Pharmaceuticals in the Environment

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Abstract
Pharmaceuticals are chemicals that are used because of their biological activity. They are often excreted unchanged and can reach the environment. Throughout developed countries, the pharmaceutical concentrations in the aquatic environment are in the same range (μg L\(^{-1}\) and below); however, it is not clear whether this holds for less-developed countries too. The health risks of active pharmaceutical ingredients (APIs) remain poorly understood. Although there are no known short-term effects on humans, long-term effects cannot be ruled out until there is more research. The significance of metabolites and transformation products resulting from the parent APIs is not yet known. Awareness of the presence of pharmaceuticals in the environment, coupled with some evidence of effects, suggests that precautionary management action to reduce the release of pharmaceuticals to the environment should be considered. As for effluent treatment, no technology works well for all compounds. Advanced effluent treatment is not sustainable because of energy consumption, efficiency, and efficacy. Therefore, its appropriateness must be assessed on a case-by-case basis. Increased handling and use measures at the source and better biodegradable pharmaceuticals are necessary in the long run for the new paradigm called “sustainable pharmacy.”
INTRODUCTION
The history of pharmaceutical sciences is an impressive success story. The products of pharmaceutical industries are present everywhere in everyday life. Pharmaceuticals are chemicals that are used because of their more or less specific biological activity. They help to pursue the modern way of living, and they contribute to our health and high standard of living. For a long time, the production of chemicals and pharmaceuticals as well as their usage and application caused heavy pollution of the environment and serious health effects. During the second half of the twentieth century, tremendous progress was made to prevent the pollution of the environment and to reduce the impact of such pollution on health. Now proper, effective treatment and prevention of emissions into the air, water, and soil are in place in developed countries and are making their way worldwide. In the 1990s, it was found that the amount of waste generated was 50–100 kg for the synthesis of 1 kg of an active pharmaceutical compound (1). This insight triggered activities within the pharmaceutical industries to reduce waste generation by various measures, such as using different and more appropriate (i.e., “greener”) solvents and developing new synthesis routes to avoid intensive waste.

However, since the end of the past century, it has been learned that the products of the pharmaceutical industries themselves, i.e., the medicinal drugs, are presenting a new type of environmental pollution and possible health risks for the consumer. It is expected that the consumption of pharmaceuticals will increase in the future because of higher standards of living and because more people are living longer and using more drugs as they age. Because of the ever increasing sensitivity of analytical instruments, pharmaceuticals have been found (as have other micropollutants, such as disinfectants, pesticides, flame retardants, de-icing fluids, and others) present in the environment in low concentrations (ng L\(^{-1}\) to μgL\(^{-1}\)) (2–4). These molecules often end up in the environment not because of improper use but because of proper use. Although some may worry about overuse, when pharmaceuticals are not completely used they are sometimes discarded via the toilet, the drain, or into waste, which are not proper disposal procedures. The presence of pharmaceuticals in the environment is a widely accepted fact. The relative rates of production, release, and use of pharmaceuticals in the next 10 to 50 years from now is not easy to predict, but pharmaceutical loading into the environment is expected to increase for several reasons. First, as the number of older people increases, extensive use of drugs (e.g., several at the same time) will increase. In addition, with an increase in living standards and with an increase the affordability of drugs, their usage will increase throughout the world, especially in rapidly growing economies. These changes have to be taken into account in the context of risk assessments of pharmaceuticals in the environment. The assumption that the production and use of pharmaceuticals may stay approximately constant is definitely wrong.

If the pharmaceuticals, their metabolites, and transformation products are not eliminated
during sewage treatment or sorbed in soil, they may enter the aquatic environment and eventually enter drinking water supplies (Figure 1, see color insert). Pharmaceutical residues from human use have been a topic for several years now. Because of their biological activity, there is concern about their presence in the aquatic environment and drinking water: Are there negative effects caused by these compounds on humans and/or environmental organisms? In the beginning, research was focused on the analysis and presence of these micropollutants. Later, research into the fate and (eco)toxic effects came into the foreground. Now, risk assessment and risk management issues are gaining momentum. Although the presence of pharmaceuticals in the environment is still a young topic, a vast amount of literature has already been published. In this article, a very brief overview of the present knowledge is given, and some important issues are addressed. For more detailed data and findings, the reader is advised to consult the numerous books and more specialized reviews that have that have already been published (e.g., References 2 and 5–12).

**ACTIVE PHARMACEUTICAL INGREDIENTS: WHAT THEY ARE**

Normally, a pharmaceutical, such as a pill or a liquid, consists of one or several active pharmaceutical ingredients (APIs), excipients, and additives, as well as inorganic salts or other organic chemicals, such as sugars, scents, pigments, and dyes. They are often of minor importance for the environment. Some medicines, however, may contain endocrine-disrupting chemical excipients and additives. Unfortunately, knowledge of the significance of excipients and additives is only available if they are chemicals that are also used for other purposes. The focus here and in ongoing research is on the APIs. From a chemical point of view, APIs cover a wide range of so-called small molecules (with molecular weights that typically range from 200 to 500 Da) with different physicochemical and biological properties. Even small changes in the chemical structure of an API may have a significant impact on its environmental fate (13). Therefore, sometimes separate assessments are necessary for each type of API, even with respect to different environmental conditions such as pH.

Some medicines contain biopharmaceutical molecules, which are medical drugs produced using biotechnology techniques other than direct extraction from a native (i.e., nonengineered) biological source. Examples are proteins (including antibodies), nucleic acids, and recombinant human insulin. Their environmental relevance is not yet clear, and they are not yet in focus of environmental research and risk management. Findings show that some are metabolized in the human body and/or are biodegradable in sewage treatment (14). Structurally related compounds, such as plasmids, have been found in the environment. Furthermore, it is known that the protein structures of prions are very stable in sewage treatment\(^1\) (15). Prions are eliminated from the water by sorption onto sewage sludge, followed by entering sludge treatment and disposal processes. To date, knowledge about the significance of biopharmaceuticals in the environment is by far too little for any conclusions.

Because biopharmaceuticals are often applied in connection with the classical small molecules, such as antineoplastic compounds, they do not solve the problem. Other groups of compounds that are of interest and that are used in medical environments are used in diagnostic applications, such as X-ray contrast media or contrast media applied in magnetic resonance imaging (MRI), and disinfectants.

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\(^1\)Prions are infectious agents 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 that is able to convert normal molecules of the protein into an 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.
PARENT COMPOUNDS, METABOLITES, AND TRANSFORMATION PRODUCTS

Pharmaceuticals can be classified according to their biological activity and purpose (e.g., antibiotics are used topically to treat bacterial infections, analgesics are used to lessen pain, and antineoplastics are used in anticancer therapy). Classification according to chemical structure is used mainly for the APIs within subgroups of medicines, e.g., within the group, or subgroups, of antibiotics, such as β-lactams, cephalosporins, penicillins, and quinolones. Other classifications refer to the mode of action (MOA), e.g., antimitabolites or alkylating agents within the group of cytotoxics and/or antineoplastics. In case of MOA classification, chemical structures of molecules within the same group can be very different and result in varying environmental fates. As for their biological activity, in general, all compounds are of interest. Because some of them are active in very low concentrations, they are of special interest despite their lower usage. These are endocrine-active pharmaceuticals, i.e., hormones such as ethinylestradiol, the main API of birth control pills (16–18). Other drugs of high importance are those used in anticancer treatment (19–21) because some of them can cause cancer themselves. Antibiotics are of special interest because of the possible promotion of resistance.

Many pharmaceuticals undergo a structural change in the bodies of humans and animals (Figure 2) before excretion, resulting in metabolites. This change is only rarely complete, i.e., normally a certain share of the parent compound (the API) is excreted together with the metabolites. Some antibiotics, for example, are metabolized up to 95%, whereas others only 5%. A study of API amounts used and excretion rates indicated that 75% of the antibiotics used in Germany are excreted unchanged, i.e., as still active APIs (22). Furthermore, metabolites, such as glucuronides and others, can be set free again by bacterial activity in sewage treatment plants (STPs) and the environment.

After their excretion and introduction into the environment, both parent compounds and metabolites can undergo structural changes by a variety of biotic and abiotic processes. Pharmaceuticals can be incompletely transformed by organisms, such as bacteria and fungi in the environment (23–25), as well as by light and other abiotic chemical processes (see below). Structural transformations may also be a result of technological processes, such as effluent treatment by oxidation, hydrolysis, and photolysis (26–30; P. Gupta & K. Kümerer, unpublished results). The resulting molecules are called transformation products (Figure 3) (31). Such structural changes result in new chemical entities with new properties.

![Figure 2](https://example.com/fig2.png)

*Figure 2* Metabolites formed in the body of humans and animals. Structural change by microorganisms (in the gut, in sewage treatment plants, in the environment) may result in different compounds. Reproduced with permission from Reference 7.
Metabolites and transformation products. Reproduced with permission from Reference 7.

**SOURCES FOR ACTIVE PHARMACEUTICAL INGREDIENTS IN THE ENVIRONMENT**

The APIs used in medicine, as well as the excipients and additives, may enter the environment by different routes via several different non-point sources, such as manufacturing plants, effluents of STPs, household waste, and landfill effluent. Pharmaceuticals applied in veterinary medicine, as growth promoters and for other purposes, are excreted by the animals (Figure 4) and reach soil. If they are not bound to soil constituents, they may reach groundwater. In the case of heavy rain events, some may also be transported to surface water from runoff. Usually, it is assumed that emissions from pharmaceutical manufacturing and production are low in Europe and North America. However, it has been found only recently that pharmaceutical manufacturing facilities can be a significant source of pharmaceuticals to the environment in the U.S. (http://toxics.usgs.gov/highlights/PMFs.html). In Norway, the input from a local manufacturer was much higher for a certain antibiotic than the ones originating from hospitals and the general public (32). Other recent investigations discovered that in Asian countries concentrations up to several mg L$^{-1}$ of API can be found in effluents of manufacturing plants (33–35). These results demonstrate the need for more data. To my knowledge, data are not available on emissions during transport and storage.

**Figure 4**
Pathways of input and distribution of pharmaceuticals in the environment. STP, sewage treatment plant. Reproduced with permission from Reference 7.
As expected, pharmaceuticals are present in hospital wastewater (6, 36–41). Concentrations of pharmaceuticals in hospital wastewater are higher than in municipal sewage. However, the total load is much lower than that related to municipal wastewater because of the much lower share of usage of pharmaceuticals in hospitals compared to the general public effluent in developed countries (32, 41). Hospital wastewater is greatly diluted by municipal wastewater, i.e., by a factor $>100$ (42). In other words, hospitals are a source of minor importance, so separate treatment of this waste may be questionable, but reduction of APIs in hospital effluent, e.g., by proper use, is still an option (see below).

In accordance with EU legislation, discarding unused drugs via household waste has been permitted since 1994. If the trash is incinerated, this is probably the most effective and environmentally sound way to handle the problem. If the waste is landfilled, the APIs will show up after some years in the effluent of the landfill (43–46). If there is no collection of the effluent, this may be a source for contamination of surface water or groundwater.

It has been found that people get rid of leftover and outdated pills and liquid pharmaceuticals by pouring them into the toilet (47–51; see also http://www.start-project.de). These findings suggest that there is a role for patient education about proper disposal of unused and expired medications in all countries. In some countries, take-back systems are in place (52, 53). Ruhoy & Daughton (51) estimate that orphaned medications from the deceased population alone account for as many as 19.7 tons of APIs disposed into U.S. sewage systems annually.

Getting people to stop flushing away their unwanted medication is one easy way to cut down on pharmaceutical pollution. According to the guidelines of the U.S. Office of National Drug Control Policy (ONDCP), unused, unneeded, or expired prescription drugs should be removed from their original containers and thrown in the trash. To prevent accidental poisonings or potential drug abuse, ONDCP recommends mixing the medicines with an undesirable substance, such as coffee grounds or kitty litter. The mix should be placed into impermeable, nondescript containers, such as empty cans or sealable plastic bags, before being tossed in the trash. However, the U.S. Food and Drug Administration recommends that certain controlled substances, such as the painkillers OxyContin® and Percocet®, are best disposed of down the drain. To ensure that drugs are disposed of in the most environmentally friendly manner, individual communities are developing pharmaceutical take-back programs that collect unwanted medications and then incinerate them.

**OCCURRENCE AND FATE IN THE ENVIRONMENT**

Meanwhile, there is evidence of the occurrence of some 160 different APIs in the aquatic environment. APIs have been found in the effluent from medical care units, landfills, municipal sewage, and STPs, and also in surface water, seawater, groundwater, and drinking water (2, 5–8, 54). Seasonal variations have been studied in sewage and reclaimed waste as well as in finished water (the resulting water after technical treatment) (55, 56). They are also detected in the Arctic environment (57). The concentrations of pharmaceuticals in surface water and effluent from STPs have been shown to be in the ng L$^{-1}$ to μgL$^{-1}$ range. Only recently, has the presence of psychoactive and illicit drugs (such as amphetamine, cocaine and its metabolite benzoylecgonine, morphine, 6-acetylmorphine, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol, methadone and its main metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, and amphetamines) been detected in surface water and wastewater (58–61). Despite the fact that knowledge about pharmaceuticals in sewage sludge and biosolids is necessary for the proper understanding of their fates and for risk assessment, only little information is available (62).

Not much is known about the occurrence, fate, and activity of metabolites. Important questions to be addressed are whether the
glucuronides, methylates, glycinites, acetyl-
ates, and sulfates are still active and whether
they can be cleaved back 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 also
excreted and can be detected in wastewater (63).
Their effects on environmental organisms may
be lower than that of their parent compounds.
However, in the case of prodrugs, the situa-
tion is probably different, as it may be for the
metabolites of several other pharmaceuticals as
has been shown for norfluoxetin (64).

The predominant fate processes for the
removal of pharmaceuticals in and from
the different environmental compartments
are sorption (of importance, for example,
for tetracyclines and quinolones) (65) and
(bio)degradation. Photodegradation and hy-
drolysis can also be significant in surface water
and technical treatment processes. Sorption
may have an impact on the spread (particle-
bound transport) and (bio)availability of
pharmaceuticals in the environment. Binding
to particles or the formation of complexes may
cause a loss in detectability as well as a loss in
activity. Sorbing APIs may diffuse into biofilms
present in sewage pipes, sludge flocks, or
stones in rivers and lakes. Colloids seem to be
an important sink for pharmaceuticals: Results
reported by Maskaoui & Zhou (66) provide
evidence that sorption to colloids provides an
important sink for the pharmaceuticals in the
aquatic environment. Such strong phar-
maceutical/colloid interactions may provide a
long-term storage of pharmaceuticals, hence,
increasing their persistence while reducing
their bioavailability in the environment. In
general, sorption may result in a biased risk
estimate as concentration in such “reservoirs”
may be much higher than when they are free
in water. As aquatic colloids are abundant,
ubiquitous, and highly powerful sorbents, an
impact on bioavailability and bioaccumulation
of pharmaceuticals is expected (66). The effects
and behavior of antibiotics in such biosolids
with high bacterial density and special condi-
tions have not yet been investigated, so little
is known about these issues. Even much less is
known about the conjugates, other metabolites,
and transformation products in this respect.

Bacteria and fungi are the two groups of or-
ganisms that are best able to degrade organic
compounds. Fungi are particularly important in
soils, but they do not usually play an important
role in the aquatic environment. Therefore, in
STPs and in surface-, ground- and seawater,
bacteria are assumed to be responsible for most
biodegradation processes. The rate and degree
of biodegradation of APIs in sewage treatment
and the aquatic environment depend on the
type and number of microorganisms present
and the API itself. The presence of pharmaceu-
ticals in the aquatic environment demonstrates
at least incomplete degradation and elimination
in sewage treatment and also that removal pro-
cesses in the aquatic environment are slow.

Often, it is assumed that metabolism and
transformation of APIs, e.g., by advanced ef-
fluent treatment, results in decreased toxicity.
In some cases, however, metabolism leads
to more active compounds (e.g., in the case
of prodrugs). The same has been found for
phototransformation and other oxidizing pro-
cesses. However, often only one end point was
monitored with one specific test. Mutagenic
and other toxic properties have been found
for the reaction products of photolysis and
(photo)oxidation processes (28, 30, 67–73;
P. Gupta, R. Gmiski, T. Haddas, N. Mathurc,
V. Mersch-Sundermann, K. Kümmerer,
unpublished).

**EFFECTS**

The risks posed to humans from pharmaceu-
ticals in the environment seem to concern
environmental hygiene rather than toxicology
and pharmacology (74). However, there are
some exceptions: Endocrine-active compounds
and hormones may interfere with sexual
development in humans, as they are highly
active compounds that interact with hormone
systems (75–78). In addition, some anticancer
drugs may cause cancer themselves—even at
very low doses—one of the threats of modern

**Elimination:**

The removal of a chemical
compound from a
certain environmental
compartment by
physical (e.g.,
sorption) or
(bio)chemical
processes, such as
(bio)degradation
chemotherapy, and antibiotics may contribute to the selection of bacteria that are resistant against antibiotics (79). Little knowledge of these issues is available.

The maximum possible intake with contaminated water within a life span (2 liters drinking water per day over 70 years) is far below the dosages used in general therapy. However, this statement relies on some assumptions: (a) that the effects and side effects during therapeutic use (short-term, high dosage) are the same in quality and quantity as during a lifelong ingestion (long-term ingestion, low dosage); (b) that the effects are the same for fetuses, babies, children, healthy adults, and elderly people; (c) and that the risk imposed by a single compound is comparable to the one imposed by a mixture. How to extrapolate data from high-dose short-term ingestion during therapy to a low-dose long-term ingestion, i.e., medication received via drinking water, is still an unresolved issue in toxicology and in ecotoxicology. Elderly people, little children, and pregnant women may be at risk (21, 80); however, they are often not specifically addressed in risk assessments.

Information about the effects of the active substances on organisms in the aquatic and terrestrial environments is increasing but still too little (81). Effects on fish, daphnia, algae, and bacteria have been demonstrated using low concentrations in long-term tests (82, 83). For diclofenac, the effective concentration for chronic fish toxicity was in the range of wastewater concentrations (see References 84–87), whereas those of propranolol and fluoxetine for zooplankton and benthic organisms were near the maximally measured STP effluent concentrations (81). In surface water, concentrations are lower and so are the environmental risks. However, targeted ecotoxicological studies are almost entirely lacking, and such investigations are needed to focus on subtle environmental effects (81). Chronic effects often do not have clearly visible results. Instead, they may cause subtle changes within longer time spans. Therefore, such effects are often overlooked, and a direct cause-and-effect relationship cannot be established on an ecosystem level.

All risk assessments are based on single compounds (74), but it has been found that mixtures might exhibit effects that differ from single compounds (16, 88–90). In addition, it has been shown that a standardized test may underestimate the effects (91). It has also been found that detrimental effects may happen by the transfer of compounds within the food web. For example, diclofenac has undoubtedly had extremely negative impacts on vulture populations in Southeast Asia, and possibly elsewhere. This nonsteroidal anti-inflammatory drug is used in veterinary practice to treat sick livestock in Asia. Dead livestock are consumed by old world vultures, which ingest the diclofenac remaining in the carcass. Unfortunately, vultures are exquisitely sensitive to this drug, and a dose of only 1 mg causes acute kidney failure and death within a few days (92). Between 2000 and 2003, high annual adult and subadult mortality (5–86%) of the oriental white-backed vulture occurred, and resulting population declines (34–95%) were associated with renal failure and visceral gout. Diclofenac residues and renal disease were reproduced experimentally in oriental white-backed vultures by direct oral exposure and through feeding vultures the remains of diclofenac-treated livestock (92). Evidence from studies of one of these species strongly implicates mortality caused by ingestion of residues of the veterinary nonsteroidal anti-inflammatory drug diclofenac. Other findings also show that veterinary use of diclofenac is likely to have been the major cause of the rapid vulture population declines across the subcontinent (93, 94). This one pharmaceutical has caused the deaths of tens of millions of vultures in Asia and left three species on the brink of extinction (populations of all species have declined by over 99% in the past decade). Only recently it was found that the nonsteroidal anti-inflammatory drug ketoprofen has the same effects on these animals. New world vultures such as the condor are seemingly not affected by diclofenac. Old world vultures do not react to other structurally related nonsteroidal anti-inflammatory drugs. Therefore, this ecological catastrophe would probably not have been
anticipated by testing. As we will never be able to test all drugs against all organisms because we do not have the knowledge, the time, and the money, other surprises cannot be ruled out in the future. This example demonstrates clearly the need to reduce the input and presence of drugs into the environment.

A subtle example of indirect effects of antibiotics was reported by Hahn & Schulz (95). Results of food selection experiments with Gammarus pulex demonstrated clear preferences for leaves conditioned in the absence versus those conditioned in the presence of two antibiotics, oxytetracycline and sulfadiazine.

Antibiotics are one of the most important groups of APIs used in medicine, and they are now present in the aquatic environment (9, 79). The unwanted effects of microbial growth have long been controlled through the use of antimicrobials such as antibiotics. In general, the emergence of resistance to antimicrobials is a highly complex process, which is not yet fully understood with respect to the significance of the interaction of bacterial populations and antibiotics, even in a medicinal environment. Bacteria resistant to antibiotics have been found in the aquatic environment (79, 96–99). Is the input of antibiotics into the environment an important factor for the emergence of resistant bacteria in the environment or is the transfer of resistance from already resistant bacteria following improper use of antibiotics much more important than the input of the antibiotic compounds themselves? The links between the presence of antimicrobials and the favoring of resistant bacteria as well as the transfer of resistance at concentrations as low as those found for antimicrobials in the environment have not yet been established. Knowledge of subinhibitory concentrations of antimicrobials and their effects on environmental bacteria is scarce and contradictory, especially with respect to resistance (for details, see Reference 79). In any case, prudent use of antibiotics is crucial for the avoidance of resistance.

Despite the presence of a large number of different human pharmaceuticals in the environment, there are very few documented examples whereby a pharmaceutical has been conclusively shown to adversely affect an ecosystem. By the 1990s, sex steroids and, in particular, estrogens, such as 17-α-ethinylestradiol (EE₂), were identified in the aquatic environment. They are likely to affect reproduction of fish. EE₂ is used exclusively in the contraceptive pill. It is widespread in the aquatic environment, albeit at sub-ng L⁻¹ concentrations in most rivers (75). However, fish are so sensitive to this drug that very low ng L⁻¹ concentrations in their water can change the female-to-male sex ratio in favor of the females because of a lack of sexual differentiation occurring in males (76) and lead to population crashes (77). Fortunately, real-world concentrations of EE₂ are lower than those that dramatically affect fish, although the margin of safety is not particularly large (75, 78).

One of these examples of medicinal drugs on fauna, that of EE₂, could, and probably should, have been foreseen (18), whereas the other (diclofenac causing the death of old world vultures) came as a complete surprise.

HAZARDS AND RISKS

The current state of knowledge on possible hazards for the fauna and flora by the occurrence of pharmaceuticals in water is strongly limited. The examples of EE₂ and diclofenac, however, as well as the issue of antibiotic resistance demonstrate our current lack of ability to predict the environmental consequences of widespread contamination of the environment by a plethora of human pharmaceuticals. Furthermore, the examples of EE₂ and diclofenac demonstrate that, although concentrations of pharmaceuticals will, in nearly all locations, be very low, such low concentrations can still, in certain circumstances, exert adverse effects on wildlife. The key uncertainties are in identifying which pharmaceuticals are of concern and which species are particularly sensitive.

Comprehensive ecotoxicological studies are only available for a few substances. The reason is not only the huge amount of substances, but also the fact that meaningful
results can only be derived from long-term studies. The identification of chronic effects, however, comes along with increased temporal and financial costs. Most of the APIs studied so far exhibit acute toxicity for aquatic organisms only at concentrations well above current measurements in surface water.

Data allowing for a sound risk assessment for metabolites and transformation products are missing more or less completely. 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, so they are called CMR compounds. It is unclear how such compounds should be handled within the risk assessment process (100). A subgroup of this particular group of compounds is the pharmaceuticals used for anticancer treatment. Information on the fate and effects in the environment and the significance for humans is scarce. For cyclophosphamide and ifosfamide, for example, risk assessments are available. With the use of different databases and different approaches, the results vary. Some state no risk, whereas others present data and include additional information that result in findings that “risk cannot be ruled out” (21). In addition to toxicity, the property of persistence is of particular importance for the assessment of the environmental significance of substances. Persistent organic pollutants increase the potential for long-term, varied effects, and longer exposures may result in multiple contaminations of the ecosystem. Such problems cannot be determined in advance with the presently available test systems (101).

**RISK MANAGEMENT**

Combinations of management strategies will likely be most effective in mitigating the risks presented by pharmaceuticals, such as pharmaceutical-return programs, consulting stakeholders, advanced effluent treatment, and incentives for the development of “green” pharmaceuticals (102). All of them are needed for an effective reduction of the input of pharmaceuticals (and other chemicals) into the environment. The one strategy that has been most extensively discussed within recent years is advanced effluent treatment. As for the third strategy, environmental protection has to include the shareholders, stakeholders, and people using the compounds, i.e., patients, doctors, nurses, and pharmacists when seeking workable solutions. The fourth strategy is emerging from the field of green chemistry. In terms of sustainability, it seems to be the most promising one in the long run.

The advanced treatment of effluents has been investigated using (photochemical) oxidation processes (e.g., 68, 96, 103), filtration (104, 105), application of powdered charcoal (106, 107), and constructed wetlands (108). Reviews on the advantages and disadvantages of the different technologies are available (12, 109–111). It has been found that each type of advanced effluent treatment has its specific limitations and, in general, some severe drawbacks (110–112). For example, mutagenic and toxic properties have been found for the reaction products of (photo)oxidation processes (28, 30, 67, 68, 70, 71). Therefore, advanced effluent treatment should not be considered as a general solution to the problem. Instead, it should be considered only as part of the solution on a case-by-case basis. Hospital contributions to the total load of pharmaceuticals in municipal wastewater is for most compounds below 10% and usually even below 3% (22, 32, 41, 105, 113–115). Therefore, it is questionable whether separate treatment of hospital effluent is an economically valid environmental goal.

A major unknown with respect to drugs as pollutants is what fractions of drug residues occurring in the ambient environment result from discarded leftover drugs (47, 51). Therefore, proper instructions to doctors, pharmacists, and patients can contribute to the reduction of the input of APIs into the aquatic environment (116). Initial results show that this approach could help to reduce the input of pharmaceuticals with unwanted environmental properties (A. Wennmalm, personal communication). Data are needed on the types,
quantities, and frequencies with which drugs accumulate in households, hospitals, facilities for elderly people, and rehabilitation hospitals (51). In a mid- to long-term perspective, prescription, therapy, and consultation practices of physicians and pharmacists as well as the patients’ use and disposal patterns of pharmaceuticals should be changed toward a higher environmental sensibility. The relationship between physicians and patients plays a key role within this strategy: Knowledge concerning the environmental relevance and problems of pharmaceuticals increases the awareness of physicians during their consultations with patients. To facilitate the integration of the problems into physicians’ everyday practice, the environmental effects of medicinal drugs should be included in the medical education and advanced training by instructors of health education and health policy. Sources of health funds can foster the demand for better ecological alternatives by changing the funding of, or reimbursement for, 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).

If an internal commission of a hospital provides a list of recommended pharmaceuticals that is the basis for hospital purchasing activities, the variety of products is reduced, resulting in savings. Limiting the drug storage space in wards reduces the share of outdated medicines and thereby the environmental burden. The internal system should allow the wards to give back not yet outdated, broken, and not yet used packages to the pharmacy. The pharmacist can handle these remainders properly. A physician familiar with infectious diseases should be present to provide advice on the proper use of antibiotics. Proper hygiene, which is not too much and not too little, at the right place and the right time can also reduce infections and the need for pharmaceuticals and disinfectants.

At this time, improvement of synthesis is very prominent in drug design, whereas the environmental properties of the molecules are somewhat underestimated. According to the principles of green chemistry, the functionality of a chemical should not only include the properties of a chemical necessary for its application, but also easy and fast degradability after its use. Taking into account the full life cycle of pharmaceuticals leads to a different understanding of the functionality necessary for a pharmaceutical (112). It means that easy degradability after use or application is taken into account even before a pharmaceutical’s synthesis ("benign by design"). Such an approach is not completely new. For example, it is quite common during the development of pharmaceuticals with respect to unwanted side effects. This can also result in economic advantages in the long run (102, 112). Researchers and drug companies should apply these principles and the knowledge of green chemistry to pharmaceuticals. The contributions of different stakeholders to the management and mitigation of pharmaceuticals in the environment are summarized in Table 1.

GREEN AND SUSTAINABLE PHARMACY

Green pharmacy includes the design of pharmaceutical products and processes that eliminate or reduce significantly the use and generation of hazardous substances and the prevention and/or reduction of environmental safety and health impacts at the source (117). “Green” focuses on the pharmaceutical itself, including only the environmental aspects. These are important points. There are additional considerations. For example, a new pharmaceutical can be green in terms of the quality and quantity of waste generated during its synthesis, and renewable feedstock might have been used, but the pharmaceutical may accumulate in the environment after excretion and create environmental or health problems. If reproduction of the renewable feedstock needs much water and fertilizer, is in competition with food production, or depends on an endangered species, it may not be called sustainable. The same holds if the compound itself is green or even sustainable, but the material

**Benign by design:** the targeted design of a chemical with optimized properties for its application and fast and full mineralization after it reaches the environment
Table 1  Opportunities to reduce the input of pharmaceuticals into the environment

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<th>Stakeholders</th>
<th>Possible measures and activities</th>
</tr>
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<tbody>
<tr>
<td>Science and humanities</td>
<td>Move on to green and sustainable pharmacy, establish together with the pharmaceutical companies and regulators criteria for the quality of data necessary for risk assessment and risk management, introduce findings into teaching, begin research into benign compounds and green and sustainable pharmacy, develop models and processes for proper information and involvement of stakeholders</td>
</tr>
<tr>
<td>Pharmaceutical companies</td>
<td>Publish data relevant for environmental assessment; publish analytical methods and results; offer suitable package sizes; integrate environmental aspects in the development of new APIs and new therapies; follow green and sustainable pharmacy practices; offer fewer over-the-counter products; establish take-back systems where not already in place; offer proper information to doctors, pharmacists, and the general public; develop a new understanding of and promote shareholder value; and adopt corporate sustainability responsibility</td>
</tr>
<tr>
<td>Wholesalers</td>
<td>Deliver not only pharmaceuticals but also proper information to users</td>
</tr>
<tr>
<td>Patients</td>
<td>Improve compliance, take APIs only if necessary and only after prescription by a physician, do not put outdated medicines down the drain, return drugs to the pharmacy if a take-back system is established or put into the household waste if appropriate (check with local authorities and pharmacies), do not use lifestyle drugs, investigate alternative treatments such as acupuncture for pain treatment</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>Inform patients and doctors, participate in take-back systems if appropriate (check with local authorities)</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Integrate the delivering pharmacy/wholesaler into the handling of outdated medicaments, inform doctors and patients, establish proper procurement, apply the Swedish classification system of pharmaceuticals (<a href="http://www.fass.se">http://www.fass.se</a>)</td>
</tr>
<tr>
<td>Physicians</td>
<td>Prescribe medication according to environmental criteria if alternatives are available, apply the Swedish classification system of pharmaceuticals (<a href="http://www.fass.se">http://www.fass.se</a>), provide proper disposal information to patients</td>
</tr>
<tr>
<td>Health insurance companies</td>
<td>Maintain appropriate medical standards for pharmaceuticals; inform doctors, pharmacists, and patients of the proper ways to use and dispose of drugs; apply the Swedish classification system of pharmaceuticals (<a href="http://www.fass.se">http://www.fass.se</a>); and create incentives for companies to dedicate themselves to sustainable pharmacy</td>
</tr>
<tr>
<td>Wastewater handling and treatment</td>
<td>Repair broken sewers and piping, reduce total water flow treated by separate piping of wastewater and rain water and thereby increase the concentration of APIs, apply affordable technologies, develop less water- and energy-demanding treatment systems and technologies, establish appropriateness of advanced treatment on a case-by-case basis</td>
</tr>
<tr>
<td>Drinking water treatment</td>
<td>Extend monitoring, use advanced treatment if necessary, inform the general public about the issue of pharmaceuticals in the environment</td>
</tr>
<tr>
<td>Banks</td>
<td>Include sustainability in the rating of pharmaceutical companies</td>
</tr>
<tr>
<td>Authorities/government agencies</td>
<td>Initiate communication between all stakeholders; develop limits and/or thresholds for APIs in different environmental areas and in drinking water; include APIs in environmental legislation; establish a more restrictive connection between environmental properties and the authorization of human pharmaceuticals; improve legislation for the management of outdated medicaments; establish incentives for the development of greener drugs, e.g., prolonged patent lifetime and funds for research; establish a country-adapted classification system for pharmaceuticals as is already in place in Sweden</td>
</tr>
</tbody>
</table>

Source: Reference 7.

API, active pharmaceutical ingredient.

flows connected to its production, distribution, and usage are very large (in terms of quantity and/or in terms of quality) or depend on nonrenewable resources. Another point is that greener products or chemicals may become less green or even problematic if they are produced and applied in high volumes. For example, if a green packaging material contains an antimicrobial to preserve its content, such as food from spoilage, this antimicrobial can contribute to resistance by being transferred to the food or by being set free into the environment when the packaging is discarded. Thus, a packaging may be green but not sustainable. A sustainable view is much broader (118). It would also ask what the origin of the food is (local, regional, or
distant source) and how long we want—versus we need—to store it. Educating people on how to handle and store food properly would be a much more sustainable approach to reduce food spoilage rather than increasing the risk of antibiotic resistance via antibiotic packaging.

These examples demonstrate the need to keep the full life cycle in focus (Figure 5). This also includes other aspects, such as corporate social responsibility and ethical questions. For example, one may argue that we cannot afford sustainable pharmaceuticals because this would result in fewer active compounds reaching the market. Or is every pharmaceutical sustainable since it offers some benefit? However, a different viewpoint is to consider how many people do not have access to suitable medication at all (119), e.g., for financial reasons. Or why are there symptoms for which no new pharmaceuticals are available? What are the costs compared to the benefits? What are undesirable side effects?

In 2002, the European Parliament and the European Commission agreed that within a generation chemicals should be produced and applied that do not have any impact on the environment (120). This should also hold for pharmaceuticals.

### SUMMARY POINTS

1. Pharmaceuticals and other chemical compounds are present as mixtures in drinking water and the environment.
2. Some pharmaceuticals are transformed to other products (i.e., metabolites and transformation products).
3. Effects and risk assessments are now performed based on single compounds.
4. Knowledge of the fate, effects, and risk of pharmaceutical discharge into the environment is not sufficient for a final risk assessment.
5. Different measures are part of risk management.
6. Benign by design is the main building block of green and sustainable pharmacy, which is the paradigm of the future.
FUTURE ISSUES
Directions for future research include the following:
1. Reduced release of pharmaceuticals into the environment;
2. Improved knowledge of the fate, effects, and risks of pharmaceuticals into the environment, including the mixtures and transformation products;
3. Distribution of proper information to patients, pharmacists, and physicians;
4. Improvement of sewage treatment;
5. Improvement in the (bio)degradability of pharmaceuticals (benign by design pharmaceuticals);
6. Promotion of sustainable pharmacy; and
7. Introduction of sustainable pharmacy in the curricula of physicians and pharmacists.

DISCLOSURE STATEMENT
The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED
13. Cunningham V. 2008. Special characteristics of pharmaceuticals related to environmental fate. See Ref. 7, pp. 23–34


Deposition, resuspension, and desorption

Dilution and diffusion

Biodegradation and transformation

Hydrolysis

Photolysis

Sorption onto sediments

Volatilization to atmosphere

Municipal or industrial sewage discharge

Dissolved transport

Deposition, resuspension, and desorption

Deposition and accumulation

Bioconcentration

Figure 1
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