now suggest that oestrogen derivatives used as contraceptives pose the greatest risk of oestrogenic effects in surface waters (SCHÄFERS 2003), despite the fact that they occur in lower concentrations than some other xeno-oestrogens (TERNES et al. 1999) (cf. Table 8).

This is explained by the high receptor affinity and environmental persistence of 17α-ethinyloestradiol compared with industrial chemicals and phyto-oestrogens whose oestrogenic potential in *in vivo* laboratory studies was found to be approximately four to five times lower (SCHÄFERS 2003).

Table 8

Examples of the oestrogenic potential of xenobiotics (xeno-oestrogens) and recorded concentrations in surface waters

Substance	**Concentration:** Surface waters [ng/l]	**Oestrogenic potential *in vitro**** (in relation to 17 β-oestradiol	**Oestrogenic potential *in vivo***	
			Effective concentration: [ng/l]	**Test parameter/ exposure period/ defined endpoint** (fish species)
17β-estradiol (natural hormone)	0.1–3.6	1	100[a]	LOEC/84 h/gonad-development (mosquito fish)
17α-ethinyloestradiol (synthetic hormone)	0.1–5	1	2[b]	LOEC/21 h/vitellogenin induction (rainbow trout)
4-nonylphenol (chemical)	7–2,720	0.00065	20,000[b]	LOEC/21 h/vitellogenin induction (rainbow trout)
Bisphenol A (chemical)	0.5–410	0.000021	160,000[c]	LOEC/71 h/vitellogenin induction (fathead minnow)
β-sitosterol (phytohormone)	60–1,500	0.000096	75,000[d]	LOEC/21 h/vitellogenin induction (rainbow trout)
*Yeast receptor test on oestrogen receptor-mediated activity				
SRU/Statement no. 12–2007/Tab. 8; data sources: WENZEL 2003; [a]DOYLE and LIM 2002; [b]JOBLING et al. 1996; [c]SOHONI et al. 2001; [d]TREMBLAY and KRAAK 1999				

4.3.2 Effects on terrestrial ecosystems

59. To date there has been little research work dedicated to the effect of pharmaceuticals on soil biocoenosis (totality of organisms coexisting in a soil). Although bioassays have been developed to test the effects of environmental chemicals on selected organisms, studies examining the effect of pharmaceuticals directly in the soil medium are few and far between. Antibiotics are the main focus of terrestrial eco-toxicology of pharmaceuticals, although more recent studies have also considered the possible effects of parasiticides.

Antimicrobial active ingredients are likely to primarily affect bacteria and monocellular organisms. Current findings regarding the growth and activity of soil bacteria are not entirely consistent and indicate both inhibition and stimulation of bacterial growth. One possible explanation could lie in the fact that the effectiveness of antibiotics is generally limited to certain bacterial strains, which explains why other bacterial strains are more successful when growth competitors have been eliminated. The study recently published by THIELEBRUHN and BECK (2005) found a dose-dependent decline in bacterial activity as a result of exposure to the two antibiotics sulphapyridine and oxytetracycline. The EC_{10} levels measured for these two active ingredients ranged between 0.2 and 160 µg/kg, whereby the bacteriostatic effects indicated a significant time dependency. The inhibition of soil bacteria was linked to a dose-dependent shift in the fungal/bacterial ratio. From this, the authors conclude that pharmaceutical antibiotics may exert temporary selection pressure on soil microorganisms, even in environmentally relevant concentrations, leading to shifts in the population structures.

60. Antibiotics are generally found to exhibit minimal toxicity towards higher soil organisms. For example, when examining the effect of tiamulin, olaquindox and metrodinazoles, JENSEN et al. (2003) obtained EC_{10} levels of between 61.2 and 722 mg/kg in reproduction tests on springtails (collembola, *Folsomia fimetaria)* and the earthworm species *Enchytraeus crypticus*.

61. Work is underway to develop parasiticides with a toxic effect on arachnids (e.g. mites), insects, protozoa, roundworms and flatworms without harming the treated organism, generally mammals. Their effect is generally based on impairing the energy metabolism or nervous system of the parasites. These active ingredients therefore have the potential to harm other organisms from the same family, even at comparatively low concentrations. For example, the insecticide avermectin (others in this active ingredient class include abamectin and ivermectin) is used *inter alia* to treat endoparasites and ectoparasites, whereby a high proportion of the active ingredient is excreted unaltered. Abamectin and ivermectin may

induce effects in very different arthropods. The intensity of the effect, and its continuing effectiveness following excretion, varies between non-target organisms such as beetles, flies and earthworms. For example, the concentrations at which effects were ascertained in long-term tests (at least 21 days) for springtails and earthworms were 0.26 and 3 mg/kg respectively. Studies by SOMMER et al. (1992) indicated a complete inhibition of larval development in dung beetles at an ivermectin concentration of 1.6 mg/kg. In the dung of animals which had been treated 17 days previously, only half of the larvae survived, even though the substance concentration had declined to 0.3 mg/kg by that time. Other studies confirm the observation that even after long periods (of up to 40 days), the level of ivermectin remaining in excreta products could damage the coprobionts. Coprobiontic insects and worms degrade excrement and are therefore of particular ecological significance for the reprocessing of the nutrients carbon, phosphate and nitrogen in the substance cycle. Various studies have confirmed the fact that faeces degradation is impaired by the use of ivermectin or anthelminthics (medicines used to treat parasitic worm infections) (ROSENKRANZ and ASSMAN 2005; SOMMER and BIBBY 2002). As ivermectin causes more pronounced effects in insects, impaired rates of degradation caused by the use of this active ingredient in grazing animals is observed primarily in locations where dung degradation is dominated by insects (SVENDSEN et al. 2003). For example, ecotoxicity tests on earthworms indicated only a minimal effect of ivermectin (SVENDSEN et al. 2005). Firstly, the use of parasiticides may inhibit populations of dung-degrading insects, and disrupt decomposition processes. As the dung-degrading larvae include future predators or pollinators, this could have indirect effects on the ecosystem as well. Furthermore, in extreme cases, reduced levels of dung degradation could have financial implications, because cattle do not feed in the direct vicinity of dung heaps, and therefore, the use of severely contaminated meadows for livestock farming is very restricted.

4.3.3 Environmental risk assessment

62. On the basis of exposure estimates and effect analyses, risk assessments may be made for selected pollutants or active pharmaceutical ingredients discharged into waterbodies. To this end, we calculate the ratios Predicted Environmental Concentration (PEC) and Predicted No Effect Concentration (PNEC). The PEC is calculated on the basis of substance data regarding consumption and discharge quantity, as well as the retention rate, sewage volume and dilution factor, and substance properties (water solubility, n-octanol/water distribution coefficient, dissociation constant for acids and bases, sorption coefficient etc.) indicating its behaviour in the environment (sorption by sediment and soil particles, degradation, accumulation). In this connection, two recently published monitoring studies were able to prove, based on a comparison of MED (Monitored Environmental Concentration) and PEC levels, that PEC levels calculated for active pharmaceutical ingredients such as carbamazepine, propranolol and diclofenac are eminently suitable for assessing environmental risk (FERRARI et al. 2003; LIEBIG et al. 2006). The PNEC is derived from the quotient of the lowest documented effective concentration and a safety margin specified for that particular active ingredient based on the available data and risks. These safety margins are determined as part of the work of the OECD (Organisation for Economic Cooperation and Development) in a consensus procedure, being determined to a large extent by the available effect data for organisms of different taxonomic groups and trophic levels: The more suitable data is available, the lower the safety margin is. If the estimated exposure concentration is the same as or higher than the minimum concentration at which an effect is anticipated – corresponding to a PEC/PNEC ratio of ≥ 1 – then discharge of that substance is considered to pose a risk for the ecosystem.

63. A study on behalf of the Federal State of Brandenburg assessed the ecotoxicity risk of 60 different human medicine ingredients or residues (HANISCH et al. 2004). It concluded that an environmental hazard potential may be linked to exposure to the active pharmaceutical ingredients ciprofloxacin HCl and clarithromycin (antibiotics), carbamazepine (antieleptic), benzalkonium chloride, cocosproprylenediamine guaniacetate, glucoprotamine, laurylpropylene diamine, polyvidone iodine (disinfectant), 17α-ethinyloestradiol (hormonal active ingredient), metformin HCl (antidiabetic) and clofibric acid (lipid reducer) (cf. Table 9). It is worth noting that the annual consumption quantities of these active ingredients do not in themselves indicate a possible risk. For example, 17α-ethinyloestradiol, with a calculated consumption volume of just 1.6 kg per annum in the state of Brandenburg, indicated the highest PEC/PNEC ratio (500) due to its high effect potential, although we would not necessarily concur with the safety margins used in this study and these results should be therefore be interpreted with some caution. For example, in other risk assessments a considerably lower safety margin was used for 17α-ethinyloestradiol, although an environmental risk was ascertained even then (cf. also MPA 2004).

Table 9

Annual consumption quantity, PEC, lowest effect level, PNEC and quotient of PEC and PNEC for 11 selected active pharmaceutical ingredients

Pharmaceutical ingredient	**Annual consumption quantity (kg)**	**PEC [µg/l]**	**Lowest effect level** Toxicity test and calculated parameter/ effective concentration [µg/l]		**Safety margin**	**PNEC [µg/l]**	**PEC/ PNEC**
Benzalkonium chloride	700	0.31	Algae toxicity, EC_{50}	24	200	0.12	2.1
Carbamazepine	--	0.82	Daphnia toxicity, NOEC	25	100	0.25	3.28
Ciprofloxacin HCl	401	0.22	Bacterial toxicity, EC_{10}	1,8	100	0.018	12.2
Clofibric acid	--	0.18	Daphnia toxicity, NOEC	10	100	0.1	1.8
17α-ethinyloestradiol	1.6	0.001	Fish toxicity, NOEC (in full life cycle test)	0.001	500	2×10^{-5}	500
Glucoprotamine	5 023	1.48	Daphnia toxicity, EC_{50}	500	1 000	0.5	2. 96
Laurylpropylene diamine	905	0.064	Fish toxicity, LC_{50}	100	5 000	0.2	3.2
Metformin HCl	7 620	5.35	Daphnia toxicity, EC_{50}	60 000	5 000	12	0.45
Polyvidone iondine	1 571	1,1	Fish toxicity, NOEC	4 600	2 500	1.84	0.6
Clarithromycin	107	0.009	Bacterial toxicity, EC50	151	25 000	0.006	1.5
Cocospropylenediamine guaniacetate	3 157	2.22	Fish toxicity, LC_{50}	1 000	25 000	0.04	55.5

-- = Consumption quantities not known; the highest substance concentration ever measured in a Brandenburg surface waterbody was used to calculate the PEC
LC_{50} (Lethal Concentration) = corresponds to the active ingredient concentration which is lethal in 50 % of the test animals following a certain exposure period (in the examples listed here between 24 and 96 hours)
NOEC (No Observed Effect Concentration) = the highest active ingredient concentration at which no noticeable effects occurred after lengthy exposure
EC_{50} (EC_{10}) (Effect Concentration) = at this substance concentration an effect occurs in 50 % (10 %) of individuals

SRU/Statement no. 12–2007/Tab. 9; data source: HANISCH et al. 2004

In the study cited, a risk potential was not derived solely on the basis of the PEC/PNEC ratio, but also with due regard for other substance properties with high environmental relevance, such as persistence and the tendency to bioaccumulation. Only two of the eleven active ingredients showed a PEC/PNEC ratio of less than one. The authors of the study also pointed out that adequate ecotoxicity data for a valid environmental risk assessment was only available for two-thirds of the substances investigated. In particular, there is a lack of studies into possible chronic effects, and hence a risk of underestimating the environmental hazard potential. For many of the active ingredients analysed, effect data was only available for one or two trophic levels. Similarly, the study was unable to consider the combined effects of active pharmaceutical ingredients.

Example of an individual substance risk analysis: 17α-ethinyloestradiol

17α-ethinyloestradiol (EE2) is primarily used in human medicine as an oral contraceptive; approximately 50 kg are consumed in Germany each year. The excretion rates of the active ingredient or its conjugate are extremely high at 85 %, the majority (50 to 90 %) being excreted in conjugated form together with urine (RANNEY 1977). The synthetic hormone enters sewage treatment plants via the sewage outflow, exhibiting moderate elimination rates during passage due to its low biodegradability and low tendency to absorption. As a result, EE2 has been detected in the outfalls of several sewage treatment plants (cf. BLAC 2003). On the other hand, the BLAC study failed to detect this active ingredient in surface waters, although the determination limit of 1 ng/l was very high compared to the anticipated substance concentration. By contrast, in the study by ADLER et al. (2001), EE2 (conjugated and free form) was detected in 30 and 50 % respectively of surface water samples. Maximum concentrations were 2.5 to 3 ng/l, with the median being less than 0.1 ng/l. Hence, it can generally be assumed that EE2 concentrations do not exceed a level of 0.1 ng/l in surface waters, with the exception of sites in the immediate vicinity of sewage treatment plant outfalls, where concentrations in excess of 1 ng/l are quite likely to occur. The median in the Adler study for sewage treatment plant outfalls was 0.4 ng/l. The lowest effect concentrations for EE2 are 1 to 2 ng/l. Hence, current findings suggest that adverse effects on the environment are only anticipated in areas of waterbody which are very heavily influenced by sewage. However, in this case, no additional safety margin was factored into the effect analysis to allow for existing uncertainties.

4.3.4 Guidelines on assessing the environmental risks of active pharmaceutical ingredients

64. The environmental risks of pharmaceuticals are currently assessed on the basis of guidelines issued by the European Agency for the Evaluation of Medicinal Products (EMEA) and VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products) (EMEA no year; 2006). A large part of the assessment is based on PEC and PNEC levels, with a graduated approach being specified both in the guidelines for human medicines and in the guidelines for veterinary medicines and feed additives. The first phase entails characterisation of the pharmaceutical product and its use, together with an assessment of exposure.

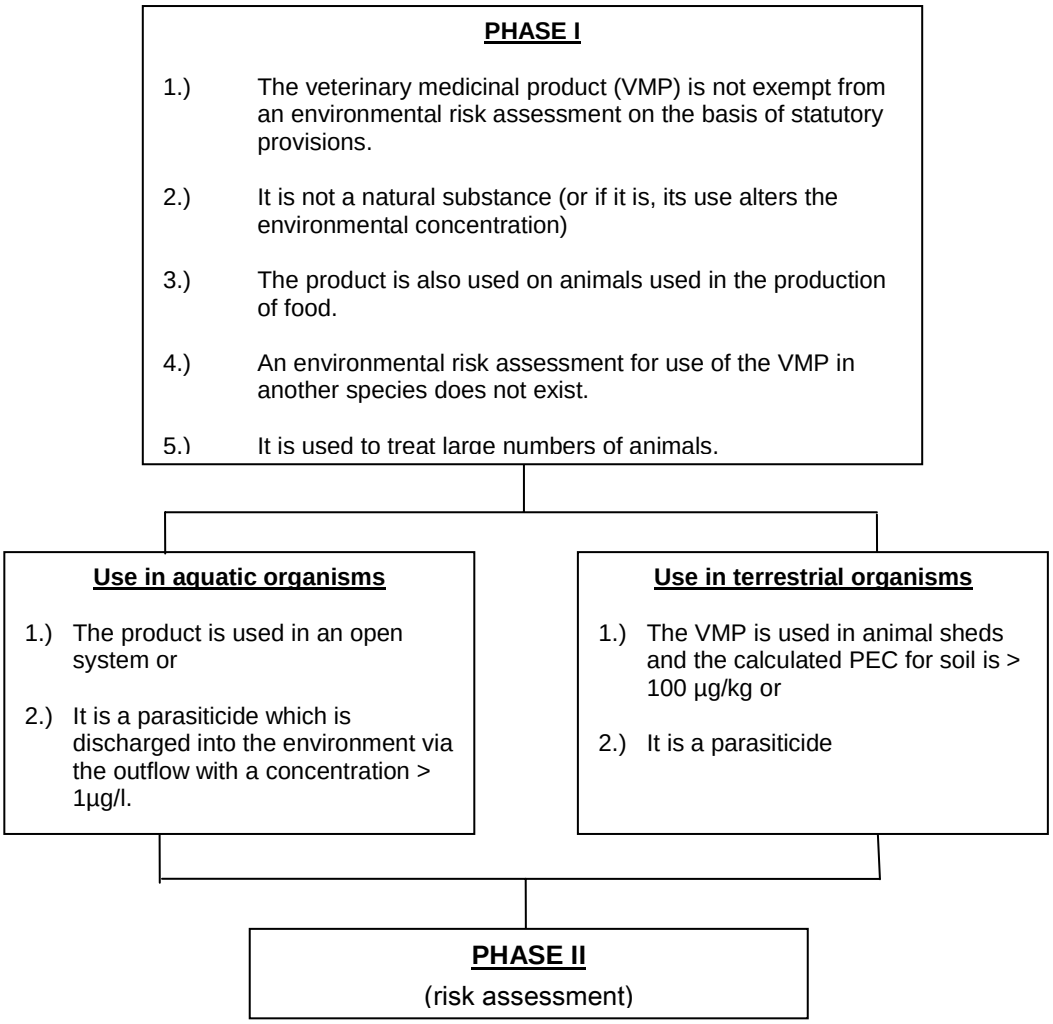
65. For example, if the calculated substance concentration (PEC) in surface water of a human medicine exceeds 10 ng/l, then an effect analysis (Phase II) is required in order to investigate the environmental risk. If the pharmaceutical in question is thought to have a particular risk potential, for example due to a reproduction-toxic effect, then in-depth testing may be necessary, even if the PEC is lower (EMEA 2006).

If the tests in Phase II indicate that the PEC/PNEC ratio is higher than 1, then the legislation governing human medicines envisages more precise characterisation of the potential risk and the preparation of instructions for preventive and safety measures, suitable labelling of the preparation, and the planning of possible future activities such as field studies for monitoring contamination and the consequences of contamination. There are currently no binding regulations governing the safety measures to be taken. Although the guidelines on European pharmaceuticals legislation stipulate that potential environmental impacts do not constitute justified grounds for prohibiting a product's circulation, a full range of possible decisions must nevertheless be available to enable safety measures to be taken. Hence, if the environmental risks are unknown, it should also be possible to restrict licensing to selected indications, or in extreme cases, if the damage outweighs the benefits, to refuse authorisation. In the case of veterinary medicines, the environmental assessment may in itself constitute sufficient reason to refuse licensing in extreme cases (cf. also 14th amendment to the German Pharmaceuticals Act (AMG)).

66. In the case of veterinary medicines, in accordance with the internationally harmonised guidelines on environmental risk assessment, the first step is to estimate the maximum anticipated environmental exposure (EMEA no year). If this concentration in the soil exceeds a threshold of 100 µg/kg, environmental experiments as stipulated in Phase II must then be carried out. The threshold for fish pharmaceuticals used in aquaculture is 1 µg/l in the outfall water. In the case of parasiticides used in the treatment of grazing animals and fish, an experimental environmental risk assessment is generally required irrespective of the exposure assessment (cf. also HICKMANN 2006). In phase II, the first step is to distinguish the area in which the VMP is used: in aquaculture, in intensive livestock farming, or in grazing animals. Based on these three areas of use, a decision is then made regarding the basic data records required. For example, in the case of intensive livestock farming, data should be provided on the physic-chemical properties of the preparations, their behaviour in the environment, such as degradation in the soil, and their effects on terrestrial and aquatic organisms. These results are used to calculate PEC levels. If comparison with the calculated exposure (PNEC) indicates an environmental risk, then more extensive studies into the environmental effects (animal B) should be conducted.

Figure 2

Simplified decision-making tree for the risk assessment of veterinary medicines (Phase I) according to VICH guidelines



Source: EMEA no year

67. The guidelines for the assessment of additives in animal nutrition (Directive 2001/79/EC) which regulate additives such as coccidiostats and histomonostats (active ingredients which prevent infection with monocellular organisms (e.g. coccidii) but which may also have an antibiotic effect) stipulate the threshold values for the summated principal residue components at which an in-depth risk assessment becomes necessary. These are: 0.1 µg/l for waterbodies, 10 µg/kg for soil, and 100 µg/kg for manure. An additional criterion is the half-life of the summated residue components in manure; if this exceeds 30 days, a more in-depth assessment is required.

Regulation 1831/2003, which regulates the licensing of additives for use in animal feed, specifies that the feed additive must not have any harmful effects on the environment (cf. no. 92).

68. For the active ingredients listed in Table 9, further environmental risk assessments or a risk management system would be necessary under the criteria of the guidelines. However, as these active pharmaceutical ingredients are predominantly found in products which were not subject to environmental risk assessment at the time of licensing (as per the guidelines), this does not apply, due to a loophole in the existing legislation, which makes no provision for the environmental risk assessment of "old" pharmaceuticals (cf. no. 114 f.).

Table 10

Examples of calculated indirect exposure to active pharmaceutical ingredients from drinking water

Substance	Maximum Concentration in drinking water [ng/l]	DWI* [ng/day]	Therapeutic dose (TD) [mg/day]	TD/DWI	I_{70}** (lifelong substance intake) [µg]
Acetylsalicylic acid	<10	<20	30	$1{,}5 \times 10^6$	511
Clofibric acid	70	140	500	3.57×10^6	3,577
Diclofenac	6	12	25	2.1×10^6	307
Propranolol	<5	<10	30	3×10^6	255
Carbamazepine	30	60	400	6.67×10^6	1,533
Tetracycline	<20	<40	1,000	2.5×10^7	1,022
17α-ethinyloestradiol	<0.5	<1	0.01	1×10^4	25.5

* DWI = daily drinking water intake
** I_{70} = lifelong substance intake (based on 2 l drinking water consumption per day over 70 years)

SRU/Statement no. 12–2007/Tab. 10; data source: WEBB et al. 2003

4.4 Risks to health

4.4.1 Indirect exposure via drinking water

69. A number of studies have undertaken analyses of active pharmaceutical ingredients in drinking water. In most cases, concentrations – where detectable at all – were in the ng range. A study conducted by WEBB et al. (2003) on behalf of the Federal State of Brandenburg calculated the daily and lifelong intake of various active ingredients based on the active ingredient concentrations ascertained in drinking water (cf. Table 10). It concluded that the calculated daily doses were at least a factor of 1,000 lower than the plasma concentrations at which a therapeutic effect will occur. In around 90 % of cases the difference was a factor as high as 150,000. The latter is roughly equivalent to a lifelong substance intake of just one-fifth of one therapeutic daily dose. Hence, the risk to human health from the unintentional intake of active pharmaceutical ingredients via drinking water is extremely negligible, even though the presence of xenobiotics in drinking water is hardly desirable in principle. A good-quality drinking water should be free from any unwanted trace substances. Furthermore, we should not forget that the administration of medicines always entails certain risks which are outweighed by the benefits only if used in accordance with the licensing terms.

4.4.2 Resistances to antibiotics

70. Antibiotics are selectively toxic substances which kill or inhibit the growth of bacteria without damaging the macroorganism. Thanks to the use of antibiotics, over the last 60 years the medical profession has been able to successfully control a wide range of infectious diseases. However, in recent years, experts have noted a continuous increase in the number of human pathogens which are resistant to antibiotics, such as tuberculosis bacilli, methicillin-resistant staphylococci (MRSA), and resistant salmonella. The emergence of multiresistant bacteria strains (bacteria which are resistant to many antibiotics) is a particular cause for concern, since the transfer of such resistances to human pathogens could lead to the emergence of infections which will only respond to a very few antibiotics, or in extreme cases cannot be treated at all. In the past, scientists have always been able to develop new active ingredients to overcome the problem of resistance. However, medical progress is no longer able to keep pace with the spread of resistance, as a result of which this development has assumed dramatic proportions. Many fear that in future, we will lack effective medicines to treat many hazardous infections diseases already thought to have been eradicated (TEUBER 2000). As early as 1998, the WHO (World Health Organization) cited the formation of resistance to antibiotics as one of the key global problems facing future health policy (WHO 1998).

71. Resistance to antibiotics occurs when bacteria develop a mechanism which renders them insensitive to the effect of the antibiotic. The DNA of the bacteria may have a gene coded for a protein or enzyme which is responsible for making the bacteria resistant to the antibiotic attack. This resistance gene may be passed on to the next generation – and from one bacterion to another – via plasmids, whereby transfer to unrelated bacteria – known as a horizontal gene transfer – is also possible. This can lead to the emergence of so-called cross-resistances – in other words, because some antibiotics act jointly on the same site, when a resistance forms, several antibiotics become ineffective simultaneously (cf. no. 70). In this way, if resistance to an active ingredient used in veterinary medicine develops, this can also affect the antibiotics used in human medicine. Cross-resistance to avoparcin-vancomycin is a well-known example of this phenomenon. This case is particularly alarming because vancomycin in human medicine is used as a so-called last-resort antibiotic – in other words, it is only used when all other antibiotics have failed (STROH 2005). Overall, the emergence and origination of resistances are very complex operations which are not yet fully understood, and caution is therefore advisable.

72. There is extensive documentation in both human and veterinary medicine that the intensive use of antibiotics leads to the proliferation of resistant strains of bacteria and becomes a problem. For example, AARESTRUP et al. (2001) documented the correlation between the use of antibiotics as feed additives and evidence of resistant strains of bacteria in farm animals. Wherever antibiotics are used or enter the environment, resistance can develop as a result of mutation, and the spread of resistant strains of bacteria may be promoted as a result of selection. In this connection, it is important to remember that resistance to antimicrobial active substances also occurs naturally in the environment, since many antibiotics are substances produced by fungi and by bacteria and other organisms to fight off bacteria. However, the abundance of antibiotics occurring naturally in the environment is very small and spatially confined to the micro-habitat of the producers (KÜMMERER 2004b).

73. There are now very clear indications that the use of active antibiotic ingredients in human medicine – particularly in hospitals – is not the only factor responsible for the spread of resistant pathogens in humans; their use in veterinary medicine also plays a pivotal role. Although the questionnaire-based survey by BYWATER and CASEWELL (2000) quantified the spread of resistance attributable to agriculture at just 4 %, the reliability of their findings is doubtful, being based purely on a survey.

By contrast, SMITH et al. (2005) documented a much closer correlation between the occurrence of antibiotic resistance in humans and the use of antibiotics in animal husbandry. In Europe, avoparcin – which, as already mentioned, is closely related to the human medicine vancomycin – was used in agriculture up until the mid-Nineties. During this period, (cross-)resistance to vancomycin among enterococci in Europe was far more common than in the USA, where avoparcin was banned, even though vancomycin was used in significantly smaller quantities in European hospitals than in American hospitals. When the use of avoparcin was discontinued in Europe, the number of proven cases of vancomycin resistance also declined. On the basis of this and other, more recent studies, we can conclude that the use of antibiotics in the treatment of animals has a much greater influence on the spread of resistance in humans than was previously assumed (JENSEN et al. 2004; KARP and ENGBERG 2004; UNICOMB et al. 2006; BfR 2003b). The principal channels via which resistant bacteria from agriculture are spread to humans are via contact with farm animals, food production from livestock farming (particularly meat, fish and dairy products), vegetables contaminated with organic fertilisers, and the airborne transport of dust from agricultural facilities (BfR 2003a). We can therefore assume that persons who have direct contact with farm animals – such as farmers, vets and abattoir employees – face a greater risk of being exposed to resistant pathogens. Particularly problematic is the transfer of resistant zoonotic pathogens (pathogens which are transferred between humans and animals).

74. In the environment, conspicuous cases of resistance to bacteria have been discovered in a variety of locations: in agricultural soils, hospital effluent, sewage treatment plants, surface waters, and in very small concentrations in groundwater. Minute levels of resistance genes were also detected in drinking water biofilms (SCHWARTZ et al. 2003). The greatest abundance was found in hospital effluent, the principal discharge route of multiresistant bacteria into the environment. In rivers, a close correlation was observed between the sewage outfall and the existence of resistance genes. Although many questions still remain unanswered, the discharge of resistant bacteria into the environment is thought to be more significant for the spread of resistance than the discharge of antibiotics (KÜMMERER 2004b). Whether or not the bacteria released at regional level are able to prevail in the ecosystem is impossible to assess at present. The extent to which the contamination of soils or surface waters with resistant bacteria contributes to the spread of resistance in humans via contact with contaminated environmental media is likewise impossible to verify. It seems unlikely that this exposure route could be responsible for a significant portion of the problem. As outlined below, direct contact with contaminated foodstuffs and animals is of far greater relevance for the spread of resistance.

4.5 Summary of the pollution situation

75. In order to assess the pollution situation, we first need to distinguish between the use of active pharmaceutical ingredients in human medicine and in veterinary medicine. Both application areas differ particularly in

terms of the discharge routes and the dominance of the active ingredients used. Pharmaceuticals are excreted by humans and animals as degradation products, and in some cases also as pharmacologically active ingredients. Representatives of all indication groups are found in the environment, whereby the number of active ingredients detected to date has been comparatively low compared with the total number of active ingredients administered. The spectrum of the most commonly prescribed active ingredients does not necessarily correspond to the spectrum of active ingredients with relevant environmental consequences.

76. *Discharge:* The vast majority of the 3,000 or more active pharmaceutical ingredients licensed for human use are discharged into the sewage after administration, either as a product of metabolism or as an unaltered active ingredient. Some of these active ingredients have a high mobility and persistence in water and are only eliminated by sewage treatment plants to a minimal extent. Hence, when used as intended, these human medicines are discharged into surface waters and ultimately into the environment. Quantitatively speaking, the most significant active ingredients here are diclofenac (analgesic), clofibric acid (cholesterol-lowering drug), carbamazepines (anticonvulsives), sulphamethoxazol (to treat bacterial infections of the urinary tract) and radiographic contrast media (to show up organ structures in X-rays). Ethinyloestradiol (a contraceptive) is one example of a pharmaceutical discharged into the environment that is only used in small quantities overall, but which has a high action specificity and is therefore active even at very low concentrations which are barely detectable through analysis.

Veterinary medicines (antibiotics, parasiticides, analgesics) enter slurry or solid manure after use via excretion products, and are applied to soil in organic fertilisers.

77. *Documentation and effect in the environment:* The highest concentrations of pharmaceuticals in the environment occur in the immediate vicinity of sewage treatment plant outfalls and in places where contaminated manure is spread. Attention should therefore focus in particular on local sites with higher contamination levels and the opportunities for reducing environmental discharges. A number of studies have investigated the secondary effects of active pharmaceutical ingredients, most of which were performed on organisms living in the water. In most cases, short-term effects were only found in these test systems at concentrations significantly higher than their environmental concentrations. Unfortunately, there have been no studies of the long-term effects of many active substances, even though scientific findings suggest that in the longer term many organisms respond to much lower concentrations than in short-term tests. Furthermore, only very few studies have analysed the interactions between several different pharmaceuticals, although there are indications of possible summating and magnifying effects. Whether or not the pharmaceuticals occurring concurrently in the environment are likely to influence one another in terms of their effects, remains largely unknown and needs to be investigated.

78. Consequently, the results currently available from laboratory studies into the effects of active pharmaceutical ingredients on the environment are inadequate for an assessment of whether surface water contamination levels from pharmaceuticals modify the composition, occurrence and lifecycles of aquatic organisms. For this reason, it is also impossible to comment on whether or not the active pharmacological principle in mammals is also valid for other organisms. Equally, no-one really knows whether the discharge of active ingredients and their degradation products into the environment poses a risk of potential environmental consequences.

79. It is known that the use of veterinary medicines to treat worm infestations in livestock (cattle, horses, sheep) has an adverse local influence on dung-degrading invertebrates which may disrupt the process of nutrient regeneration. There is a lack of systematic studies which would enable us to gauge the degree of lasting damage to the local environment, and it is therefore impossible to conclusively assess the risk of environmental consequences of active ingredients used to treat worm infestations. The same is also true of other veterinary medicines applied to the soil, especially antibiotics, for which there is likewise a lack of assessment-relevant data. As a precautionary measure, the use of active antibiotic substances in agriculture should focus more strongly on the treatment of diseased animals than at present. Some active substances are widely spread throughout the environment without any harmful effects on organisms. For many active substances, however, there is no proof that they are devoid of environmental risks, and further studies are needed. Moreover, after passing through the soil or as a result of elutriation active pharmaceutical ingredients used in animals may enter the surface water and then be transported into the groundwater or the ocean.

80. Proof that the handling of active pharmaceutical ingredients is without environmental risks can probably be obtained with a reasonable amount of effort, would, moreover, be essential for a rational, resource-conserving decision on the broad use of pharmaceuticals. An extensive environmental monitoring system using bio-indicators would be appropriate here. However, such a programme would need to make allowance for the natural variations in the test parameters and the frequently changing pollution situations. It is important not to expect too much from such studies, and interpretation of the data will not be easy, given the complexity of the system.

81. *Environmental risk assessment:* Despite the existing knowledge deficit, environmental risks have already been indicated for a number of active substances. These include the frequently administered drug for the treatment

of pain and inflammation, diclofenac, which is suspected of causing kidney damage e.g. in fish. The oestrogenic effect of 17α-ethinyloestradiol deserves particular mention in connection with the environmental risk emanating from an active substance which is discharged in small quantities.

82. Overall, current findings suggest that adverse environmental effects from the discharge of pharmaceuticals are likely to occur primarily in cases where particularly high substance concentrations occur, as in the direct vicinity of sewage treatment plant outfalls and in locations where contaminated manure or organic fertilisers are spread onto soil. Active pharmaceutical ingredients which give particular cause for concern in this connection include analgesics, hormonal active substances, antibiotics, and parasiticides.

83. *Health and other risks:* Current scientific knowledge suggests that the discharge of pharmaceutical products into the environment and their transfer into drinking water does not pose a health risk for humans, because the concentrations are much lower than in therapeutic application. Nevertheless, the contamination of water with pharmaceuticals may pose a substantial and expensive problem for the extraction of high-quality drinking water, because health safety is only one aspect of drinking water quality; other aspects include colour, odour, taste and purity from unwanted trace substances.

84. The growing spread of multiresistant bacterial strains in clinics and the contamination of sewage sludge with antibiotics are an escalating cause for concern. Firstly, there is a risk of upsetting the bacterial purification stage in sewage treatment plants; and secondly, in the case of multiresistant pathogens, the risks to human health are self-evident. Multiresistant tuberculosis pathogens are currently causing serious problems, even though this infectious disease was thought to have been eradicated in the past. The use of active antibiotic ingredients in agriculture is evidently partly to blame for this entire problem, and the obvious solution would be to cut down on the use of antibiotics in farming. Resistant bacteria are thought to be transferred primarily via human contact with animals or contaminated agricultural products, rather than via contact with antibiotic-contaminated environmental media such as soil and sewage sludge.

5 Legal provisions to protect the environment

85. A European licensing procedure for pharmaceuticals has been in place since 26 January 1965 (Directive 65/65/EEC). At that time, following a number of negative experiences such as the thalidomide scandal, patient safety was the number one priority. It was not until much later that environmental concerns were incorporated into the licensing procedure. The statutory provisions governing the licensing of pharmaceuticals now distinguish between human medicines, veterinary medicines and feed additives.

Provisions stipulating that the licensing procedure must also include testing of the environmental risks of preparations have existed for veterinary and human medicines since 1990 and 1993 respectively (see below). All pharmaceuticals which were already in circulation prior to the entry into force of these provisions, which are responsible for a large proportion of the active ingredients detected in environmental media, were never subjected to environmental testing. For this reason, a suitable "existing substances programme" for veterinary and human medicines has been under consideration for some time.

5.1 Human medicines

86. An environmental risk assessment for human medicines was introduced in 1993 with Directive 93/39/EEC. This was later followed by the adoption of Directive 2001/837EC on the Community code relating to medical products for human use, which established that as well as outlining a pharmaceutical product's potential risks to the environment, insofar as this affected the licence application, when applying for a licence manufacturers should also cite the reasons for possible precautions and safety measures relating to the storage of the product, its administration to patients and the disposal of waste products.

87. In 2001, the European Commission presented a proposal to reform European medicinal products legislation (COM 2001/404) aimed primarily at strengthening the safety of medicinal products and tightening up the European licensing procedure. On the basis of proposals by the European Council, the reform also made allowance for environmental aspects (KERN 2004). The reform was implemented *inter alia* with Directive 2004/27/EC amending Directive 2001/83/EC. Under current legislation, the environmental impacts of medicinal products for human use must be tested, and this assessment must be included with the licence application. This applies to all new licences.

In individual cases, the legislation envisages special provisions to limit environmental impacts. There is evidently a lack of defining detail regarding the form such measures might take. In individual cases, environmental impacts could be limited by imposing restrictions on usage. The Directive additionally states that potential environmental impacts do not constitute a criterion for refusing a marketing licence, in line with the basic principle that the therapeutic benefits for patients should be weighed up against possible harmful effects on the environment. While we support this principle, we would add that the therapeutic benefits must outweigh the alternatives, and that measures should be taken to prevent widescale, less controllable use, e.g. in the form of marketing without prescription for self-medication. The licensing process should be further developed to create a system which

weighs up all the alternatives and justifies the need for treatment, including a consideration of the overall environmental burden, which is lacking in the current approach to pharmaceutical legislation. However, the problem of the huge imbalance in the justification of environmental impacts in new licences compared with those of existing medicines has been largely underestimated; at best, this can be considered a procedural problem, but it fails to do justice to the real environmental risk.

88. Directive 2004/27/EC was implemented in German law by the 14th Act to amend the Pharmaceuticals Act (AMG). A European guideline on the assessment of human medicines was recently adopted which entered into force on 1 December 2006 (EMEA 2006).

5.2 Veterinary medicines

89. Environmental assessment for veterinary medicines was introduced with binding effect with EU Directive 90/676/EEC of 13 December 1990 (RÖNNEFAHRT et al. 2002). Standard ecotoxicity tests e.g. on earthworms, water fleas and algae – where significant exposure is expected – are now a compulsory part of licensing. A concrete test scheme for veterinary medicines was not introduced until 1998, with the entry into force of a European guideline to assess the environmental risk of veterinary medicines, which has since been replaced by an internationally harmonised (VICH) guideline (EMEA 1997; EMEA no year). For this reason, all active ingredients used in veterinary medicine licensed prior to that date are exempt from environmental assessment under the guidelines. The same also applied until the entry into force of Directive 2004/28/EC for generic products based on the licenses already existing for the reference products, even no provision was made for environmental risk assessment at the time of licensing. A complete environmental risk assessment is now likewise required for generic products, bibliographic licences and extension procedures (5 years after the initial licensing, pharmaceuticals legislation permits a single extension of the licence).

90. For veterinary medicines only, licensing may be refused if a severe environmental risk is ascertained. The current Directive 2004/28/EC (amendment to Directive 2001/82/EC) states that *"the authorisation shall be refused if the risk-benefit balance of the veterinary medicinal product is, under the authorised conditions of use, unfavourable*". The Directive also contains clear definitions of the terms "risk" and "risk-benefit balance". Hence, the term "risk" includes "*any risk of undesirable effects on the environment*". Risk-benefit balance is defined as "*An evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined above*." Hence, environmental compatibility is a binding criterion for the licensing of veterinary medicines.

91. The aforementioned Directives were, for the most part, implemented at national level with the 5th, 7th and 14th amendments to the German Pharmaceuticals Act (AMG). For example, section § 28 of the AMG states that if an environmental impact assessment of a new veterinary medicine gives cause for concern, the competent Federal authority (Federal Institute for Risk Assessment, Federal Institute for Pharmaceuticals and Medical Products), in consultation with the Federal Environmental Agency, will decide on any conditions that should be imposed in order to protect the environment. The conditions imposed aim to reduce environmental contamination, for example by restricting access to surface waters by grazing animals treated with medicinal products. The experiences of the Federal Environmental Agency, which has been assessing the environmental impacts of veterinary medicines since 1998, indicate that the licences of such active ingredients - especially in the case of antibiotics and parasiticides – should often be subject to certain conditions designed to protect the environment. For example, in the period 1998 to 2004, a total of 329 veterinary medicines were assessed, 87 of which were only granted authorisation subject to certain conditions, and 4 were refused (UBA 2005). Admittedly, the usefulness of such conditions is questionable, as long as there is no adequate monitoring system to verify their compliance.

5.3 Feed additives

92. A European environmental assessment concept was adopted in 2001 (2001/79/EC) for feed additives other than enzymes and microorganisms (cf. no. 67).

On 22 September 2003, the European Parliament and the Council adopted the new Regulation on additives for use in animal nutrition (EC 1831/2003). The Regulation aims to establish a Community procedure authorising the placing on the market and use of feed additives. According to this Regulation, only technological, sensory, nutritional and zootechnical additives, plus coccidiostats and histomonostats, may be licensed as feed additives. This also includes substances which have a positive influence on animal production and the performance and wellbeing of the animals. Veterinary medicines are not generally classed as feed additives, with the exception of coccidiostats and histomonostats. The latter, however, are still undergoing testing to determine whether a time limit until 31 December 2012 should be imposed on their authorisation. The Regulation stipulates that antibiotics, with the exception of the coccidiostats and histomonostats already mentioned, must no longer be used as feed additives with effect from 1 January 2006.

The text of the Regulation also cites the purpose of achieving the maximum possible level of protection for the health of humans, animals and the environment, and therefore concludes that the feed additive must not have any harmful effects on the health of animals or humans or on the environment.

6 Measures to minimise the pollution situation

6.1 Documentation of active ingredient consumption and monitoring

93. In the past, most studies investigating water contamination with active pharmaceutical ingredients have tended to focus on individual pharmaceuticals in one area of the environment. One exception to this are the in-depth studies examining the discharge and behaviour of such substances in aquatic systems published by BLAC in 1998 and 2003. Overall, however, much broader documentation of environmental pollution with pharmaceuticals is still needed. However, comprehensive monitoring is neither technically feasible nor desirable, given the disproportionately high input required in relation to the benefits obtained. Nevertheless, targeted programmes to monitor the pollution situation at selected sites for selected pharmaceuticals with model-like environmental behaviour are an indispensable research tool. For this reason, we would recommend that measurements of active pharmaceutical ingredients with a high environmental relevance in terms of their effect, persistence or mobility should be incorporated into existing programmes, such as those required under the Water Framework Directive. For example, clofibric acid is considered a marker substance for detecting the distribution of active ingredients in the environment.

94. The lack of a systematic approach to the collation of environmentally relevant data remains a major obstacle to the satisfactory environmental risk assessment of pharmaceuticals. The environmental risk assessment methods used in the licensing of pharmaceuticals are now sophisticated, but necessarily focus on the individual substance or preparation. However, there is no reliable data available on the consumption volumes for all licensed preparations of an active ingredient, and a major imbalance in the assessment-relevant data available for new licences versus medicines already on the market.

Also particularly unsatisfactory is the fact that it is impossible to reliably trace the actual use of pharmaceuticals in agriculture. For example, there has only been one study which attempted to calculate the consumption of veterinary medicines in Germany. Similarly, it is almost impossible to delimit those regions with intensive livestock farming from other regions, yet the discharge of active ingredients into waterbodies and soils will differ significantly between such regions, and consequently, different measures will need to be taken. For example, the system of documenting antibiotic consumption needs to be tightened up in order to ascertain whether the development of antibiotic consumption for therapeutic purposes in fact (as suspected and partially documented) reflects a response by users designed to circumvent the ban on their use as additives in feedstuffs. The Federal Office of Consumer Protection and Food Safety (BVL) also stresses that when monitoring the distribution channels of antimicrobial substances, enforcement needs to be improved and a statutory basis created for the collation of consumption data, in order to effectively minimise the risk of the emergence of multiresistant pathogens (BVL 2005).

95. Under current legislation, vets and farmers are obliged to keep records of the administration and use of prescription-only pharmaceuticals and those only available from pharmacies (Article 66, para. (2) of Directive 2004/28/EC). The purpose of this statutory provision is to restrict the occurrence of undesirable pharmaceutical residues in animal food products. These measures are intended to help increase the transparency of the pharmaceuticals trade in livestock farming and to make the illegal purchase and use of medicines more difficult. The data collated in this way would lend itself to a risk assessment of the environmental relevance of pharmaceutical discharges. However, this would require a similarly comprehensive overview of the pharmaceuticals trade in human medicine, and the pharmacies would need to become involved in the documentation of medicine sales.

96. To date, there have been no adequate studies into the discharge of pharmaceuticals from fish farms in Germany. This area in particular has substantial gaps in the control of substance use. At the same time, the fish farmers themselves are in need of competent advice regarding the detection, treatment and prevention of fish disease.

Ornamental fish breeding and keeping is another example of an area with substantial deficits in the control and tracking of pharmaceutical pathways. Large quantities of active ingredients are evidently being purchased through various channels (pharmacies, vets, via the Internet), and substances are also being used which have not been licensed for the treatment of fish (cf. also HUSCHEK and KRENGEL 2003). As well as the illegal use of pharmaceuticals and chemicals, other problems include the misadministration of drugs and the improper disposal of contaminated treatment water and residues. As with fish farming for food production, there is a lack of competent advice and points of contact for consumers and breeders, since only very few vets are specialists in fish diseases. The responsible authorities – in this case the veterinary authorities – often lack sufficient staff to meet their control duties in this area satisfactorily. This is something which needs to be addressed, because relevant quantities of pollutants enter the environment via this form of pharmaceutical use. The necessary capacities and links between the competent authorities for monitoring purposes should be created and optimised as a matter of urgency. Furthermore, public education of consumers and farmers should also be improved. One obvious solution would be to set up a centre of excellence to act as a point of contact for the wide range of questions arising in conjunction with fish health.

6.2 Human medicines

6.2.1 Consumption quantities and disposal

97. For some human medicines which are used in large quantities, an environmental risk has already been established, despite the fact that the data available is often very limited. This concerns a range of active substances including clarithromycin (antibiotic), carbamazepine (anticonvulsive), benzalkonium chloride (disinfectant), 17α-ethinyloestradiol (contraceptive) and metformin HCl (antidiabetic). The use of medicines in Germany is constantly on the increase. For this reason, there is an ever more pressing need to evaluate the relevance of discharges, as rising consumption levels inevitably lead to rising discharges into the environment (DINGERMANN 2006). As part of the current reorganisation of the healthcare system, the use of high-dose and super-effective active pharmaceutical ingredients in patients is being stepped up, particularly in large intensive-care wards. By shortening the amount of time spent in hospital (so-called *fast-track* mobilisation) and specialising in certain treatment areas (healthcare spectrum based on so-called *diagnosis related groups* – DRG), the intensity of medicine consumption inevitably increases, because the first few days of medical care are especially drug-intensive.

It would be difficult to justify a ban on the use of a given medicinal product on environmental protection grounds alone. In any case, very high yardsticks would need to be applied to any restriction of the licence. For this reason, measures to reduce discharges into the environment should initially concentrate on improved public education about the environmental risks of certain active ingredients and ensuring the suitable disposal, in accordance with the substance risk, of pharmaceutical residues which have passed their expiry date or are no longer required. The statutory provisions for the licensing of new medicines stipulate that if there is a proven environmental risk, the responsible authorities – in this case, the Federal Environmental Agency – should submit proposals to minimise the risk. However, the provisions governing how this should be executed have not yet been drafted.

98. The best way of ensuring that pharmaceutical residues are properly disposed of in accordance with the substance risk is via a pharmacy-based collection system, since the pharmacist has the necessary technical expertise to assess the potential substance risk. Directive 2004/27/EC called on Member States to set up a suitable return system for medicine residues by the end of October 2005. In Germany, 15,000 out of a total of 21,000 public pharmacies are currently linked to the return system of the largest supplier (JUNG 2005). In addition, depending on the local authority collection system, medicine residues may usually be returned to local authority problem waste collection points. We can assume that Germany meets nearly all of the requirements under European law. Clear labelling of preparations which may pose a potential environmental hazard would be very helpful, both for consumers, and for pharmacists and doctors. Labelling should also be linked, for example, to a note in the packet insert that this medication should under no circumstances be disposed of via the sewer system, but should be returned to the pharmacist if at all possible.

99. Prescribing the correct packet size to suit the treatment requirement is another way of helping to reduce the quantities of medicines that are disposed of. The Packaging Ordinance envisages a three-part system with classification on the basis of short (N1), medium (N2) and long (N3) treatment durations (§ 1 of the Packaging Ordinance (PackungsV)). Pharmacists and doctors are being called upon to recommend or prescribe appropriate packet sizes to suit the intended treatment.

6.2.2 Sewage purification

Sewage

100. Pharmaceuticals tend to be readily soluble, mobile substances, the bulk of which pass unreduced through sewage treatment plants. For some active ingredients, degradation in the sewage treatment plant depends to a large extent on the operating conditions, such as the age of the sludge (HEBERER 2006). As only a portion of pharmaceuticals are removed in conventional mechanical-biological sewage treatment, however, more complex procedures would be needed in order to improve sewage purification. The joint EU project POSEIDON explored possible purification methods. Ozone treatment of the purified sewage and the Advanced Oxidation Process (AOP), which combines the use of ozone, hydrogen peroxide and UV radiation, were both found to be very effective (TERNES 2004). It has already been pointed out that aeration algae, supplemented by microfiltration and ultrafiltration membranes, would aid the further reduction of pollutant levels in effluent (SRU 2004, no. 498 ff.). For effective elimination of dissolved environmental chemicals and pharmaceuticals, however, nanomembrane filtration techniques or complex oxidation processes using ozone or peroxide plus active carbon filtration would need to be added. A study by HERBERER and FELDMANN (2004) documented the high efficiency of nano and reverse osmosis filtration techniques in reducing pharmaceutical contamination; the elimination rates were in excess of 97 %.

Experiments involving the ozonation of treated, real Berlin sewage in a semi-technical plant confirmed the results of the POSEIDON project. With the exception of a few substances, primarily radiographic contrast media, the active pharmaceutical ingredients investigated were eliminated in full. The elimination rate for radiographic contrast media was increased to a maximum of 60 % via the addition of hydrogen peroxide. An ultra-filtration system connected upstream was found to be unnecessary.

An analysis of the treated water using various ecotoxicity tests found no indications of an ecotoxicity risk potential for the oxidation products. The cost of the procedure was estimated at 1.0 to 2.2 Cent per m³ sewage (BAHR et al. 2007).

101. SCHRADER et al. (2006) used a test sewage treatment plant with real sewage without the addition of further substances to examine the effectiveness of a number of techniques, including membrane activation reactor, downstream membrane filtration, the addition of powdered active carbon to the activated sludge, and ozonation. The active pharmaceutical ingredients analysed – ibuprofen, naproxen, carbamazepine and the insect repellent diethyltoluamide (DEET) – were removed at rates ranging from 33 to 97 % primarily via active carbon; ozonation also indicated good elimination rates. Ozonation leads to the creation of oxidation products, in which the group of active pharmaceutical ingredients is inactivated. The effects of these by-products in the environment need to be investigated in greater detail, as do the effects of the metabolic products of pharmaceuticals that are excreted by humans and animals.

Ultimately, there is no technique currently available which eliminates all active pharmaceutical ingredients equally effectively. Overall, however, it can be said that techniques are now available which will facilitate a further significant reduction of pharmaceutical residues in sewage. Large-scale technical trials and further investigation are needed, particularly for sensitive waterbodies and sites with particularly high contamination levels and a particular pharmaceutical spectrum.

102. It has been roughly estimated that the installation and operation of a sewage ozonation plant would increase sewage purification costs by approximately 0.01 to 0.05 Euro per m³, while the costs for the addition of active carbon are estimated at around 0.2 Euro per m³, and for membrane technology at between 0.3 and 0.5 Euro per m³ or 0.19 Euro per m³, depending on the type of technology used. Further developments in this field are likely to help bring the costs down (LIEBIG 2005; SCHRADER et al. 2006; TERNES et al. 2004; BAHR et al. 2007). In selected cases, the actual costs may deviate significantly, depending on the local sewage treatment plant constellation, sewage composition, and purification targets. The district sewage board Klärwerk Steinhäule, for example, has ascertained that the use of active carbon treatment simultaneously reduces the COD (chemical oxygen demand) and phosphorous levels (which determine waste water charges) to such an extent that active carbon treatment becomes more cost-effective (FUHRMANN 2006). It should be noted that the debate surrounding the use of this technique is not only concerned with reducing active pharmaceutical ingredients, but also with improving the elimination performance of the sewage treatment plants for numerous other organic pollutants.

103. These types of techniques could also be a potential solution for reducing discharges of heavily contaminated effluent – particularly seepage from old household waste landfill sites or from large hospitals and specialist clinics which may represent a significant local source of pharmaceutical discharges into the environment. As most hospitals in Germany are connected to the local authority sewer, in such cases sewage purification systems for separate treatment of this effluent or effluent subflow would need to be created. This would be significantly cheaper than treating all the sewage in a sewage treatment plant (KIFFMEYER et al. 2004). Incidentally, recent studies by HEBERER and FELDMANN (2005) indicate that for some active ingredients, pharmaceutical emission levels from hospitals are now less significant than the emissions from household waste water. For example, in the Berlin suburb of Ruhleben, hospitals with a total of 12,600 beds were responsible for less than 20 % of the active ingredients carbamazepine and diclofenac; similarly low or lower proportions were also ascertained for other selected active ingredients, including some tumour inhibitors.

104. When deciding on the use of more advanced sewage purification techniques, in view of the factors cited above, it is first necessary to precisely weigh up the costs against the benefits. For landfill leachate, more advanced sewage purification techniques for direct discharges are already considered the best available technology pursuant to Annex 51 of the Waste Water Ordinance. For example, leachate from the landfill sites Ansbach and Backnang-Steinbach are treated in a biological reactor with downstream ultrafiltration and active carbon adsorbers, achieving high elimination rates for numerous active pharmaceutical ingredients, while other active substances (such as diclofenac) are hardly removed at all. Studies on sewage treatment plants with an inlet of landfill leachate (indirect discharge) have shown that the load proportion of active pharmaceutical ingredients from landfill leachate in the sewage treatment plant inlet – depending on the active substance – is comparatively low, ranging from < 1 to 26 % (SCHNEIDER et al. 2005).

Sewage sludge

105. A portion of the active pharmaceutical ingredients eliminated in sewage treatment plants enters the sewage sludge (cf. Section 4.2.1). The proportion of active ingredients transferred into the sewage sludge depends to a large extent on the respective substance properties. For example, sorption experiments on sewage sludge found negligible sorption coefficients for carbamazepine, diazepam, ethinyloestradiol, the cytostatics cyclophosphamide and ifosphamide, phenazone, ibuprofen and clofibric acid. Only diclofenac exhibited a relevant degree of sorption (TERNES et al. 2004). However, when substances are bonded to organic

sediment, it is a well-known fact that remobilisation for analysis purposes often fails. Analyses of sewage sludge in Hamburg and Baden-Wuerttemberg revealed concentrations of various active pharmaceutical ingredients in the region of a few µg/kg of dry substance (BLAC 2003; Ministerium für Umwelt und Verkehr Baden-Württemberg 2002). By contrast, analyses of sewage sludge in North Rhine-Westphalia found no evidence of oestrogens (MUNLV NRW 2004). Overall, however, there is little data available on active pharmaceutical ingredients in sewage sludge and their behaviour in soils following the application thereof. In Germany, 66 % of sewage sludge is used in agriculture, landscape gardening and composting (data for 2003, UBA 2006). The active pharmaceutical ingredients and metabolites applied with the sewage sludge may, in turn, enter the surface water and groundwater via elutriation and seepage if they are not degraded in the soil or very firmly bonded. Compared with other discharge paths into the environment, the volume of pharmaceuticals discharged via the material recovery of sewage sludge is relatively low. However, as sewage sludge acts as a sink for many other organic and inorganic pollutants, its agricultural use should be gradually phased out as a means of preventive soil conservation, as already recommended by the German Advisory Council on the Environment (SRU) on a number of occasions (SRU 2004; 2002), to avoid spreading the pollutants.

6.3 Veterinary medicines and feed additives

106. With veterinary medicines, the main concern is the spread of resistance caused by the use of antibiotics in animal farming. However, discharges of active pharmaceutical ingredients into agricultural land that is already contaminated with pesticides and other pollutants and subject to compression should be further reduced as a precaution. Earlier on, we pointed out that measures to avoid or minimise the use of active pharmaceutical ingredients are needed for veterinary medicines (SRU 2004). In addition to the use of antibiotics, this also includes the use of parasiticides. In this connection, we emphatically welcome the European-wide ban on antibiotics as feed additives.

107. Other ways of reducing the use of pharmaceuticals include the Danish model for the handling of antibiotics in agriculture, organic farming, and the guidelines of the German Veterinary Chamber (Bundestierärztekammer, BTK). Denmark banned the use of antibiotics in animal feed as growth promoters in the year 2000. Other measures to reduce the use of active ingredients included the requirement for vets to report all uses of active ingredients to an official data collection agency, a ban on profits from the sale of such products, the control of vets and farmers by a regional veterinary officer, stringent conditions governing treatment with active antibiotic ingredients, the licensing of fluorochinolones only in clearly defined exceptional cases, and effective control of zoonotic pathogens (WHEELBROOK 2002).

108. The Richtlinien des Ökolandbaus (guidelines of the organic growers' association) likewise outline restrictions on the administration of pharmaceuticals. For example, the prophylactic use of so-called chemico-synthetic agents and hormones is inadmissible, except in specific cases where the use of certain drugs is prescribed by law. Certain active ingredients such as avermectin may only be used in clearly defined exceptional cases. The same applies to measures to interrupt the lactation phase using antibiotics (known as drying agents) in order to protect against infection of the uterus, alleviate pain and relieve stress in the organism; in organic farming, this is only admissible for medical indications in problem animals (Bioland e. V. 2006; Demeter Marktforum 2002; Naturland 2006). As a result, drying agents (antibiotics) are used less frequently in organic farms than in conventional farms (BOEHNCKE 2006; BRINKMANN und WINCKLER 2004). Furthermore, the marketing of organic animals treated with medicines is more stringently regulated than in conventional livestock farming (cf. Council Regulation No. 2091/91 of 24 June 1991 on organic production of agricultural products and foodstuffs).

109. A positive mention should also be given to the recently published guidelines on the careful handling of antimicrobially active veterinary medicines issued by the German Veterinary Chamber (Bundestierärztekammer, BTK), aimed at minimising resistance (BTK. no year). Inter alia, the BTK recommendations on the handling of antibiotics in livestock farming indicate that

- Medicines should only be administered after a thorough veterinary diagnosis including clinical examination (evidence and differentiation of pathogens),
- Prophylactic administration is to be avoided
- Treatment must always be given under veterinary supervision
- The duration of the treatment should be limited to a bare minimum, and
- Last-resort antibiotics from human medicine should only be used in individual animals for short periods and only if strictly indicated.

To date, however, these or other guidelines have not been anchored either in national or European law.

110. Although some progress has been made in efforts to reduce the use of pharmaceuticals in agriculture, further reductions are advisable as a precautionary measure, since there are still indications of improper or even illegal use of such active substances. This is indicated, inter alia, by traces of chloramphenicol, a substance which has been banned for more than ten years, and of other unlicensed

active substances found in various media (ALEXY et al. 2004; BVL 2004; 2006). Similarly, some unscrupulous individuals have evidently responded to the phasing-out of active antibiotic ingredients in feed by increasing the use for therapeutic purposes, primarily to treat animals that are not acutely sick.

111. The BVT believes that the use of active microbial drugs is only justifiable for treatment purposes or on metaphylactic grounds. The SRU likewise feels that the non-specific treatment of healthy animals simply because other individuals in the herd are sick should be restricted as far as possible. Measures such as high farming standards, appropriate conditions and stall hygiene are all key factors of preventive healthcare protection in animal husbandry. Simple measures such as a lower population density and an improved stall climate can make a significant contribution to animal health, which in turn helps to minimise the use of pharmaceuticals. Instead of administering antibiotics prophylactically, it is preferable to step up protective inoculations, optimise the feed quantity and structure (KTBL 2005), and use alternative treatment approaches such as adding lactobacilli to the feed to protect from selected gastro-intestinal infections (personal communication from Dr. Thomas große Beilage, 23 March 2006).

Banning the use of antibiotics for prophylactic purposes is not only a useful way of reducing the risk of escalating resistance, but can also be seen as an incentive to step up preventive healthcare in livestock farming and breeding and to adapt the animals' living conditions more closely to their natural requirements, which would be a desirable measure in any case. A further step for improving animal health is to modify breeding with a view to animal welfare. For example, correlations have been documented between the breeding of high-performance animals and their susceptibility to disease. Concentrating on fewer breeding lines also leads to inbreeding depression in the long term, which in turn may result in a higher susceptibility to disease. For example, the effective population size of the Holstein Friesen cow has fallen to a critical level of just 50 animals.

Other factors which encourage the spread of disease include homogeneous herds in terms of age and breed (which is financially desirable), and the focussing of farms in specific regions (BARTH et al. 2004). A critical examination of current breeding practices is needed. The health, robustness and adaptability of the animals should assume an important role in breeding, alongside production factors. Concepts and strategies to preserve the genetic diversity of livestock and fish species are likewise advisable in order to counteract a genetic depletion in breeding lines. In this connection, we welcome the fact that the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) is currently working on a strategy to "preserve agro-biodiversity, maximise potential and ensure sustainable usage" (BMELV 2006).

112. Additionally, serious consideration should be given to the possibility of a far-ranging ban on all last-resort antibiotics or related active ingredients in veterinary medicine. For example, the Federal Institute for Risk Assessment recommends that the use of third- and fourth-generation fluorochinolones and cephalosporines should be confined to the treatment of individual animals, and is only permissible if treatment with other antibiotics has failed. The continued licensing of fourth-generation cephalosporines as veterinary medicines should be prohibited (BfR 2003b; 2003a). Industry often argues that the development of new antibiotics is only worthwhile if they can be used both in human and veterinary medicine. One option for defusing this argument would be to provide research and development funding to protect the marketing of such products.

113. The measures outlined above indicate a number of opportunities for reducing the discharge of pharmaceuticals into organic fertilisers. There are currently no controls whatsoever of the discharge of pharmaceuticals into the soil via organic fertilisers involving "old" pharmaceuticals, yet the current system of organic fertiliser management is known to be responsible for far more obvious, longstanding, extensively documented environmental problems, such as eutrophication and high emissions of ammonia. A consistent improvement to the management of organic fertilisers with adequately dimensioned slurry storage capacities, compliance with the recommended application times, adaptation to the nutrient requirements of the specific crops and low-emission application techniques may all help to reduce contamination of the environment with active pharmaceutical ingredients. One such example is a rule under the Fertilisers Ordinance which states that a distance of 3 metres from waterbodies must be observed (Ordinance on the Principles of Good Fertilising Practice of 14 January 2006). However, this does not facilitate the selective avoidance of potentially harmful discharges of pharmaceuticals into the soil and water. To this end, more in-depth knowledge of the behaviour of the active pharmaceutical ingredients in organic fertilisers and in agricultural soils is needed. On this basis, recommendations should be formulated for the handling of organic fertilisers contaminated with pharmaceuticals, depending on the active substance used, which should encompass storage and treatment (KTBL 2005) as well as possible restrictions on application (good agricultural practice for organic fertilisers contaminated with pharmaceuticals), except where licensing conditions are prescribed within the context of an old pharmaceuticals programme. The amended Ordinance Governing Installations for Handling Substances Hazardous to Water (VAwS of 18 January 2006) extends the required slurry storage capacity to at least six months with effect from 2009, and may therefore help to create the requirements e.g. for the required longer storage of slurry contaminated with pharmaceuticals prior to application.

However, these recommendations cannot be effective unless they are consistently enforced and monitored. The persistent eutrophication of large parts of Germany due to excessive nutrient discharges from organic fertilisers, and the contract infringement proceedings initiated against Germany by the European Commission for failing to enforce the EC Nitrates Directive, would suggest that the enforcement of an eco-friendly organic fertiliser management system is far from guaranteed.

6.4 Statutory provisions on pharmaceuticals licensing

114. The current statutory provisions to protect the environment from the risks associated with pharmaceuticals and the guidelines on environmental risk assessment have led to a greater integration of environmental concerns into pharmaceuticals licensing. Nevertheless, loopholes still exist in the statutory provisions. For example, there has been no assessment to date of the environmental risks associated with so-called "old" pharmaceuticals. As environmental risk assessment for the licensing of human medicines was not introduced until 1993, and for veterinary medicines in 1990, with the corresponding guidelines being adopted in late 2006 and 1998 respectively, the bulk of licensed medical products fall under this heading. An environmental risk assessment is now required for all new authorisations. Comprehensive implementation of these new statutory requirements is definitely needed. The Federal Environmental Agency is currently working on a concept to assess old veterinary medicines (personal communication from Jan Koschorreck of the Federal Environmental Agency, 21 October 2005). This concept involves drafting a list of active ingredient-related priorities, particularly antibiotics and parasiticides. The programme envisages an environmental risk assessment at active ingredient level (monographs) rather than at the level of individual veterinary medicinal products, which should allow clearer, more efficient characterisation of the risk. However, a similar programme is also needed for human medicines, although here new products covered by the latest legislation are being introduced on a much wider scale and displacing the old products. Hence, at European level we need to devise and implement an old pharmaceuticals programme for active ingredients in human and veterinary medicines. In both cases, priority lists should be drawn up and utilised early on, in order to limit the amount of work involved and ensure that it is structured effectively.

7 Summary and recommendations

115. In assessing what needs to be done to protect the environment from the unwanted side-effects of pharmaceuticals, there is a need for relevant data on chronic effects in ecotoxicity studies as well as figures on the total volumes of active substances sold. A blanket reduction in the discharge of pharmaceuticals into the environment is needed for some active substances, while for others it is sufficient to concentrate on areas of particular pollution and specifically measures for reducing transfer into waterbodies. To this end, we must tighten up the existing statutory provisions and make available the necessary implementation structures and capacities.

For the reasons cited above, the German Government should focus in particular on the following measures:

Rectification of the data deficit for licensed pharmaceuticals

116. Pharmaceuticals are a vital element in the detection and treatment of diseases, after which time they enter the environment. Because obligations to collate environmentally relevant data were not introduced in the licensing procedure until 1 January 1998 for veterinary medicines and 1 December 2006 for human medicines, there are still significant data gaps for many pharmaceuticals which have been on the market for a long time, vis-à-vis their impacts on the environment. In particular, there is a lack of information regarding ecotoxicity analyses and chronic effects. For many frequently and intensively used active substances, it is currently impossible to perform a substance risk assessment regarding the consequences of pharmaceutical discharge into the environment. Given the marketing intensity of many products and the proven persistence and widespread presence of certain pharmaceutical substances in the environment, this imbalance in the basic data situation is unacceptable.

In particular, there are few active substance-related, summative considerations of the possible environmental risks, because until now environmental risk assessment has been confined to single products. A project group set up by a combination of manufacturers, regulators and scientists would undoubtedly be able to propose and implement an economical, problem-oriented and targeted procedure on the basis of existing guidelines. The aim must be to positively appraise long-established active substances in terms of their usefulness and safe application, but also to rectify long-overdue information deficits in terms of their environmental relevance.

Based on similar programmes for existing chemicals or pesticides, a European programme for "old" pharmaceuticals should be devised and promptly implemented. An integrative approach encompassing all consumption data is crucial, particularly for those active substances which are marketed by numerous manufacturers in a range of different preparations and consumed in large quantities.

We would recommend that a project group comprised of manufacturers, regulators and scientists should be set up to identify the priority active pharmaceutical ingredients for environmental risk assessment and rectify the existing information shortfalls as efficiently as possible. Environmental protection targets should be formulated in detail and model approaches highlighted with a proven

ability to contain the effects of actual environmental contamination, while at the same time conserving resources.

The current substance monitoring programmes should be supplemented with continuous documentation of surface water and soil contamination for at least some selected active pharmaceutical ingredients. The possibility of including selected active pharmaceutical ingredients in the list of priority hazardous substances under the Water Framework Directive (WFD) should be examined, with the aim of deriving quality targets for these substances. When assessing the pollution situation, the various protection targets for environmental quality should be carefully weighed up against an appraisal of the pharmaceutical product's benefits.

In order to improve the risk assessment of veterinary medicines, a binding records system should be set up to determine the overall consumption of pharmaceuticals by livestock facilities, and up-to-date data made accessible to the responsible authorities. The current legal obligation for vets to keep records of prescription-only medicines and those only available from pharmacies could provide a useful basis for recording the consumption of antibiotics and parasiticides in agriculture. Suitable administrative competencies and capacities on the part of the supervisory authorities must be provided to ensure proper licensing of animal production centres; the current provision is inadequate.

In collaboration with the industry, a system should be devised for recording the consumption quantities of human medicines. Compulsory record-keeping should be extended to include pharmacies, and the total pharmaceuticals sold should be recorded as a sum total for each of the principal active ingredients. The data would then need to be processed, to derive an overview of the total active pharmaceutical ingredients used. Reliable consumption data and active ingredient spectra are essential in order to make a reliable assessment of the environmental risks.

Reducing the use of antibiotics

117. The growing (multi-)resistance of human pathogens poses a serious problem for current healthcare, and this problem looks set to escalate in future. The risk is closely linked to the intensity with which antibiotics are used, and concerns the use of antibiotics in animals as well as humans. For the broad application of antibiotics as a preventive treatment of entire livestock herds and flocks, especially in the largest farms, the attainable business benefit is often disproportionate to the potential environmental damages associated with the generation of resistant pathogens. Furthermore, the use of antibiotics in agriculture causes soil pollution, the long-term consequences of which are impossible to evaluate due to the lack of assessment-relevant data. There is also a range of medicine-free solutions available for the preventive healthcare of animals, including an improved shed climate, lower population densities, optimised food quality, and careful portion structuring.

For all the aforementioned reasons, an overall reduction in the use of antibiotics is urgently needed, together with a separation between the various active ingredients and effect mechanisms used in human medicine and veterinary medicine. Possible measures include:

– In livestock farming, it is essential to reduce the prophylactic use of highly effective medicines such as antibiotics to a bare minimum. To this end, additional conditions and incentives should be created to optimise farming conditions. The success of such measures must be reflected in a reduction in the consumption of antibiotics, particularly once the ban on the addition of antibiotics to feed becomes fully effective.

– The agricultural use of so-called last resort antibiotics targeting problematic human pathogens should be strictly confined to justified suspicious cases, and then only to treat individual animals. It is only by using them restrictively that we will be able to preserve the effectiveness of these antibiotics against disease pathogens which are otherwise difficult to treat. The recent draft guidelines on the handling of antibiotics in animal husbandry should be made legally binding.

– In livestock farming, decision-making regarding the choice of pharmaceuticals and the acceptance of the need to minimise discharges should be improved. The example of ornamental fish breeding has flagged up some of the major loopholes in the monitoring and advice available regarding the use of veterinary medicines. Suitable advisory and monitoring capacity must be provided in order to rectify these deficits.

Integrative concepts to assess the environmental risk of pharmaceuticals

118. When licensing a new pharmaceutical product, it is only necessary to assess the environmental relevance of the anticipated active ingredient discharge. The licensing procedures and associated implementation provisions are therefore restricted to the individual pharmaceutical product. However, the environmental risk of an additional substance discharge is determined partly by the relative equilibrium of the active ingredient in relation to other comparable active structures. A conclusive assessment of the situation and a decision regarding the required action will generally entail an integrative evaluation of all factors which are relevant to the effect. This approach goes far beyond the currently established concept of authorisation checks and monitoring the safe application of medicines once launched on the market.

119. The environmental risk of a pharmaceutical discharge is derived using a quotient based on the anticipated concentration in the environment and the

concentrations which have been found to produce environmental effects (PEC/PNEC). Additional safety margins are usually added to the quotient to compensate for information deficits in the assessment-relevant data, with several factors being combined in one series in some cases. The procedure gives an important insight into a drug's environmental relevance and facilitates the selection of active ingredients with a small quotient which therefore do not require any further treatment. For active ingredients with a large quotient, it is advisable to use a data-based procedure with a close methodological relationship to the protection targets. All substances with similar effects found at the same location would then need to be included in the effect analysis. When performing an environmental risk assessment, if assessment-relevant data is available, caution is advisable when adding extra safety margins to derive the PNEC, so as to avoid over-estimating the risk.

– In cases where extensive ecotoxicity data is available for an active pharmaceutical ingredient, a final assessment should be made incorporating all other ingredients with a similar effect. It is necessary to investigate whether the forecasted effects from laboratory test systems are in fact qualitatively confirmed by real locations contaminated with active ingredients.

– In order to assess the actual environmental risk, we need to develop dedicated concepts which highlight the opportunities for grouping substances and for the integrated determination of potential consequences. The implementation of such concepts need not be resource-intensive, and may ultimately help to reduce input. In order to assess active substances existing concurrently which act via the same mechanisms, we need to gradually develop a series of balanced, integrative approaches with an emphasis on the effect endpoints in relation to the protection target, which are capable of at least grading the combined effects on a scale. Environmental effects which act primarily via the chemical structure could be recorded in summative form using chemical analytical techniques.

Reducing the discharge of pharmaceuticals into the environment

120. Regarding the use of pharmaceuticals in human medicine, the options currently available focus on a raft of measures designed to optimise the use of pharmaceuticals and improve sewage purification. Studies of pharmaceutical pollution in the inlets or outfalls of sewage treatment plants indicate that purification is insufficiently effective for many active substances, and even purified sewage exhibits pharmaceutical contamination which could lead to relevant pollution levels in the proximity of sewage treatment plant outfalls. For such locations with points of higher pollution levels, it will be necessary to weigh up between the various protection targets, the use of the drug itself, and containing its spread in the environment with complex and resource-consuming technical measures.

Ecologically sensitive sections of waterbodies and regions where a relatively high proportion of the water is reprocessed for drinking water extraction are subject to more stringent demands vis-à-vis minimising the primary discharge of medicines. The relative significance of high point discharges of pharmaceuticals with a non-average active ingredient spectrum from large hospitals should be compared with diffuse discharges from non-hospital treatment with medicines.

– There are now new effective sewage purification technologies e.g. using ozonation or active carbon filtration which offer superior purification efficiency, even for pharmaceuticals which have until now remained in the effluent. Their use would be particularly desirable at locations affecting sensitive waterbodies or those with a comparatively high level of pollution. It is necessary to investigate whether their use on a larger scale could additionally be promoted via waste water fees. The introduction of more advanced sewage purification techniques should also be considered for large intensive-care wards, which are stepping up the use of high-dose, super-effective active pharmaceutical ingredients in patients as part of the on-going reorganisation of the healthcare system.

– Only a few pharmaceuticals are enriched in sewage sludge. However, because sewage sludge acts as a sink for numerous other pollutants, the gradual phasing out of their agricultural use is advisable, so as to avoid diffuse distribution of unwanted by-products onto the soil.

– In order to ensure that doctors, pharmacists and consumers are better-informed about the existing environmental risks of selected active ingredients, medicines should be clearly labelled on the packaging, together with a warning that pharmaceutical residues should not be disposed of via the sewerage system, but should instead be submitted to a pharmacy for disposal.

– Active pharmaceutical ingredients are diffusely applied to soils in the form of organic fertilisers. Studies indicate that the concentration of pharmaceutical substances in organic fertilisers may be reduced through storage and treatment. The strength and implementability of this option for reducing the unplanned spread of active pharmaceutical ingredients should be further investigated as a matter of urgency. As soon as it is possible to confirm that these measures are effective and help to preserve the nutrient cycle, they should be made an integral part of binding guidelines.

Glossary

AMG	=	German Pharmaceuticals Act
Adrenoreceptor	=	Receptors in sympathetic innervated tissue which respond physiologically to the natural transmitter substances adrenaline and noradrenaline
Analgesic	=	Substance to relieve pain
Antagonist	=	Counterpart
Anthelminthic	=	Active ingredient used in the treatment of worm infections
Antibiotic	=	In its original sense, this term referred to the natural metabolic products of fungi and bacteria which in small quantities inhibit the growth of or kill bacteria and monocellular organisms. The term “antibiotics” is now commonly used to refer to all active ingredients used in the treatment of infectious bacterial diseases.
Antidiabetic (diabetes)	=	Active ingredients used in the treatment of metabolic diseases
Antieleptic	=	Active ingredients used in the treatment of epilepsy
Antihypertensives	=	Active ingredients to treat arterial hypertension
Antiinfective	=	Antibacterial substances
Parasiticide	=	Active ingredients used in the treatment of parasites
Antiphlogistic	=	Anti-inflammatory drug
Antitussive	=	Drug used to alleviate coughing
AOP	=	Advanced Oxidation Process (wet oxidation technique for the purification of water. Ozone and hydrogen peroxide are used as oxidation agents)
Arthropods	=	Phylum of animals including lobsters, crabs, spiders, centipedes and millipedes
Avermectin	=	Class of active ingredients used in the treatment of parasites
Benthic	=	Living on or in the sediment
BLAC	=	Federal/Länder Task Force on Chemical Safety
BMU	=	Federal Ministry for the Environment, Nature Conservation and Nuclear Safety
Bronchospasmolytic	=	Active ingredients which relieve spasms in the bronchial muscles (used in the treatment of asthma and bronchitis)
BVT	=	German Association for Animal Health
BVL	=	Federal Office of Consumer Protection and Food Safety
Chinolones	=	Group of antibiotics which inhibit the enzyme gyrase. Inhibiting this enzyme stops cut pieces of DNA from joining together.
COD	=	Chemical oxygen demand
DAB	=	German Pharmacopoeia
DEET	=	Diethyltoluamide (insect repellent)
Dermatics	=	Medicines used in the treatment of skin diseases
DFG	=	German Research Foundation
DWI	=	Daily Drinking Water Intake (daily intake of substance with drinking water)
EC_{10}	=	Substance concentration at which an effect occurs in 10 % of test animals
EC_{50}	=	Substance concentration at which an effect occurs in 50 % of test animals

EMEA	=	European Agency for the Evaluation of Medicinal Products
Endoparasiticide	=	Active ingredient used in the treatment of endoparasites (such as tapeworms)
Endectoparasiticide	=	Active ingredient used in the simultaneous treatment of ectoparasites and endoparasites (lice and worms)
Enterococci	=	Genus of bacteria which includes lactobacilli
Fibrates	=	Active pharmaceutical ingredients used in the treatment of metabolic disorders (primarily to lower triglycerides in the blood)
Full Life Cycle Test	=	Experiments over the animals' entire life cycle
Glycoside	=	Chemical compound in which an alcohol is bound to a sugar part via a glycosidic compound
GSI	=	(Gonadosomatic Index) Ratio indicating the mass of the sex organs to the total body mass
Histomonostats	=	Active ingredient to treat certain monocellular infections (so-called histomonads)
I_{70}	=	Lifelong substance intake (based on consumption of 2 litres of drinking water per day over a period of 70 years)
In vitro	=	Operations occurring outside of the living organism (in the test tube)
In vivo	=	Operations occurring within the living organism
Imposex	=	Female animals additionally develop parts of the male reproductive system
Cardiac drug	=	Medicine which acts on the muscle of the heart
Coccidiostat	=	Active ingredient used in the treatment of certain monocellular infections (so-called coccidiosis)
Contraceptive	=	Agent used to prevent pregnancy
Coprobionts	=	Organisms which live on or from dung
LC_{50}	=	Substance concentration which causes mortality in 50 % of test animals
Leucocytes	=	White blood corpuscles
LOEC	=	Lowest Observed Effect Concentration (lowest concentration at which an effect occurs)
LOAEC	=	Lowest Observed Adverse Effect Concentration (lowest concentration at which an adverse effect occurs)
MBT	=	Mechanical-biological treatment
MEC	=	Monitored Environmental Concentration (substance concentration measured in the environment)
Metaphylaxis	=	In animal medicine, refers to the preventive treatment of an entire herd (of animals which are not yet sick) because individual animals are unwell (due to infections or parasite infestation) (for example, giving antibiotics to the entire herd or flock in order to prevent the spread of an infection which has already affected one animal)
MRSA	=	Methicillin-resistant staphylococci
MRT	=	Magnetic resonance tomography
NOEC	=	No Observed Effect Concentration (maximum substance concentration at which no effect occurs)
OECD	=	Organisation for Economic Cooperation and Development
Ozonation	=	The treatment of sewage with ozone to eliminate microorganisms and pollutants
PEC	=	Predicted Environmental Concentration (assumed substance concentration in the environment)

PNEC	=	Predicted No Effect Concentration (assumed maximum substance concentration at which no effect occurs)
PET	=	Positron emission tomography
Podophyllotoxins	=	Mitosis inhibitors (cytostatic used in the treatment of tumours)
Serotonin	=	Tissue hormone or neurotransmitter in the central nervous system
Statins	=	Group of medicines belonging to the active ingredient class of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors, used *inter alia* to lower cholesterol
Synergistic	=	Acting together, i.e. supporting one another
Taxanes	=	Naturally occurring substances which inhibit cell division or cell growth (used in the treatment of cancer)
VICH	=	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products
VMP	=	Veterinary medicinal product
Vitellogenin	=	An egg yolk precursor protein expressed in the livers of oviparous fish
WHO	=	World Health Organisation
WFD	=	Water Framework Directive
Xenooestrogens	=	Synthetically produced substances with oestrogenic effect potential
Xenobiotics	=	A manufactured chemical compound that is not produced by living organisms
Zoonotic pathogens	=	Disease pathogens which are transferable between humans and animals
Cytostatics	=	Active ingredients which inhibit cellular growth (used in the treatment of leukaemia, cancer and tumours)

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