Review

The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges

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ABSTRACT

Intensive research on pharmaceuticals in the environment started about 15 years ago. Since then a vast amount of literature has been published. The input and presence of active pharmaceutical ingredients (APIs) and their fate in the environment were and is still of high interest. As it has been extensively demonstrated that the active compounds are present in the environment some of the research interest has moved from analysis of the compounds, which is still undertaken, to effect studies in the lab and in field trials. It has been found that environmental concentrations can cause effects in wildlife if proper tools are applied for effect assessment. The question of mixture toxicity has gained more and more attention. It has been learned that classical tests may underestimate effects and risks. Work has been done in the field of risk assessment and risk management. As for risk management strategies to eliminate pharmaceuticals from wastewater or from the effluent of sewage treatment plants have been proposed and investigated. A tremendous amount of literature can now be found describing technical management measures such as oxidative or photolytic effluent treatment, filtering techniques, and application of charcoal. It has been learned however, that each of these approaches has its specific shortcomings. Therefore, additional approaches such as including people handling and using the compounds, and focusing on the properties of the compounds ("green pharmacy") came into focus. Accordingly, this review gives an overview of the present state of knowledge presenting typical results and lines of discussion. This review makes no claim to give a complete overview including the full detailed body of knowledge of pharmaceuticals in the environment. Rather, it addresses important and typical topics to stimulate discussion.

1. Introduction

Pharmaceuticals from human use in the environment have been a topic for several years now. In the beginning research was focused on the analysis of these micro-pollutants. However, it is important to stress that in the few examples in which we really know that drugs have effects on the environment (estrogens and their effects on fish and the effects of diclofenac on vultures), biological effects studies preceded chemical analyses. This is important to stress in order to demonstrate that chemical analyses following up biological effect data may also be an efficient way to find the most problematic chemicals.

Later, research into their fate and (eco-)toxic effects came into the foreground. Currently, risk assessment and risk management issues are gaining momentum. Though the study of pharmaceuticals in the environment is still a fairly new topic, a vast amount of literature has already been published, making it impossible to cover all topics and issues in this review. Therefore, in this paper the focus will be more on open questions and discussion of risk management approaches than on an exhaustive collection of all detailed findings. For data that are more detailed and findings, the reader is advised to seek help in the numerous books and reviews that have already been published (e.g. Kümmerer, 2001a,b, 2004, 2008a; Heberer, 2002; Williams, 2005; Ternes and Joss, 2006).

1.1. Small molecules and biopharmaceuticals

Pharmaceutically active compounds (sometimes called active pharmaceutical ingredients or APIs) are complex molecules with different functionalities and physico-chemical and biological properties. They are developed and used because of their more or less specific biological activity. Most of them are polar compounds. The molecular weights of the chemical molecules range typically from 200 to 500/1000 Da. Such APIs are called "small molecules". These are the ones which are currently being researched and detected in the environment. They are part of the compounds

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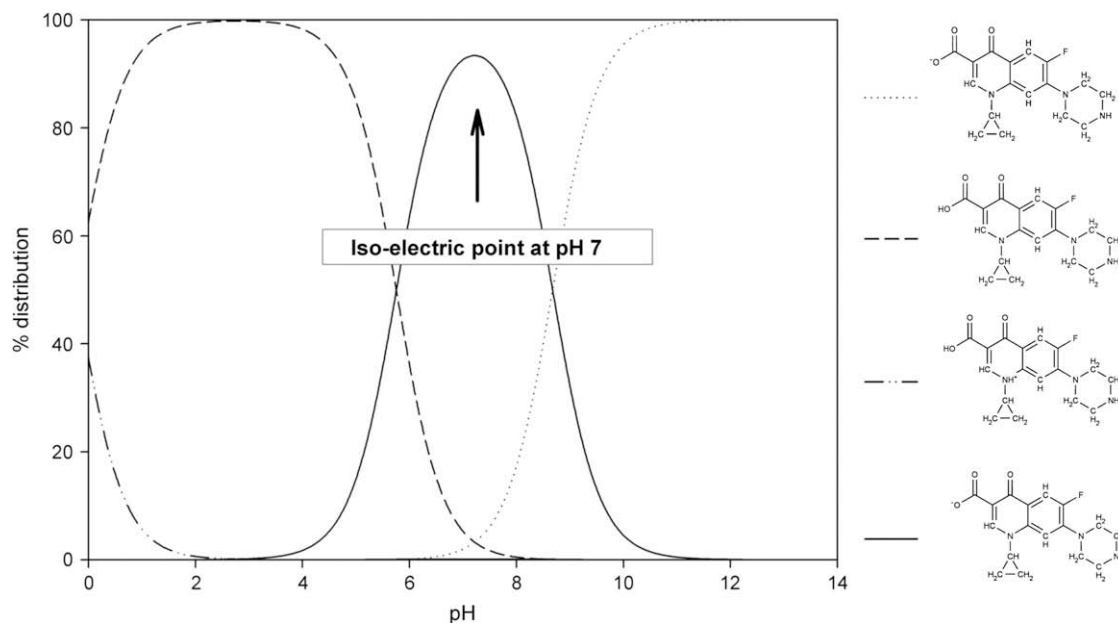 *E-mail address:* Klaus.Kuemmerer@uniklinik-freiburg.de

Fig. 1. Zwitterionic character of ciprofloxacin. Dependent on pH additional different chemical species can be formed by internal protonation, i.e. the shift of protons between the basic amino functions and acidic carboxyl groups. Calculator Plugins were used for structure property prediction and calculation, Marvin 4.1.1, 2006, ChemAxon (http://www.chemaxon.com).

called "micro-pollutants" because they are often found in the μg L^{-1} or ng L^{-1} range in the aquatic environment.

Some medicines contain molecules based on protein ("biopharmaceuticals"). Biopharmaceuticals may be defined as medical drugs produced using biotechnology by means other than direct extraction from a native (i.e. non-engineered) biological source. Examples are proteins (including antibodies) and nucleic acids. The first and best-known example was recombinant human insulin. Biopharmaceuticals are not typically regarded as biopharmaceuticals by the industry. Not all of the naturally occurring compounds which are used as drugs are biopharmaceuticals. For example estrogen is not regarded as a biopharmaceutical. The environmental relevance of biopharmaceuticals is not yet clear and they are not the focus of environmental research and risk management. One view is that they are not relevant because they are closely related to natural products and are therefore expected to be quickly biodegraded or are denatured, i.e. inactivated in the environment. The other view is that naturally occurring compounds are not in every case easily biodegraded, and modified natural compounds even less so. Structurally related compounds such as plasmids have been found in the environment (Schlüter et al., 2007; Kümmerer, 2009). Furthermore, it is known that the protein structures[1] known as prions are very stable.

Besides the active substances, formulations may also incorporate adjuvants and in some instances pigments and dyes. They are often of minor importance for the environment. Some medicines contain endocrine disrupting chemicals as adjuvants, e.g. Di-*n*-butylphthalat (DBP) (Koch et al., 2005).

1.2. Structure matters

Pharmaceuticals and disinfectants can be classified according to their purpose and biological activity (e.g. antibiotics, analgesics, anti-neoplastics, anti-inflammatory substances, antibiotics, antihistamines, X-ray contrast media, surface disinfectants, etc.). The classification of small molecule APIs by their chemical structure is used mainly for the active substances within subgroups of medicines, e.g. within the group of antibiotics or subgroups within the antibiotics such as β-lactams, cephalosporins, penicillins or quinolones. In this case one may expect that the compounds can be treated as groups with respect to chemical behavior. However, even smaller changes in the chemical structure may have a significant impact on solubility and polarity as well as other properties that govern their environmental fate to some extent. Other classifications refer to the mode of action (MOA), e.g. anti-metabolites or alkylating agents within the group of cytotoxics/anti-neoplastics. In the case of classification according to MOA, chemical structures of molecules within the same group can be very different and therefore their environmental fate can differ too. In this case, compounds cannot be handled as a group with respect to environmental issues. A closely related chemical structure may be accompanied by an identical or at least a similar mode of action (e.g. β-lactam antibiotics). However, as the example of anti-neoplastics shows, it might also be very different: alkylating, anti-metabolic, mitosis-inhibiting or intercalating substances can, but need not necessarily, belong to different chemical classes. Compared to most bulk chemicals, pharmaceutically active compounds are often complex molecules with special properties, e.g. dependence of the octanol–water partition coefficient (K_{ow}) on pH (see Fig. 1; Cunningham, 2008).

APIs often have basic or acidic functionalities, sometimes even within the same molecule (see Fig. 1). Under environmental conditions molecules can be neutral, cationic, anionic, or

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[1] A prion (proteinaceous infectious particle, -on by analogy to virion) is an infectious agent composed only of protein. They cause a number of diseases in a variety of animals and Creutzfeldt–Jakob disease CJD) in humans. Prions are believed to infect and propagate by refolding abnormally into a structure which is able to convert normal molecules of the protein into the abnormally structured form. This altered structure renders them quite resistant to denaturation by chemical treatments and physical agents (proteases, heat, radiation and formalin), making disposal and containment of these particles difficult. Prions can be denatured by subjecting them to a temperature of 134 °C in a pressurized steam autoclave (see http://en.wikipedia.org/wiki/Prion, Whyte et al., 2003).
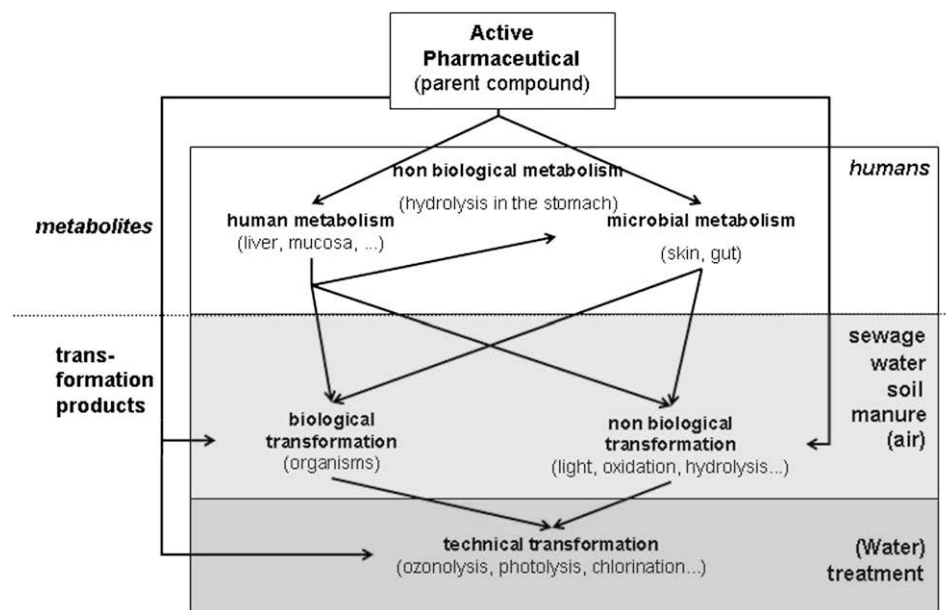
Fig. 2. Metabolites and transformation products (Kümmerer, 2008b).

zwitterionic. The pK_a values $= -\log 10\ K_a$ (where K_a is the acid dissociation constant) of ciprofloxacin are 6.16 and 8.63. At a pH of 7.04, the iso-electric point of ciprofloxacin, the molecule carries both a negative and a positive charge, i.e. it is neutral as an entity despite the charges within the molecule. The log K_{ow} of ciprofloxacin at pH 7.04 is calculated to be about -1.74 and was experimentally determined to be -0.28 (Meylan and Howard, 1995). Other compounds such as ceftazidime are inner salts, i.e. they are already zwitter ions and can additionally form other zwitterions. This makes their environmental behavior even more complex. Not only are different pharmaceuticals of special interest with respect to the compounds themselves, but also because of the differences in their occurrence, their fate and their effects on humans or on other target organisms such as bacteria or parasites, and on non-target organisms in the environment.

1.3. Parent compounds, metabolites, transformation products and their elimination

In recent years it has been learned that not only are the APIs themselves important, but also the molecules resulting from these parent compounds due to structural changes taking place in the environment. A chemical can undergo different structural changes by a variety of biotic and non-biotic processes after its introduction into the environment. Structural transformations may also be a result of effluent treatment (Qiting and Xiheng, 1988; Ravina et al., 2002; Schröder, 2002; Ternes et al., 2003; Zühlke et al., 2004; Lee et al., 2007; Trautwein et al., 2008; Méndez-Arriaga et al., 2008). Many pharmaceuticals are bio-transformed by organisms such as bacteria and fungi in the environment (Haiß and Kümmerer, 2006; Gröning et al., 2007). Nomenclature used by different authors is often somewhat confusing (Längin et al., 2008). For example, the term biodegradation is very often used. However, primary degradation, partial degradation and full mineralization are only rarely differentiated. With the advent of pharmaceuticals as environmental contaminants the situation got even more complicated.

Many pharmaceuticals undergo a structural change in the body of humans and animals, respectively. This could be due to microorganisms in the gut or by human enzymes such as cytochromes. Metabolites are the result of such a process. However, the naming

and meaning of "metabolite" in publications is somewhat confusing. The term metabolite is used for compounds resulting from the structural change of pharmaceuticals within the human body, not differentiating biochemical processes performed by human enzymes from the ones due to bacterial activity in the alimentary system and the ones present on skin or non-biotic processes such as hydrolysis in the stomach. The term is also used for molecules resulting from structural change by fungi and bacteria in the environment and sometimes even for structural changes that are the result of non-biotic processes such as oxidation, hydrolysis and photolysis (e.g. Méndez-Arriaga et al., 2008) in different environmental compartments such as surface water, soil or sewage treatment.

As with metabolism, the chemical structure of the active molecules can be changed by biotransformation, biodegradation, and non-biotic transformation such as photo transformation and hydrolysis. Such a structural change results in a change in their physico-chemical and pharmaceutical properties. It is normally assumed that metabolism and other transformation processes of APIs leads to decreased toxicity. In some cases however, metabolism leads to more active compounds (e.g. in the case of pro-drugs). The same has been found for photo transformation and other oxidizing processes (Burhenne et al., 1997).

However, in order to prevent any misconception in addressing different molecules and processes, it is necessary to be clear with nomenclature. Therefore, we recommend using the term "metabolite" only for the molecules resulting from changes of the chemical structure within the body or on the skin of humans and treated animals (Längin et al., 2008; Fig. 2). Metabolites may be formed by biological and/or non-biological processes. They may also result from the activity of metabolic pathways of humans and treated animals, as well as from changes performed by other organisms living within or on the body of humans and treated animals, and from non-biotic processes occurring there. It refers to the different processes by adding additional words such as "bacterial" metabolite – if the process is known.

Additional molecules may be formed after the excretion of parent compounds and metabolites into the environment. This should be referred to as transformation. Accordingly, molecules resulting from the change of the structure of a molecule after

excretion, i.e. in the environment should be named "transformation product", which includes both biotic and non-biotic processes. Transformation processes can be those such as hydrolysis and photo-oxidation, or biotic ones. Structural transformations may also be a result of effluent treatment. In other words, the term metabolite should only be used for compounds which have been changed within or on the human body, the bodies of treated animals, and plants, but not environmental bacteria or fungi. Many pharmaceuticals and their metabolites are further bio-transformed into transformation products by organisms such as bacteria and fungi in the environment. The term transformation product also includes molecules resulting from chemical reactions in technical facilities such as sewage and drinking water treatment plants. The products of such transformations can be termed photo products, or transformation products resulting from hydrolysis or oxidation, etc.

Another point is the often careless use of the term "elimination". By some authors it is used in the sense of full mineralization. However, elimination only means that the (parent) compound of interest is not detectable anymore by compound specific analysis in the compartment or phase of sampling. This could be perhaps simply because it has been removed from the compartment of interest, e.g. the water phase. In this case, removal is an adequate expression for this situation too. Monitoring by compound specific detection such as flame ionization detection, UV-Vis detection or mass spectrometry informs only about the primary elimination; it just indicates the degree to which the parent compound is lost. For example, the introduction of a hydroxyl group results in a new molecule with different physico-chemical properties, fate and toxicity. However, this cannot be quantified and sometimes not even be detected by compound specific analysis, because the transformation product is a new molecule that may not be recognized anymore or may not even be present in the sample after clean up.

In contrast to common opinion, labeling with radioactive ^{14}C can only give some additional information (Junker et al., 2006). The information that can be gained in such trials depends strongly on the location of ^{14}C in the molecule. If it is located in a side chain that is easily removed and mineralized it just indicates the mineralization of this part of the molecule. Years ago, this information was only accessible by the use of such labeled compounds. However, with the widespread availability of mass spectrometric techniques such information can be gained without labeled molecules. If radioactivity is found in a solid phase it can be calculated that a certain share of the parent molecule and/or transformation products is adsorbed or incorporated into this solid phase. However, in order to get more detailed information, a thorough analysis, e.g. by chromatographic and mass spectrometric methods is still necessary.

The proper and adequate use of the terms related to the fate of organic chemicals in the environment is advised in order to prevent confusion in the assessment of the fate and risks connected to the presence of these molecules in the environment.

2. Consumption, use patterns and other sources

There is no data available about the total worldwide use of pharmaceuticals. The consumption and application of pharmaceuticals may vary considerably from country to country (Verbrugh and de Neeling, 2003; Goossens et al., 2005, 2007; Schuster et al., 2008). If there are legislative changes imposed on the health system it may happen that some compounds are not used any more or others gain more importance, e.g. for economical reasons. According to United Nations' figures, 2.3% of Japanese women of reproductive age take a contraceptive pill containing ethinylestradiol as the main active compound, compared to 16% in North America and up to 59% in Europe (United Nations, 2004). Some pharmaceuticals are sold over the counter without prescription in some countries, while in others they are only available by prescription. Some antibiotics such as streptomycins are used in the growing of fruits (pomology) while others are used in bee-keeping. Again, the situation may vary from country to country. The heavy use of streptomycins in the growing of fruits in the US is being discussed as a possible reason for the high resistance of pathogenic bacteria against these compounds (http://www.plantpath.wisc.edu/fpath/antibiotic-use.htm). In Germany, the use of these antibiotics for this purpose has been banned. Antimicrobials are among the most widely used pharmaceutical compounds in animals (Boxall et al., 2003a,b; Sarmah et al., 2006). These drugs are used in animal husbandry for veterinary purposes, or as growth promoters (particularly in large-scale animal farming and intensive livestock treatment).

In 2001 about 50,000 different drugs were registered in Germany, 2700 of which accounted for 90% of the total consumption and which, in turn, contained about 900 different active substances, corresponding to 38,000 t of active compounds (Greiner and Rönnefahrt, 2003). Some data for other countries are found elsewhere (Ongerth and Khan, 2004; Kümmerer, 2004; Sattelberger, 1999). A total of 6000–7000 t per year of active substances are of potential environmental concern in Germany, which is approx. 0.45 kg per capita and year. Data for Australia are in the same range according to data presented by Ongerth and Khan (2004).

2.1. Manufacturers

Because of good manufacturing practice (GMP) regulations (required for the manufacturing of pharmaceuticals) and the frequently high economic value of the active substances, the amount of emissions occurring during manufacturing has been thought to be negligible. Indeed, such emissions are assumed to be low in Europe and North America. However, manufacturers have not yet published data with regard to this. It has only recently been found that in Asian countries concentrations for single compounds up to several mg L^{-1} can be found in effluents (Larsson et al., 2007; Li et al., 2008a,b). However, even in Norway the input from a local manufacturer was high (Thomas, 2008). To the author's best knowledge, no data are available on emissions during transport and storage.

2.2. Hospitals

As to be expected, pharmaceuticals are present in hospital wastewater (Brown et al., 2006; Steger-Hartmann et al., 1996; Kümmerer and Helmers, 1997; Hartmann et al., 1999; Kümmerer, 2001a,b; Hädrich, 2006; Gómez et al., 2006; Seifrtová et al., 2008; Schuster et al., 2008). The concentrations of pharmaceuticals in hospital wastewater are higher than in municipal sewage. However, the total substance flow is much lower because of the much lower share of effluent from hospitals in municipal effluent in developed countries. The dilution of hospital wastewater by municipal wastewater is by much more than a factor of 100 (Kümmerer and Helmers, 1997, 2000).

2.3. Private households

Outdated medicines or their remainders are sometimes disposed of down household drains. In accordance with EU-legislation, the discarding of unused drugs via household waste has been permitted since 1994. It is reported that approximately one third of the total volume of pharmaceuticals sold in Germany (Greiner and Rönnefahrt, 2003; Rönnefahrt, 2005) and about 25% of that sold in Austria (Sattelberger, 1999) is disposed of with

household waste or down the drain. A recently conducted poll has found that 17.7% of those surveyed get rid of excess and outdated pills by pouring them into the toilet, and, about 20% do the same with liquid pharmaceuticals (Götz and Keil, 2007; http://www.start-project.de). A survey carried out in the UK investigating the household disposal of unused and expired pharmaceuticals interviewed members of 400 households, predominantly from south-eastern England, and was the basis for a conceptual model to assess the pathways of human pharmaceuticals into the environment. The model demonstrated that the disposal of unused pharmaceuticals, either by household waste or via the sink or toilet, may be a prominent route that requires greater attention (Bound and Voulvoulis, 2005). More than half of the patients surveyed in a study conducted in the US reported storing unused and expired medications in their homes, and more than half had flushed them down a toilet. Only 22.9% reported returning medication to a pharmacy for disposal. Less than 20% had ever been given advice about medication disposal by a health care provider (Seehusen and Edwards, 2006). In a study performed in Kuwait (Abahussain et al., 2006) almost half of the respondents (45.4%) obtained medicines by prescription more than three times a year and almost all had unwanted medicines in their homes. The reasons for possessing unused medication were mostly due to a change of medication by the doctor (48.9%), or self-discontinuation (25.8%). Their most common method of disposal was to throw unwanted medicines in the trash (76.5%) or flush them down the drain (11.2%). The results of this study suggests that there is a role for patient education on the proper disposal of unused and expired medications in all countries. In some countries take-back systems are already in place (Niquille and Bugnon, 2008). In the EU and the US (http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html) it is legal to throw unused, unneeded or expired drugs in the trash. If the trash is incinerated this is probably the most effective and environmentally sound way to handle the problem. If the waste is landfilled it is a bad solution which only postpones the problem. The APIs will probably show up after some years in the effluent of the landfill (see below). The US FDA advises without an additional explanation that some drugs be flushed down the toilet (!) instead of thrown in the trash (http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html), which is surprising as the APIs will directly end up in STPs.

2.4. Landfills

If disposed of with household waste, compounds end up on landfill sites where they can enter the landfill effluent (Eckel et al., 1993; Holm et al., 1995; Ahel and Jeličic, 2001; Metzger, 2004). If there is no collection of the effluent, this may be a source for contamination of surface water or ground water. The contribution to this from disposed, unused drugs is not known in many countries, just as the amount released during manufacturing remains unknown.

3. Occurrence and fate in the environment

3.1. Occurrence

The input of pharmaceuticals, disinfectants, diagnostics and personal care products into the environment after use is the typical situation. They are recognized as being an important part of the chemicals that are present in low concentrations in the environment (Schwarzenbach et al., 2007). If the drugs, their metabolites and transformation products are not eliminated during sewage treatment, they may enter the aquatic environment and eventually reach drinking water. The active compounds as well as expedients may enter the environment by different routes via several different non-point sources such as effluents of sewage treatment plants (STPs), waste, and landfill effluent or treatment of animals. Some pharmaceuticals are used as tracers for anthropogenic impact on waters by hydrologists (Möller et al., 2000, 2002; Elbaz-Poulichet et al., 2002; Verplanck et al., 2005; Buerge et al., 2006).

Most of the studies conducted until now describe the occurrence of compounds in environmental compartments. Medical substances have been measured in the effluent of medical care units, sewage and the effluent of sewage treatment plants, in surface water, ground water, and in drinking water (Heberer, 2002). Seasonal variations have been studied in sewage and reclaimed wastewater, as well as in finished water (Loraine and Pettigrove, 2006; Alexy et al., 2006). Pharmaceuticals have also been detected in the effluent from landfill sites (see above). Systematic studies of the occurrence of pharmaceuticals in the environment are now available for several countries. Meanwhile, there is evidence of the occurrence of some 160 different drugs in STP effluent, surface water and groundwater. Some APIs have even been detected in drinking water. They have also been detected in the arctic environment (Kallenborn et al., 2008).

The concentrations of pharmaceuticals in surface waters and the effluent from STPs have been shown to lie in the $ng\,L^{-1}$ to $\mu g\,L^{-1}$ range. The findings of recent years have been confirmed for different countries and different environmental compartments (Kümmerer, 2008b). Only recently psycho-active and illicit drugs such as amphetamine, cocaine and its metabolite benzoylecgonine, morphine, 6-acetylmorphine, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, methadone and its main metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, and amphetamines have been detected in surface water and wastewater. Daily and seasonal variability was examined and revealed fluctuations in the concentrations of nicotine, paraxanthine, amphetamine, cocaine, and ecstasy during the week. Estimations of consumption were made using the total concentrations found in wastewater (Zuccato et al., 2005; Boleda et al., 2007; Huerta-Fontela et al., 2008; Castiglioni et al., 2008).

Compared to the free water phase, the analysis of APIs is difficult in biosolids and sewage sludge, despite the fact that knowledge about pharmaceuticals in sewage sludge and biosolids is necessary for the proper understanding of fate and for risk assessment (Jones-Lepp and Stevens, 2007).

Little is known about the occurrence, fate or activity of metabolites. An important question to be addressed is whether the glucoronides, methylates, glycinates, acetylates, and sulfates are still active, and whether they can be cleaved by bacteria during sewage treatment and in the environment. This would result in the active compound being set free again. Other types of metabolites are excreted too and can be detected in wastewater (Miao et al., 2005). Their effects on environmental organisms may be lower than that of the parent. However, in the case of pro-drugs the situation is probably different, as it may also be for the metabolites of several other pharmaceuticals as has been shown, for example, for norfluoxetin (Nałecz-Jawecki, 2007).

As outlined above, several different non-biotic processes may lead to the removal of chemicals from sewage, surface water, ground water and soil. The predominant fate processes for pharmaceuticals in the different environmental compartments are sorption (e.g. tetracyclines and quinolones) and (bio)degradation. Photodegradation and hydrolysis can also be significant.

3.2. Elimination by adsorption and complexation

The disappearance of a substance does not necessarily indicate biological or photochemical degradation. An important pathway

for elimination is sorption of pharmaceuticals, which depends on the extent of neutral and ionic species present and the characteristics of the target particles. Sorption may have an impact on the spread and (bio)availability of pharmaceuticals in the environment (particle bound transport), and their removal during wastewater treatment. Some antibiotics, e.g. tetracyclines, are known to have a tendency to bind to soil particles or to form complexes with ions which are present (Marengo et al., 1997; Plate, 1991; Rabølle and Spliid, 2000; Tolls, 2001; Boxall et al., 2002; Thiele-Bruhn, 2003; ter Laak et al., 2006a,b). Therefore, the disappearance of a substance does not necessarily indicate biological or photochemical degradation.

The sorption of antibiotics is especially affected by the amount and nature of free and suspended particles in the water phase and soil organic matter (SOM), and soil minerals and distribution coefficients (K_d) (Thiele-Bruhn, 2003). Binding to particles or the formation of complexes may cause a loss in detectability, as well as a loss in antibacterial activity. The loss of antibacterial activity, for example, was demonstrated for an aquaculture antimicrobial in sea water driven by the formation of complexes with the magnesium and calcium present in marine water (Lunestad and Goksøyr, 1990). Tetracyclines are able to form complexes with double cations, such as calcium or magnesium. This finding is not only interesting from the degradation point of view, but it also underlines the problematic nature of applying such potentially inactive antibiotics in aquaculture, and especially in marine fish farming as it clearly shows the necessity of using considerably more antibiotics for treating fish in marine water. The log K_{ow} is not sufficient for the assessment of the sorption and distribution behavior of antibiotics. In general, the sorption behavior of antibiotics depends heavily on the chemical structure of the compounds. In contrast to highly lipophilic "classical" environmental contaminants such as PCBs or chlorinated pesticides such as aldrine, dieldrine or DDT, which are not ionisable, antibiotics are complex chemical molecules which may contain acidic and basic groups within the same molecule. Ionic interactions are possible sorption mechanisms. Therefore, sorption or distribution between two phases such as water and sludge or water and soil (log K_D) depends on pH. The solubility, hydrophobicity, distribution, and sorption of pharmaceuticals such as ciprofloxacin are pH-dependent. Some pharmaceuticals also contain planar aromatic structures which are favorable for intercalation, for example into the layers of some clay minerals. Therefore, the sorption of such compounds depends not only on the log K_{ow}, which is the lipophilicity of the sorbed molecule, but it is also governed by pH, redox potential, stereo chemical structure and chemical nature of both the sorbent and the sorbed molecule. This is a fundamentally new aspect compared to most bulk chemicals and to some of the classical environmental contaminants such as polychlorinated biphenyls.

Contrary to what would be expected from log K_{ow}, it was found that ciprofloxacin sorbs well onto active sludge or sediments, for example (Wiethan et al., 2000; Golet et al., 2002). Normally, this is expected for compounds with a log K_{ow} above 3 or 4. Some compounds such as quinolones or tetracyclines are eliminated by more than 50% due to sorption to sewage sludge. Antibiotics may diffuse into biofilms, present in sewage pipes, sludge flocks or stones in rivers and lakes. This may result in a biased risk estimate as the concentrations in such "reservoirs" may be much higher than in the free water phase. The effects and behavior of antibiotics in such biosolids with high bacterial density and special conditions has not yet been investigated. It is not known how strongly the antibiotics are sorbed to sludge, particulate matter, biosolids such as sewage sludge, and sediments, and under what circumstances they are (bio)available and

active after sorption. Little is known about conjugates and other metabolites in this respect.

3.3. Biodegradation and photodegradation

Substances reaching the environment may undergo different reactions, resulting in partial or complete transformation and/or degradation of the parent compound (including mineralization if the degradation to carbon dioxide, sulphate, nitrate, and other inorganic compounds is complete). Sometimes total degradation does not take place and the process is stopped before mineralization has been completed. These intermediates, i.e. the stable products of biotransformation, can be even more stable than the parent compounds. They often also vary in their toxicity and have a higher potential for accumulation compared to the parent compound. Bacteria and fungi are the two groups of organisms that are best able to degrade organic compounds. Fungi are particularly important in soils, but do not usually play an important role in the aquatic environment. Therefore, in sewage treatment plants (STPs), surface, ground and marine bacteria are assumed to be responsible for most biodegradation processes.

Pre-adapted bacteria normally give better biodegradation results. Since antibiotics are designed to be active against bacteria this point is of particular importance for biodegradability testing of antibiotics. It must be assumed that microbial degradation will be slower in surface water than in the sewage system due to its lower bacterial density and lower diversity. In our own investigations, more than 20 antibiotics representing the most important groups of antibiotics were found not to be readily biodegradable (Al-Ahmad et al., 1999; Kümmerer et al., 2000; Alexy et al., 2004). The presence of pharmaceuticals in the aquatic environment demonstrates at the very least their incomplete degradation and elimination in sewage treatment. The importance of transformation products in photo-transformation has been demonstrated (Méndez-Arriaga et al., 2008; Calza et al., 2008). The authors found that hydroxyl transformation products were the most important residual compounds after the photocatalytic treatment of ibuprofen and amiloride, respectively. The inhibition of bioluminescence from Vibro fischeri as a toxicity parameter increased during the period of irradiation due to the residual concentration of the generated hydroxyl metabolites.

4. Effects

In the beginning, chronic effects, i.e. the effects seen in short-term testing (e.g. toxicity against Daphnia with 96 h), often at concentrations which are higher than those found in the environment have been studied. Soon it became obvious that realistic concentrations, i.e. at levels measured in the environment in chronic tests, e.g. full life cycle tests, should be applied. Furthermore, there is a difference in terms of endpoints of a certain test. Some tests indicate general toxic responses, others, i.e. targeted tests such as the induction of vitellogenin in fish by estrogens (Sumpter et al., 2006), are based on mechanism of action. In addition, the selection of species is important. There are presumably sensitive or insensitive species with respect to a certain endpoint. Additionally, it has been found that standardized tests may underestimate effects (Backhaus and Grimme, 1999; Kümmerer et al., 2004). Cleuvers (2008) found that toxicity of a mixture of non-steroidal anti-inflammatory drugs against Daphnia was considerably higher even at concentrations in which the single substances showed no or only very slight effects. Remarkably, reproduction was decreased by 100% at concentrations where no effects on survival could be observed, which means that this

destructive effect on the Daphnia population would be totally overlooked by an acute test using the same concentrations. Effects occurred even at the lowest treatment level with concentrations that were still 1000–5000 times higher than measured concentrations in the environment. Thus, testing with lower concentrations and more compounds is recommended. This may have affected the risk assessments, for example, if tests with a more general endpoint such as narcosis in an acute test and insensitive organisms are used for risk assessment, the risk would be underestimated. However, if the concentration of the test compound is much higher than those found in the environment, the risk is overestimated. If effects are found in the latter case, these results may give some guidance for test and compound selection. Testing at lower, more realistic concentrations are then necessary. Therefore, the concentrations to be used during testing may be different, i.e. lower for surface water than for sewage and higher with respect to local situations such as those reported at production sites (Larsson et al., 2007; Li et al., 2008a,b; Thomas et al., 2007).

4.1. Single compounds

The active ingredients of medications have been selected or designed because of their activity against organisms. Within the last several years their effects on other organisms such as fish have also been studied. For most human medicines analysed, acute effects on aquatic organisms are unlikely, except in the case of accidental spills.

The amount of information that is available on the effects of active substances on organisms in the aquatic and terrestrial environment is increasing but still too low (Fent et al., 2006). The high concentrations of some compounds, i.e. in the g per liter range, have been found to produce acute effects in environmental organisms. In the meantime, effects on *Daphnia*, algae and bacteria have also been demonstrated using low concentrations in chronic tests. Often these studies examined antibiotics (Holten Lützhøft et al., 1999; Halling-Sørensen, 2000; Backhaus and Grimme, 1999; Al-Ahmad et al., 1999; Kümmerer et al., 2000; Boxall et al., 2003a; Yamashita et al., 2006) and drugs such as diclofenac, ibuprofen, carbamazepine and the antidepressant fluoxetine. For the pharmaceuticals investigated the chronic lowest observed effect concentrations (LOEC) in standard laboratory organisms are about two orders of magnitude higher than the maximal concentrations found in STP effluents (Fent et al., 2006). For diclofenac, the LOEC for fish toxicity was in the range of wastewater concentrations (Schwaiger et al., 2004; Triebskorn et al., 2004, 2005; Hoeger et al., 2007), whereas the LOEC of propranolol and fluoxetine for zooplankton and benthic organisms were near maximal measured STP effluent concentrations (Fent et al., 2006). In surface water, concentrations are lower and so are the environmental risks. However, targeted ecotoxicological studies are almost entirely lacking and investigations are needed which focus on subtle environmental effects (Fent et al., 2006).

4.2. Mixtures

All risk assessment is based on single compounds. Furthermore, pharmaceuticals do not occur as isolated, pure substances in an environmental compartment. They are present as multi-component mixtures in the environment. Most pharmaceuticals can either be transformed by physical and chemical processes in the environment and/or taken up by some organism and subsequently bio-transformed (see above). From an environmental perspective, even individual pharmaceuticals thus ultimately have to be regarded as a multi-component chemical mixture (parent compound plus transformation products and metabolites). However, it has been found that mixtures might exhibit different effects than single compounds (Silva et al., 2002; Cleuvers, 2004, 2008; Backhaus et al., 2004, 2008; Pomati et al., 2007). In general, knowledge about the toxicity of mixtures of compounds is limited. This new field of ecotoxicology is just beginning and much remains to be learned. Some drugs act via the same or very similar modes of action and share the same receptor. Therefore, additive effects are to be expected. As for resistance against antibiotics, it is well known from the medical literature that cross resistance is quite common, i.e. resistance acquired by contact with a certain antibiotic creates resistance that also works against other antibiotics within or even across different classes of antibiotics. It has also been found that effect thresholds of cephalosporine antibiotics may be lower by several orders of magnitude in the presence of the cytotoxic anti-metabolite 5-fluorouracil applied in anti-cancer therapy (Kümmerer et al., 2009). In consequence, because the release of pharmaceuticals to the aquatic environment occurs permanently and usually as mixtures, an accurate prediction of the chronic mixture toxicity is indispensable for an environmental risk assessment.

4.3. Indirect effects

It has been found that detrimental effects may happen if compounds are transferred within the food web. Between 2000 and 2003, high annual adult and subadult mortality (5–86%) in the oriental white-backed vulture and the resulting declines in population (34–95%) were associated with renal failure and visceral gout. A direct correlation of residues of the anti-inflammatory drug diclofenac with renal failure was found. Diclofenac residues and renal disease were reproduced experimentally in oriental white-backed vultures by direct oral exposure and through feeding vultures diclofenac-treated livestock (Oaks et al., 2004). The evidence strongly implicates mortality caused by ingestion of residues of the veterinary non-steroidal anti-inflammatory drug diclofenac to be the major cause of the population decline. Other findings show that veterinary use of diclofenac is likely to have been the major cause of the rapid vulture population declines across the subcontinent (Swan et al., 2006; Taggart et al., 2007).

Another example of indirect effects of antibiotics was reported by Hahn and Schulz (2007). Results of food selection experiments with *Gammarus pulex* demonstrated clear preferences for leaves conditioned in the absence vs. those conditioned in the presence of two antibiotics, oxytetracycline and sulfadiazine.

5. Risk assessment

Publication of the EU guideline on environmental risk assessment for human pharmaceuticals (http://www.google.de/search?q=EU+guideline+on+environmental+risk+assessment&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:de:official&client=firefox-a) was seen in 2006.

The risk of adverse effects on humans through the ingestion of pharmaceuticals present in drinking water seems to be negligible. Thus, the risks posed to humans from pharmaceuticals in the environment seem to concern environmental hygiene rather than toxicology or pharmacology. The maximum possible intake within a life-span (2 l of drinking water per day over 70 years) is far below the dosages used in therapy (Christensen, 1998; Kümmerer and Al-Ahmad, 1998). However, this statement relies on some assumptions: (i) that effects and side effects during therapeutical use (short-term, high dosage) are the same in quality and quantity as for lifelong ingestion (long-term ingestion, low dosage); (ii) that the effects are the same for fetuses, babies, children, healthy adults and elderly people; and (iii) that the risk posed by a single

compound is comparable to the one posed by a mixture. As for the last point, it has been found that elderly people who take several different medications at a time suffer more often from unwanted side effects of drugs during therapy. How to extrapolate data from high dose, short-term ingestion during therapy to low dose, long-term ingestion, i.e. "medication" via drinking water is still an unresolved issue in toxicology and ecotoxicology.

Data enabling a realistic assessment for metabolites and transformation products are missing. Furthermore, up to now risk assessments have been undertaken for single substances only and not for mixtures. Some of the APIs have carcinogenic, mutagenic or reproductive toxic effects ("CMR-compounds"). It is unclear whether such compounds should be treated as "however"-compounds. Besides toxicity, the property of persistence is of particular importance in the assessment of the environmental significance of substances. Persistent organic pollutants (POPs) increase the potential for long-term and hence varied effects, while the longer the exposure lasts increases the potential for multiple contamination of the ecosystem. This cannot be tested in advance with the presently available test systems (Cairns and Mount, 1992). Standard tests developed for bulk chemicals are often used for effect assessment and biodegradability testing (e.g. according to OECD series 200 and 300). It is unclear to what extent the test systems have to be modified to obtain reliable results (Kümmerer et al., 2004).

6. Risk management

6.1. General strategies for the reduction of the input of pharmaceuticals into the environment

Pharmaceuticals are ubiquitous water and soil contaminants that may have subtle detrimental effects on aquatic organisms, and also possibly on human health. The risks of pharmaceuticals, or pharmaceutically active compounds, remain poorly understood. However, awareness of the presence of pharmaceuticals in the environment, coupled with evidence of effects, suggests that precautionary management action to reduce the release of pharmaceuticals into the environment should be considered.

Opportunities for reducing the input of pharmaceuticals into the aquatic environment are possible by taking advantage of several different approaches. Combinations of management strategies will likely be most effective in mitigating the risks presented by pharmaceuticals. In a recent study the scope of the issue and possible management strategies were examined from the perspectives of expert stakeholders drawn from government, academia, and the

pharmaceutical and consulting industries, each of whom was involved in scientific research or policy and management activity in Canada, the United States, or Europe (Doerr-MacEwen and Haight, 2006). Twenty-seven interviewees were asked about their views on management strategies such as pharmaceutical-return programs, advanced effluent treatment and incentives for the development of "green" pharmaceuticals. The interviewees believed that advanced wastewater treatment technology, education of medical professionals to reduce over prescription, pharmaceutical-return programs coupled with public education, and requirements for all municipalities to have at least a second cleansing step were the most effective management strategies in order to reduce the environmental impacts of pharmaceuticals. According to the principle of sustainability, the entire life cycle of a compound has to be taken into account to identify opportunities for risk management and risk reduction.

Looking from a temporal perspective and at the types of actions that could be taken, three classes of measures can be identified (Fig. 3, http://www.start-project.de).

All three of them are required in order to achieve an effective reduction in the input of pharmaceuticals (and other chemicals) into the environment. The one that has been most extensively discussed within recent years is the technical approach. As for the second approach, we have to learn that environmental protection must include the shareholders, the stakeholders and the people using the compounds, that is patients, doctors and nurses, and pharmacists, when seeking for solutions that will work. The third strategy is emerging from the field of green chemistry (Anastas and Warner, 1998). Until now it is the least developed of the three approaches. However, in terms of sustainability it seems to be the most promising one in the long run. Contributions of the different stakeholders to risk management are summarized in Table 1.

6.2. Advanced effluent treatment

The objective of advanced effluent treatment is to further reduce adverse environmental effects of pharmaceuticals, such as hormone effects and pathogenic effects of the effluent. In recent years advanced effluent treatment has been extensively studied. Much research and development effort is currently being directed towards advances in municipal wastewater treatment aiming at reducing the effluent content of micro-pollutants and pathogens.

As for the different sources of human pharmaceuticals in the aquatic environment, hospitals have been seen as a main goal. However, point sources such as hospitals are likely to be of only minor importance (Kümmerer and Henninger, 2003; Heberer and
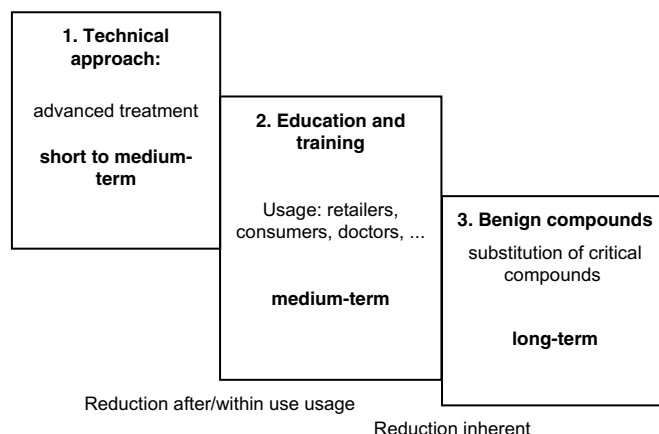

Fig. 3. Principal strategies to reduce the input of chemicals into the environment (Kümmerer, 2007).

Table 1
Opportunities to reduce the input of pharmaceuticals into the environment.

Who	Possible measures and activities
Pharmaceutical companies	Publication of data relevant for environmental assessment, publication of analytical methods and results, offering appropriate package sizes, integration of environmental aspects in the development of new APIs and new therapies, dedication to green pharmacy, less over the counter products, establish take-back systems where not already in place, proper information of doctors, pharmacists and the general public
Patients	Improvement of compliance, intake of APIs only if necessary and only after prescription by a medical doctor, expired medications not disposed of down the drain; instead returned to pharmacy if take-back system is established or into the household waste if appropriate (check with local authorities and pharmacies), no lifestyle drugs
Pharmacists	Information of patients, participation in take-back systems if appropriate (check with local authorities)
Hospitals	Integration of the delivering pharmacy/wholesaler into handling expired medications, informing doctors and patients, establishing proper procurement, applying the Swedish classification system (http://www.fass.se)
Medical doctors	Prescribing according to environmental criteria if alternatives are available, applying the Swedish classification system (http://www.fass.se), informing of patients
Health insurance providers	Maintaining necessary medical standards and demonstrating reduction potential and economical benefits, informing doctors and patients, applying the Swedish classification system (http://www.fass.se)
Wastewater handling and treatment	Reduction of input through broken sewerage/piping, reduction of total water flow to be treated (separate transport of wastewater and rain water) thereby increasing concentration of APIs, applying affordable technologies, development of less water- and energy-demanding treatment systems and technologies
Drinking water treatment	Extended monitoring, advanced treatment if necessary, information of the general public
Authorities	Initiation and back up of communication between all stakeholders, development of limits/thresholds for APIs in different environmental compartments and drinking water, establishing country-adapted classification systems for pharmaceuticals as already in place in Sweden, applying the Swedish classification system (http://www.fass.se)
Politics	Inclusion of APIs in environmental legislation, more restrictive connection between environmental properties and authorization of human pharmaceuticals, improvement of legislation for the management of expired medications, establishing incentives for the development of greener drugs, e.g. prolonged patent life time

Feldmann, 2004; Bayerisches Landesamt für Umwelt, 2005; Hädrich, 2006; Heinzmann et al., 2006; Thomas et al., 2007; Schuster et al., 2008). The contribution of hospitals to the total load of pharmaceuticals in municipal wastewater is for most compounds below 10%, with many even below 3%. Therefore, in contrast to the common assumption (Putschew et al., 2007; Joss et al., 2008) it is questionable whether separate treatment of hospital effluent is a valid environmental and economical goal.

The advanced treatment of effluents has been investigated using (photochemical) oxidation processes (e.g. Qiting and Xiheng, 1988; Zwiener and Frimmel, 2004; Ravina et al., 2002; Kiffmeyer, 2003; Ternes et al., 2003; Watkinson et al., 2007; Strässle, 2007; Isidori et al., 2007), filtration (Schröder, 2002; Drewes et al., 2002; Heberer and Feldmann, 2005), application of powdered charcoal (Metzger et al., 2005; Nowotny et al., 2007) and the use of man-made wetlands (Matamoros and Bayona, 2006). Reviews on the advantages and disadvantages of the different technologies are available (Schulte-Oehlmann et al., 2007; Jones et al., 2007; Wenzel et al.,

2008; Ternes and Joss, 2006). However, all of these technologies have more or less specific shortcomings:

- Efficiency may depend strongly on the type of compound.
- None of the technologies can remove all of the compounds (Qiting and Xiheng, 1988; Ravina et al., 2002; Schröder, 2002; Ternes et al., 2003; Wenzel et al., 2008).
- Will they work for future compounds?
- Mutagenic and toxic properties have been found for reaction products of (photo) oxidation processes (Isidori et al., 2005, 2007; Lee et al., 2007; Wei-Hsiang and Young, 2008).
- Prolongation of hydraulic retention time results only in minimal improvement of elimination rates, with no additional benefits. It may cause high costs because of the necessity to enlarge the STPs.
- Resistance in bio-membrane reactors: enrichment of antibiotics and resistant bacteria as a cause of increasing resistance? No information is currently available on this topic.
- Resistance material and APIs will not fully be retained by membranes.
- Combined sewer overflow in case of storm water will not be treated.
- Sewage that infiltrated the ground due to leaking sewage pipes before it reaches STP is not treated.
- Technologies depend on a high input of energy and a minimal water flow. Therefore, it is possibly less affordable in less developed countries.
- Costs are not clear and whether they are affordable is not known. Different authors present different data depending on the assumptions made and it is questionable whether the additional costs are acceptable (Dohmann, 2004; Jones et al., 2007; Joss et al., 2008).
- In principle, they are not compatible with sustainable development as they are the end of the pipe technologies and not affordable in all countries. Energy demand causes high emissions CO_2 (Jones et al., 2007).
- The application of powdered charcoal seems to be a promising approach for advanced treatment. It removes not only pharmaceuticals but some other classes of micro-pollutants too and avoids some of the critical points addressed above, but not all of them. However, it resembles the other approaches in not fulfilling the criteria of sustainability. Additionally, slow sand filtration that is already established in some European STPs may be equally effective.

Wenzel et al. (2008) investigated the advantages and disadvantages of advanced wastewater treatment of micro-pollutants using environmental life cycle assessment (LCA) and a literature review of advanced treatment performance. The LCA evaluation included sand filtration, ozonation and membrane bioreactors and assessed the effect of extending existing tertiary treatment with these technologies on a variety of micro-pollutants (heavy metals, endocrine disruptors, PAH, phthalates, and detergents). The authors assessed the 'environmental break-even' point where the removal of micro-pollutants and reduction in (eco-)toxicity would outweigh the increased resource- and energy consumption. In scenarios it was found that more environmental impact may be induced than removed by the advanced treatment. The study showed that among the three technologies, sand filtration has the best balance between prevented and induced impacts, and sand filtration proved to have a net environmental benefit under the assumptions used in the study. But the outcome of the study suggests that this is not always the case for ozonization and membrane bioreactors. Because of the limitations identified for the advanced effluent treatment, other (additional) approaches are necessary.

6.3. Training, education and information

Proper and effective risk management strategies need knowledge about sources. In this context, one has to know the size of substance flows associated with the different sources of pharmaceuticals, such as households and hospitals. It has been found that hospitals are only of minor importance in terms of flows of pharmaceuticals into the environment. Therefore, advanced effluent treatment in this case will not be very effective. However, hospitals can reduce their contribution by other measures such as appropriate training and education of staff and patients.

Properly informing doctors, pharmacists and patients can contribute to a reduction of the input of APIs into the aquatic environment (http://www.start-project.de; Götz and Keil, 2007; http://www.fass.de). Proper information about how to handle left over drugs will result in a reduction of the environmental burden of drugs. A major unknown with respect to drugs as pollutants is which fractions of drug residues occurring in the ambient environment result from the discarding of leftover drugs (Götz and Keil, 2007; Ruhoy and Daughton, 2007). Data are needed on the types, quantities, and frequencies with which drugs accumulate in households, hospitals, convalescent homes, and rehabilitation hospitals. Absence of this data has prevented assessments of the significance of drug accumulation and disposal as a contributing source of drug residues in the environment.

From a mid- to long-term perspective, the prescription, therapy and consultation practices of physicians and pharmacists as well as the patients' use and disposal patterns of pharmaceuticals should be changed towards higher environmental sensibility. The relationship between physicians and patients plays a key role within this strategy (http://www.start-project.de): knowledge and information about the environmental relevance of pharmaceuticals raise the awareness of physicians in the consultation of patients. In order to facilitate the integration of the problem into physicians' everyday practice, it has to be implemented during medical education and advanced training by policy makers in education and health care. Health funds can foster the demand for ecological alternatives by means of changes in the funding of pharmaceuticals and therapies. This increased demand can support the pharmaceutical industry in supplying a sustainable product range (e.g. varieties of packaging sizes and potencies).

The amount of contrast media necessary in an MRI can drastically be reduced by modern technology (Ehritt-Braun et al., 1994). If an internal commission of a hospital recommends a positive list of recommendable pharmaceuticals that is the basis for purchasing activities, the variety of products is reduced and savings will result. The furniture in the wards should not allow for too much storage space. This reduces the share of expired medicines, and thereby the environmental burden. The internal system should allow the wards to give back unexpired broken and unused packages to the pharmacy. The pharmacist can handle these remainders properly. A medical doctor who is a specialist in infectious diseases should be present and can give advice in the proper use of antibiotics. Proper hygiene, that is, not too much, not too little, at the right place and the right time can also contribute to a reduction in infections and the need for pharmaceuticals and disinfectants.

7. Green and sustainable pharmacy

According to the principles of green chemistry (Anastas and Warner, 1998), the functionality of a chemical should not only include the properties of a chemical necessary for its application, but also fast and easy degradability after its use. Taking into account the full life cycle of chemicals will lead to a different understanding of the functionality necessary for a chemical. In the present

discussion improvement of synthesis and renewable feedstock are very prominent, whereas the environmental properties of the molecules have been discussed less. Applying these principles and the knowledge of green chemistry to pharmaceuticals is necessary in the future. One aspect of it is the third, long-term oriented strategy of Fig. 1 (Kümmerer, 2007). It means that easy degradability after use or application is taken into account even before a pharmaceutical's synthesis ("benign by design"). There may be potential problems in introducing green chemistry in terms of economy. However, this is already happening at least for optimized and new synthesis routes (Lapkin and Constable, 2008). One may argue that finding good lead compounds is a great challenge even without taking the environment into consideration. However, there is no need to find new lead structures in the first place. The modification of known lead structures can be a promising way. Glufosfamide (http://www.thresholdpharm.com/sec/glufosfamide) is such an example. A new product is scheduled for animal and human drug trials which is similar to an older version of a birth control pill from the drugmaker Schering–Plough (Lubick, 2008). The new-old drug uses natural estrogens paired with a biodegradable progesterone.

Responding to the green and sustainable pharmacy challenge may also result in new marketing opportunities. Research within industry and within academia is necessary to reach this goal. However, it can be reached if conditions are appropriate (Kümmerer and Schramm, 2008). The argument that we cannot deny patients access to any drug is not a very convincing one. Experience shows that quite a lot of lead structures are abandoned within drug development for economical reasons. Other drugs are not developed because their expected revenue is too low. Furthermore, many people on this planet do not have access to certain drugs for economical reasons.

The benign by design approach is not completely new. For example, it is quite common during the development of pharmaceuticals unwanted side effects to be taken into consideration. This can also result in economic advantages in the long run and will fit into green pharmacy (Daughton, 2004; Kümmerer, 2007). Examples of pesticides and detergents, complexing agents and some pharmaceuticals (Kümmerer et al., 2000; Kümmerer, 2007; Kümmerer and Al-Ahmad, 1998) demonstrate the feasibility of this approach. Benign-by-design pharmacology is a large, complex, and fascinating subject area that industry should address soon.

8. Conclusion

It should be pointed out that although a lot of essential knowledge has been published within the last decade, it is still too sparse to allow us to perform a thorough and accurate risk assessment and proper risk management. There is still an urgent need to fill the gaps in our knowledge.

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