Veterinary and Human Health Care Pollutants

Chemical characteristics and their potential risks

Introduction

Today, the use of human and veterinary pharmaceuticals for the treatment of diseases is indispensable. There are more than 3000 active pharmaceutical ingredients (APIs) used as analgesics, antibiotics, antivirals, beta-blockers, contraceptives, lipid regulators, sedatives, and impotence drugs (Ternes et al., 2004; Richardson et al., 2005). The persistent application of pharmaceuticals results in a continuous and omnipresent contamination by APIs, in their original form or as transformation products, of aquatic environments and soils particularly (Ferrari et al., 2003; Sarmah et al., 2006; Gros et al., 2007; Larsson et al., 2007). During the last decades, continuous exposure to these substances resulted in relatively new research areas being established – the fields of environmental toxicology and environmental chemistry. These disciplines are driven by the improved ability to measure these micro-pollutants. From the knowledge gained, they have raised awareness that exposure of the environment to pharmaceuticals can adversely affect ecosystems and the environment. It has also been established that these pharmaceuticals are highly active even at very low concentrations (Crane et al., 2006; Hernando et al., 2006; Klavarioti et al., 2009). Even human health might be affected by APIs that are released into the environment, as exemplified by the formation of multi drug-resistant microbial strains (Phillips et al., 2004; Hersher, 2012). In this context, evidence for the development of antibiotic-resistant bacterial strains of tuberculosis (Zager and McNerney, 2008; Hersher, 2012), salmonella (Kingsley et al., 2009), and *Escherichia coli (E.coli;* Rogers et al., 2011), or for the generation of antiviral drug-resistant influenza viruses (de Jong et al., 2005) has been found. To date, the occurrence and fate of pharmaceuticals in the environment have been extensively assessed and documented in high-income countries (Sacher et al., 2001; Heberer, 2002; Kolpin et al., 2002; Ternes et al., 2004; Jones et al., 2005; Togola and Budzinski, 2008; Vulliet and Cren-Olivé, 2011). However, environmental data about APIs in low- and middle-income countries is limited and their risks to environmental health in low- and middle-income countries have been poorly assessed and documented (Richardson et al., 2005; Larsson et al., 2007; Zhao et al., 2010; Rehman et al., 2015). In this context, more investigation of the occurrence and the fate of APIs in low- and middle-income countries is required.

Even in low- and middle-income countries, APIs should be considered as significant environmental risk factors.

Active pharmaceutical ingredients are omnipresent in aquatic environments and soils, in their original form or as transformation products. Exposure of the environment to pharmaceuticals can adversely affect ecosystems and the environment even at very low concentrations.

Main Issues

- The bulk of the pharmaceutical production has and is being relocated from high- to low- and middle-income countries, such as China, India, and Pakistan. These countries are producing large amounts of APIs and the generic forms of the drugs are extensively produced in low- and middle-income countries as well (Pricewaterhouse Coopers, 2012; Rehman et al., 2015). The increased production of APIs in low- and middle-income countries is mainly driven by the lower production costs that are possible in these countries and by the growing demands and markets for APIs in these countries (Rehman et al., 2015)

- Often in low- and middle-income countries the industrial effluents act as a considerable number of point source of micro-pollutants of environmental systems (Larsson et al., 2007) as they are released untreated into the environment (Rehman et al., 2015)

- The consumption of APIs increases in densely populated areas with the availability of cheaper generic drugs and with improving living standards (Zhang and Geißen, 2010; IMS Institute for Healthcare Informatics, 2012)

- Excessive animal livestock farming (aquafarming (Food and Agriculture Organization, 2010) fish, crustacean, mussels or the farming of cattle, chicken and pork (BBC, 2013; Food and Agriculture Organization, 2013; Richard, 2013) is being carried out increasingly in many low- and middle-income countries with veterinary APIs being used intensively and in an uncontrolled manner (Mitema et al., 2001; Sarmah et al., 2006; Ok et al., 2011)

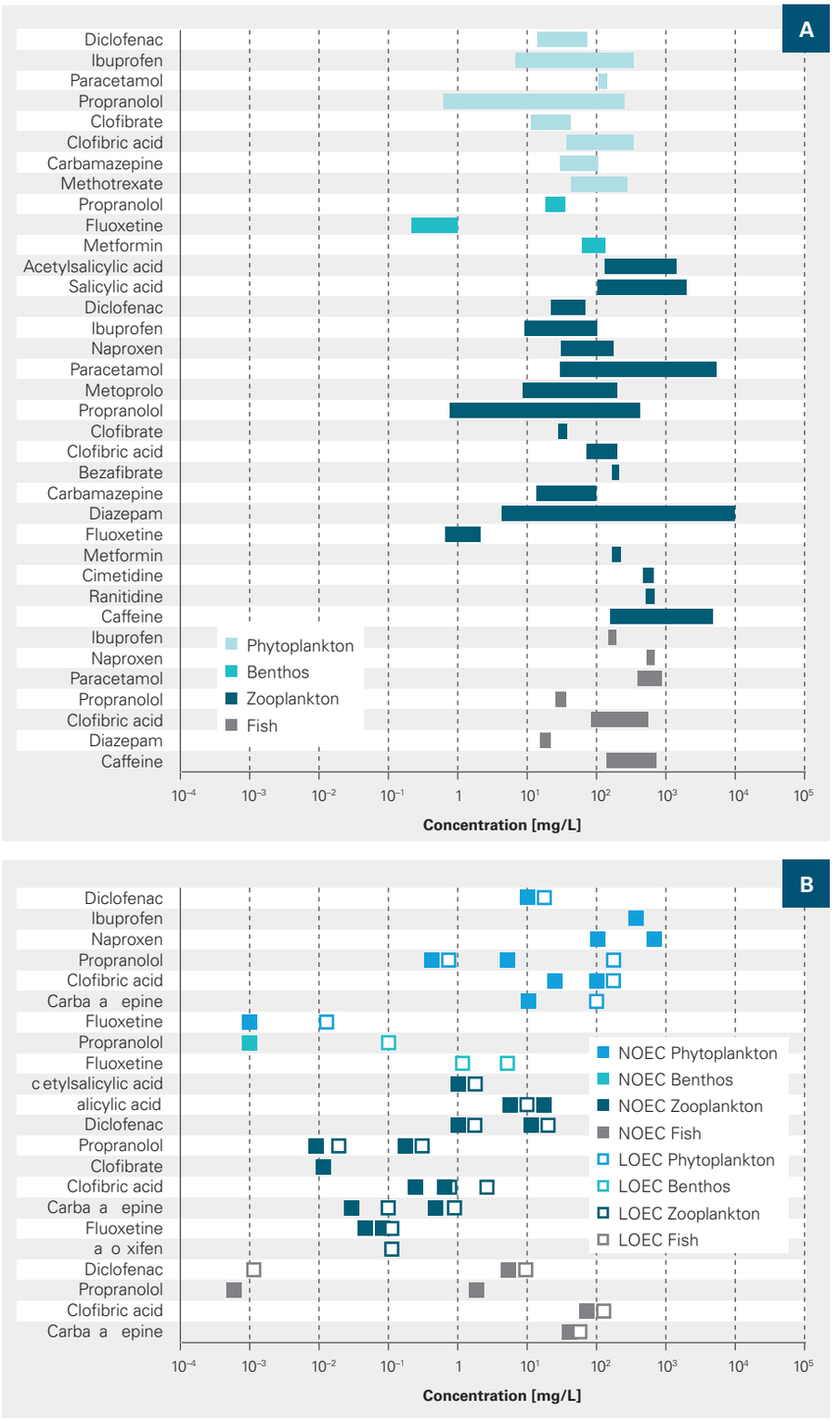

Figure 9: *Acute (A) and chronic (B) toxicity of individual APIs in different aquatic organisms of different trophic levels (phytoplankton, benthos, zooplankton, and fish). The acute values represent data from different organisms and/or experiments and range over several orders of magnitude for an individual API. The chronic values illustrated are the lowest observed effect concentrations (LOEC) and no observed effect concentrations (NOEC). One data point is referring to one species and/or one experiment (Kümmerer, 2008)*

Toxicological potential

APIs are designed to be persistent and to have a highly bioactive potential even at low environmental concentrations (Heberer, 2002; Fatta-Kassinos et al., 2011; Köck-Schulmeyer et al., 2013). Since their widespread occurrence in the environment (Heberer, 2002; Fent et al., 2006; Fatta-Kassinos et al., 2011), and since they have shown eco-toxicological effects, especially to aquatic systems (Crane et al., 2006; Hernando et al., 2006; Ernst et al., 2012), concern about their effects on the environmental has increased during recent years (Voigt and Bruggemann, 2008; Kümmerer, 2009b). Figure 9 illustrates the high toxic potential of individual APIs on aquatic organisms of different trophic levels. Environmental concentrations of these pharmaceuticals at ng/L and µg/L levels are able to impair considerably the health of water organisms, causing them to show chronic and acute toxic effects (Kümmerer, 2008; Ecotox Centre, 2015). The antidepressant fluoxetine and the beta-blocker propranolol, especially, are acutely toxic to benthos and zooplankton (Figure 9 (A)). Even a chronic exposure of from 0.001 to about 0.0.1 mg/L of the anti-inflammatory drug diclofenac and the antidepressant fluoxetine can cause perceptible adverse effects in fish or phytoplankton (Figure 9B).

The proposals of the quality standards of the Ecotox Centre of Eawag/EPFL (École polytechnique fédérale de Lausanne) also show that even concentrations of several APIs at a level of ng/L can be enough to adversely affect the health of water organisms and to interrupt the interaction. Acute risks to the health of water organisms are assumed when the environmental levels of APIs in surface waters exceed the MAC-EQS and chronic effects to water organisms can be assumed if the environmental water concentrations surpass the AA-EQS (Ecotox Centre, 2015). The proposed MAC-EQS for the antibiotic azithromycin is 90 ng/L, for clarithromycin it is 110 ng/L, and for ciprofloxacin, 363 ng/L. For the hormone preparation and contraceptives 17-ß-ethinylestradiol, 17-ß-estradiol and estrone the AA-EQS are 0.037, 0.4, and 3.6 ng/L, respectively. The analgesic diclofenac has an AA-EQS of 50 ng/L and for the antibiotics erythromycin, clarithromycin, and ciprofloxacin the AA-EQS values of 40, 60 and 89 ng/L, respectively, are determined (Ecotox Centre, 2015).

Physicochemical characteristics

APIs are complex molecules with a molecule weight ranging from 200 to 1000 Dalton and with varying physicochemical and biological properties and functionalities. According to their ionic nature, most of the APIs are po-

lar and consequently remain in aquatic systems (Kümmerer, 2008). Nevertheless some APIs, such as several antibiotics, can have lipophilic characteristics as well (Hamscher et al., 2003; Sarmah et al., 2006; Kümmerer, 2009a) and, therefore, they can adsorb to organic material, such as soil particles, sediments, feces, sewage sludge, and manure. Most of the APIs have a low volatility, which is mainly due to their relatively high molecular weights and their highly hydrophilic characteristics (Hernando et al., 2006).

Consumption

In general, it can be assumed that about several hundred thousand tonnes of pharmaceuticals are consumed worldwide. The annual global consumption of pharmaceuticals per capita is predicted to be of the order of 15 g, while in industrial countries a consumption of pharmaceuticals of between 50 and 150 g per capita per year can be assumed (Ternes and Joss, 2007).

According to our literature search, it can be assumed that more comprehensive data about the consumption and production of pharmaceuticals is not readily available (if at all) to the general public – neither in high- nor in low- and middle-income countries. Since this is the case, it is not possible to compare the consumption and the production of pharmaceuticals in high- and in low- and middle-income countries in more detail. Just the available data on the expenditures of pharmaceutical companies can be used to approximate their production and the consumption in individual countries or lending groups. This is shown in the chapter "Input pathways of pharmaceuticals" and in the following paragraph.

Generally, the production, demand, and consumption of pharmaceuticals is dependent on several factors. The outsourcing of the pharmaceutical manufacturing facilities from Organisation for Economic Development and Cooperation (OECD) to non-OECD countries is driven mainly by the lower production costs in these countries. This, together with the excessive and increased production of generic drugs in low- and middle-income countries, causes a high increase in the production of human and veterinary pharmaceuticals in low- and middle-income countries with fast growing economies, such as China, India, Pakistan, etc. (IMS Institute for Healthcare Informatics, 2012; PricewaterhouseCoopers, 2012; Rehman et al., 2015). Along these lines, PricewaterhouseCoopers (2012) predicts that the 2011 sales of pharmaceuticals in China of US$66.9 billion can increase until 2020 by 163%. In India the US$15.6 billion industry of 2011 can have increased 213% by 2020. In the fast followers (including Argentina, Egypt, Indonesia, Mexico, Pakistan, Poland, Romania, South Africa, Thailand, Turkey, Ukraine, Venezuela, and Vietnam) 2020 can see a growth of 125% in their US$76.6 billion industry. In comparison, in high-income countries the trends in sales of pharmaceuticals will be less pronounced or even decline. For instance, for the USA it is predicted that the sales of US$337 billion will increase by just 26% while in the large EU countries (France, Germany, Italy, Spain, and the UK) the sales of US$205 billion will decrease by 5% from 2011 to 2020 (PricewaterhouseCoopers, 2012). This data are shown in Figure 12 and discussed again in the chapter on "Future trends and hot spots". However, according to these data on the sales of pharmaceuticals the following conclusion can be drawn: In low- and middle-income countries there will be a growing trend in the production of pharmaceuticals during the next years.

In addition, because of future demographic changes, such as improved living standards, the increases in the average life span and the population will be more pronounced in low- and middle-income countries (The World Bank Group, 2014). The demand for pharmaceuticals and the production of lower cost generic drugs, especially in the low- and middle-income countries with strong economies, might increase during the next decades (Kümmerer, 2009b; IMS Institute for Healthcare Informatics, 2012; PricewaterhouseCoopers, 2008; The World Bank Group, 2014). Together, these suggest an increase in demand for and, accordingly, the availability of pharmaceuticals in low- and middle-income countries as well.

For these reasons consumption in low- and middle-income countries with strong economies will be stimulated and will provoke the release of high amounts of pharmaceuticals into the environment. This might give rise to outcomes that impair human health – the formation of multidrug-resistant microbes and to the degradation of aquatic ecosystems – in countries with lower incomes as well (Mitema et al., 2001; Richardson et al., 2005; Zager and McNerney, 2008; Larsson, 2010; Rogers et al., 2011; Zhao et al., 2010; Ok et al., 2011).

Nevertheless, although no comprehensive data about the consumption of pharmaceuticals are available, especially for low- and middle-income countries, some case examples can be found that show that in these countries high quantities of pharmaceuticals are used as well. For instance, Richardson et al. (2005) assumed that in 2004 about 15,770 tonne of antibiotics for human application were used in Hong Kong and the Pearl River Delta region of south China. In the same region, the same amount or even more is used in the agricultural sector as food additives or as veterinary agents for livestock as well. Given the immense number of industrial/pharmaceutical manu-

Production and consumption of human and veterinary pharmaceuticals is rapidly increasing in low- and middle-income countries with fast growing economies, e.g. China, India and Pakistan. This may enhance outcomes that impair human health such as the formation of multidrug-resistant microbes or the degradation of aquatic ecosystems.

facturing facilities in this region, Richardson et al. (2005) suppose that it is possible to find here even higher environmental concentrations of pharmaceuticals and other micro-pollutants with wider distribution than there are in western countries such as Europe, the UK, and the USA. Therefore, overcrowded areas and areas with high agricultural and industrial activities – which is the case in Hong Kong and the Pearl River Delta region – are significant sources of APIs and other industrial chemicals, which pose risks to environmental and human health. This is especially so if there are no, or inadequate or insufficient, wastewater treatment facilities available, which is often the case in low- and middle-income countries (Richardson et al., 2005; Blacksmith Institute and Green Cross, 2012).

In addition, Mitema et al. (2001) identified that in Kenya alone, large volumes – about 14.6 tonne – of active antimicrobials were used in animal food prodution. In 1999, the main antibiotics used in the animal husbandry sector in Kenya were aminoglycosides, ß-lactams, tetracyclines, nitrofurans, quiniolones, and sulfonamides. Between 469 and 39,866 kg were used annually. In general, there is an even greater lack of data on the application of steroids and other growth promoters in the agricultural sector than there is for the human consumption of antibiotics.

A screening for pharmaceuticals of human urine samples from Durban, South Africa, within the scope of the Valorization of Urine Nutrients in Africa (VUNA) project (www.vuna.ch; Etter et al., 2015) shows that APIs, which can cause adverse effects to aquatic environments (Ecotox Centre, 2015), are available, consumed, and excreted as well. The most prominently consumed and excreted APIs of this region are the antibiotics sulfamethoxazole and its metabolite N-acetyl-sulfamethoxazole, trimethoprim, the transformation product of the beta-blocker atenol, atenolol acid, and the analgesic diclofenac (Bischel et al., 2015). Further investigations show that in other countries with low incomes, such as Pakistan, considerable levels of the antibiotics ciprofloxin, oxytetracycline, oflaxacin, and sulfamethoxazole in concentrations of up to 4 µg/L, and the analgesic diclofenac up to a concentration of 8 µg/L, have been measured in domestic wastewater (Rehman et al., 2015).

The groups of APIs of highest eco-toxicological concern, which will play an increasing role in low- and middle-income countries, are highlighted in the following section. For most of these pharmaceutical groups, except antibiotics (Okeke et al., 2005a; Hersher, 2012) and antivirals (Richman et al., 2004; Dilernia et al., 2007; Baggaley et al., 2010), the environmental concentrations in surface waters are generally not supposed to affect human health, therefore the impacts on human health of just the antibiotics and the antivirals are discussed in more detail.

Active pharmaceutical ingredients of environmental concern

A) Analgesics and anti-inflammatory drugs

Paracetamol, acetylsalicylic acid, ibuprofen, fenoprofen, mephenamic acid, naproxen, indomethacin, and diclofenac are common and broadly used as painkillers and anti-inflammatory agents.

Consumption

Worldwide, the annual use of these agents amounts to several kilotonnes (Cleuvers, 2004). Given their low prices and that these agents can be obtained mainly without prescription – they are referred to as over-the-counter-drugs – the pattern of their consumption is relatively incomprehensible (Oaks et al., 2004). The anti-inflammatory drugs ease pain mainly by the inhibition of cyclooxygenase 1 and/or 2 (Vane and Botting, 1998).

Environmental behavior and occurrence

Given the immense consumption of these agents, their persistence, and their high water solubility, several anti-inflammatory drugs or their transformation products can reach considerable environmental concentrations – up to µg/L (Ternes, 1998; Stumpf et al., 1999; Heberer, 2002; Ferrari et al., 2003; Jiménez et al., 2012; Tredoux et al., 2012). This is especially so for the analgesic diclofenac, which is well-known for its high persistence in aquatic environments. Even with state of the art wastewater treatment facilities it is difficult to degrade this API effectively (Zhang et al., 2008). In Côte d'Ivoire, the maximal concentrations of the anti-inflammatory agent diclofenac above 1 µg/L were found in surface water (Weber et al., 2014; Figure 16). In domestic wastewater in Pakistan, diclofenac concentrations up to 8 µg/L were measured (Rehman et al., 2015). In addition, in France (Deblonde et al., 2011) a maximum concentration of diclofenac of 3.1 µg/L was measured in domestic wastewater while in Spain (Gracia-Lor et al., 2012) the value was 1.49 µg/L. Even in groundwater samples in Germany, diclofenac concentrations at a magnitude of ng/L were detected (Sacher et al., 2001; Heberer et al., 2011).

Toxicity

In order to evaluate the eco-toxicological potential of anti-inflammatory drugs in more detail, there is evidence that even low concentrations (0.5 µg/L) of diclofenac showed toxic effects to the organs of a brown trout (*Salmo trutta f. fario*; Hoeger et al., 2005). In addition, the findings of Schwaiger et al. (2004) show that exposure to 5 µg/L of diclofenac is enough to initiate renal lesions and cause adverse effects to the gills of rainbow trout (*Oncorhynchus mykiss*). Moreover, diclofonac is well-known for its alarming eco-toxicological potential, since Oaks et al. (2004) showed that the population of oriental white-backed vultures (*Gyps bengalensis*) in Pakistan had been endangered through eating the carcasses of diclofenac-treated livestock. This ingestion of dead livestock with accumulated residuals of diclofenac by the vultures was leading to renal failure and death. According to the Ecotox Centre, the chronic environmental standard value (AA-EQS) of 0.05 µg/L for diclofenac should not be exceeded in the long term in order to protect aquatic environments. For ibuprofen, the proposed AA-EQS value is 0.3 µg/L and for naproxen it is 1.7 µg/L (Ecotox Centre, 2015).

B) Antibiotics

Active antibiotic substances, such as sulfadimidine, sulfadiazine, cloxacillin, benzylpenicillin, bacitracin, oxytetracycline, and virginiamycin, are used to treat disease and promote the growth of livestock and in aquaculture (Sarmah et al., 2006; Kemper, 2008). Antibiotics like clarithromycin and erythromycin, sulfamethoxazole and trimethoprim are more likely to be used for human treatment (Kemper, 2008; Ernst et al., 2012). Table 2 represents a small collection of antibiotics used for veterinary and human treatments.

Consumption

Worldwide, humans are using approximately 100–200 thousand tonne of antibiotics and the lack of global data about the amount used for veterinary purposes makes it even more difficult to estimate total consumption (Wise, 2002; Sarmah et al., 2006; Rehman et al., 2015). Although the number of studies on the occurrence, fate, and ecotoxicology of antibiotics have increased within the last decades, the processes and the behaviors of these agents in the environment, especially in the long term, are quite unclear (Kümmerer, 2009a).

Environmental behavior and occurrence

Antibiotics can diffuse and accumulate in water systems and soils by having polar and partly apolar properties (Sarmah et al., 2006; Kümmerer, 2009a). This is especially the case if the application of veterinary products is not controlled and regulated and domestic and municipal wastewater and the effluents of hospitals are not treated sufficiently. This is often the case in low- and middle-income countries where antibiotics can be released into the environment through the discharge of untreated industrial wastewaters (Mitema et al., 2001; Larsson et al., 2007; Duong et al., 2008; Ok et al., 2011). For example, the concentration of antibiotics in the effluents of WWTPs in the Pearl River Delta in South China were found to range from 0.009 to 2.054 µg/L (Xu et al., 2007). In untreated hospital wastewaters in Vietnam, the concentrations of fluoroquinolone antibacterial agents were found to be from 1.1 to 44 µg/L for ciprofloxacin and from 0.9 to 17 µg/L for norfloxacin (Duong et al., 2008). Treated wastewater effluents adjacent to an industrial estate near Hyderabad, India, which houses 90 bulk drug manufacturers, contained maximal concentrations of antibiotic-fluoroquinolones of about 31,000 µg/L of ciprofloxacin and 900 µg/L of enrofloxycin (Larsson et al., 2007). In the Poudre River in Colorado, USA, which has urban and agricultural influences, the average concentrations of several tetracyclines and sulfonamides were found to range between 0.05 and 0.17 µg/L (Yang et al., 2004).

Anti-inflammatory drugs such as diclofenac are well-known for an alarming ecotoxicological potential. Ingestion of dead livestock with accumulated residuals of diclofenac by vultures has led to widespread renal failure and death in Pakistan.

Furthermore, antibiotic agents can remain parly in soils as well. Hamscher et al. (2002) found the highest average concentrations of tetracycline (ranging from 86.2 to 198.7 µg/kg) and of chlortetracycline (ranging from 4.6 to 7.3 µg/kg) in soil layers up to 30 cm deep in a field with intensive livestock farming in northern Germany. In another study, they revealed that tylosin, tetracyclines, sulfamethazine, and chloramphenicol, mainly, can be traced in dust samples from a German pig-fattening farm in concentrations of about 12,500 µg/kg dust (Hamscher et al., 2003). These environmental concentrations of antibiotics in water systems and soils indicate that antibiotics have the potential to remain or even accumulate in water and soils.

Toxicity

The eco-toxicological classification of Table 2 shows the maximum measured environmental concentrations of different antibacterial substances found in sewage effluent, surface water, groundwater, or drinking water in Germany. The table also indicates whether the individual subs-

tance should be considered as a priority pharmaceutical or not. This prioritization of pharmaceuticals is based on:

- The eco-toxicological effect of concentrations of the pharmaceutical on water organisms
- The occurrence in the aquatic environment
- The consumption rates of APIs between 2002 and 2009.

This prioritization was undertaken by the IWW Water Centre and the German Federal Environmental Agency (GFEA); Bergmann et al., 2011.

However, this classification in Table 2 must be treated with caution, because it is determined by monitoring and measuring environmental concentrations in Germany. What has to be taken into account is that some antibiotics that pose a risk to environmental health, which are not often used in Germany, can be used intensively in low- and middle-income countries and vice versa. Furthermore, it has to be considered that often in lower-income countries water treatment systems are not available or are less effective than the ones in higher-income countries. Even in industrial countries, sewage treatment plants (STPs) have problems in dealing with and eliminating antibiotic agents (Xu et al., 2007; Kümmerer, 2008). In addition, it is suggested that high concentrations of antibiotics in STPs might interrupt the microbiological depletion of pharmaceuticals and other chemical pollutions by inhibiting the proliferation of, or killing, the non-target microbial communities that are required for the biological purification of wastewater (Kümmerer, 2009a). In general, antibiotic agents that are found to pose risks to aquatic systems in industrial countries should not be used in low- and middle-income ones. This suggestion is made because often in these regions there is no monitoring of these compounds and there are probably not enough financial resources available to remediate contaminated sites (Blacksmith Institute and Green Cross, 2011, 2013).

For example, the use of quinolones is restricted in industrial countries because they act as a highly effective group of antibacterial drugs for human infections. They are well-known for their capability to generate cross-resistance and they have the potential to accumulate in sediments because of their low rates of biodegradation. In contrast, in China and Chile these antibiotics are used widely, without any restrictions, in aquaculture (Cabello, 2006).

Table 2: Selection of active antibacterial substances used for veterinary and human purposes (Sarmah et al., 2006; Kemper, 2008; Bergmann et al., 2011)

Class	Compounds	Primary usage	Potential side effects	Eco-toxicological classification [A]
Aminoglycosides				
	Apramycin	Pigs only	Neurotoxic	NA
	Gentamycin	All animals, humans	Nephrotoxic	NA
	Kanamycin	Dogs, pigs, cattle, horses	Ototoxic, nephrotoxic	NA
	Neomycin	All animals		NA
	Sisomycin	Humans only	Ototoxic, nephrotoxic	NA
	Spectinomycin	Pigs, cattle, poultry, sheep		NA
	Streptomycin	Obsolete		NA
ß-Lactams: penicillins				
	Amoxicillin	All animals, humans	Allergic reactions	P
	Ampicillin	All animals		NA
	Azlocillin	Humans		NA
	Benzylpenicillin	All animals		NA
	Cloxacillin	Cattle		NA
	Dicloxacillin	Cattle		NA
	Flucloxacillin	Humans		NA
	Methicillin	Humans		NA
	Mezlocillin	Humans		
	Nafcillin	Humans		NA
	Oxacillin	Cattle		NA
	Piperacillin	Humans		NA
	Phenoxymethylcillin	Humans		NA
	Penicillin G	Humans		

Class	Compounds	Primary usage	Potential side effects	Eco-toxicological classification [A]
Cephalosporines				
	Cefalexin	Dogs	Cross allergic reactions to ß-lactams	NA
	Cefalotin	Humans		NA
	Cefazolin	Humans		NA
	Ceftiofur	Cattle, pigs		
	Cefotaxim	Humans		NA
	Cefotiam	Humans		NA
	Cefquinom	Cattle, pigs		NA
Fenicoles				
	Chloramphenicole	Cats, dogs	Anemia	P
Fluoroquinolones				
	Ciprofloxacin	Humans	Arthropathy in young animals	P
	Enrofloxacin	All animals, aqua-planting (Holmström et al., 2003)		
	Marbofloxacin	All animals		NA
	Flumequin	Humans, aqua-planting (Cabello, 2006)		NA
	Ofloxacin	Humans		
Lincosamides				
	Clindamycin	Dogs, humans	Gastro-intestinal problems	P
	Lincomycin	Pigs, cats, dogs, cattle		P
Macrolides				
	Azithromycin	Humans		
	Clarithromycin	Humans		P
	Erythromycin	Humans, cattle, chicken		P
	Roxithromycin	Humans		NA
	Spiramycin	All animals		NA
	Tylosin	Animals only		
	Vancomycin	Humans		NA
Sulfonamides				
	Sulfanilamide	Humans		NA
	Sulfadimethoxine	Cattle, pigs, chicken		P
	Sulfadimidine	Cattle, sheep, chicken		P
	Sulfamethoxazole	Humans		P
	Sulfapyridine	Pigs		NA
	Sulfathiazole	Humans		NA
Trimethoprim		In combination with sulfonamides		
Tetracyclines				
	Chlortetracycline	Cattle, pigs	Hepatotoxic	P
	Doxycycline	Humans, cats, dogs		P
	Oxytetracycline	Humans, cattle, sheep, pigs, Aqua-planting (Holmström et al., 2003)		P
	Tetracycline	Humans, horse, sheep, pigs		P

A: Declaration if the substance has been assigned to the list of priority substances affecting water organisms as classified by IWW and the GFEA (Bergmann et al., 2011) with
P = high priority substances and
(P) = moderate priority substances.
NA means that these compounds are not prioritized pharmaceuticals or that too little data or no data for prioritization was possible.
MEC_{max} – maximum measured environmental concentration in surface water in Germany, with
= MEC_{max} > 1 µg/L; = MEC_{max} > 0.1 µg/L; = MEC_{max} < 0.01 µg/L.

Antibiotic-resistant bacteria will be most problematic in developing countries where the infectious disease rates are high and newer and more effective antibiotic agents are unaffordable.

Concerning environmental toxicity, the release of antibiotics into the environment can directly affect organisms because of their acute and chronic toxicity. However, primary organisms, such as bacteria, fungi, and microalgae, seem to be more sensitive to exposure to antibiotics compared to vertebrates and invertebrates, because antibiotics were designed to eliminate microorganisms. High environmental concentrations of antibiotics may lead to an interruption of the food web system.

The following are examples of the direct toxicity of antibiotics to aquatic organisms. *Vibrio fisheri* showed significant adverse effects to ciprofloxacin at concentrations of 5000 µg/L (Hernando et al., 2007) and the growth of the microalgae *Microcystis aeruginosa* was inhibited at concentrations lower than 100 µg/L (Halling-Sørensen, 2000). After conducting a 7 day experiment with static concentrations of sulfamethoxazole and levofloxacin ranging from 100 to 1000 µg/L, phytotoxic effects were observed in the water plant *Limna gibba* (Brain et al., 2004).

From the environmental prospective, and according to the data of the IWW and the GFEA, the antibiotics amoxicillin, chloramphenicole, chlortetracycline, ciprofloxacin, clindamycin, doxycycline, erythromycin, oxytetracycline, sulfadimidine, sulfamethoxazole, roxithromycin, and tetracycline were found to be the most relevant ones (Bergmann et al., 2011). For instance, according to the Ecotox Centre, the chronic environmental standard (AA-EQS value) of ciproflaxin is 0.089 µg/L, of erythromycin is 0.04 µg/L, and of sulfamethoxazole is 0.6 µg/L (Ecotox Centre, 2015).

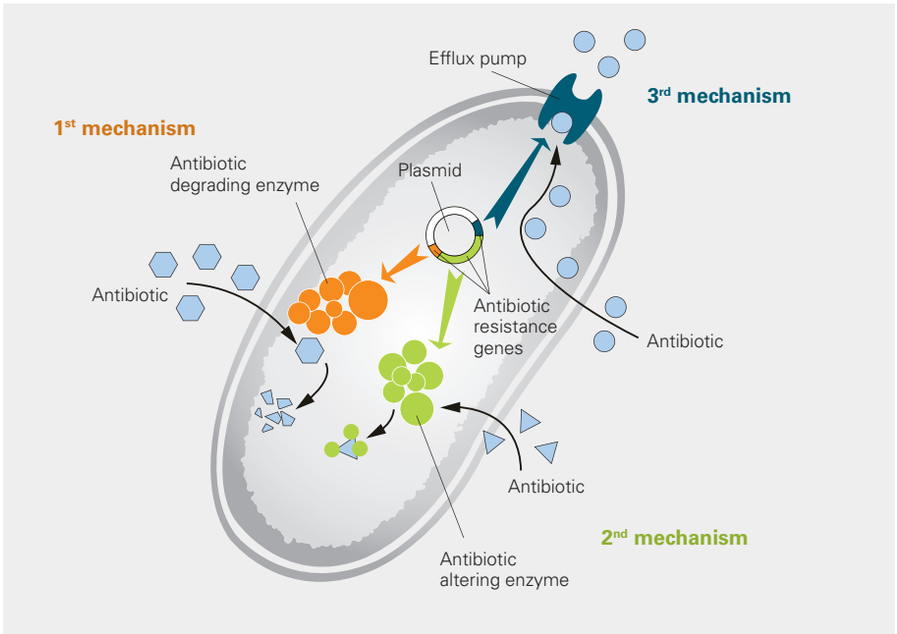

Figure 10: *Three bacterial mechanisms leading to resistance to antibiotics (Byarugaba, 2010)*

Concerning human toxicity, it has been shown that exposure to antibiotics can result in the formation of antibiotic-resistant genes and bacteria strains (Cabello, 2006; Duong et al., 2008; Kümmerer, 2009a; Sosa et al., 2010; Ernst et al., 2012). The formation of antibiotic-resistant bacteria will be most problematic in developing countries where the infectious disease rates are high and people are unable to pay for the newer and more cost intensive antibiotic agents (Kümmerer, 2009a). The formation of antibiotic-resistant bacteria and the interactions between bacterial populations and antibiotics are highly complex processes that are not completely understood (Martinez and Baquero, 2000; Kemper, 2008; Kümmerer, 2008). Nevertheless, it is known that the emergence of antibiotic-resistant bacteria can be induced by different mechanisms. Three of those are presented in Figure 10.

The main mechanisms (the 1st and 2nd mechanism) inducing antibacterial resistance are encoded by plasmids. Plasmids are circular, double stranded DNA molecules including, among other elements, beneficial genetic information that improves the survival of bacteria. This genetic material is transmissible to other bacteria. Expression or suppression of a specific gene *in vivo* can lead to resistance to antibiotics by promoting or inhibiting the production of specific enzymes (Fluit et al., 2001). For instance, for inducing resistance, an enzyme is required that is able to inactivate or degrade the antimicrobial agent by molecular scissioning through hydrolase or other processes (Figure 10, orange pellets, 1st mechanism). In addition, resistance to antibacterial drugs can be prompted by the induction of specific enzymes that are able to either modify and inactivate the antibiotic agent or that inhibit the antimicrobial agent's target receptor (Figure 10, green pellets, 2nd mechanism; Stewart and Costerton, 2001).

Moreover, through changes or inhibition of the bacterial plasma membrane permeability, according to changes in the pore channels or membrane structure, the uptake of antibiotics can be reduced. In addition, antibiotics can be actively pumped out of the cell by transport proteins or so-called efflux pumps (Fluit et al., 2001; Schaechter, 2009; Küster et al., 2013; 3rd mechanism).

In low-income countries, the increased emergence of the resistance of *Salmonella enterica*, subspecies *enterica*, serotype Typhi to the antibacterial agents ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole poses

a risk to human health. This formation of multidrug-resistant typhoid strains is causing increased outbreaks of typhus especially in regions where there are no appropriate health care systems and where newer and more expensive antibiotics are less available (Okeke et al., 2005b). The resistance of *Staphylococcus aureus* to vancomycin and methicillin is another prominent example of the antibiotic resistance of bacteria in the medical sector (Sieradzki et al., 1999). Several known antibiotic-resistant zoonotic bacteria that have the potency to transfer infectious diseases from animals to humans and hence pose risks to human health are shown in Table 3 (Kemper, 2008).

Table 3: Resistances in zoonotic bacteria (Kemper, 2008)

Species	Clinical disease in humans	Possible resistance against	Literature
Escherichia coli	Diarrhea, urinary tract infections, septicemia	ß-Lactams Tetracyclines Streptomycin/ spectinomycin Sulfonamides Cimethoprim Chinolones Chloramphenicoles Gentamycin/Kanamycin/ Neomycin	Angulo et al., 2004; Helmuth et al., 2004
Salmonella spp.	Diarrhea	ß-Lactams Tetracyclines Streptomycin/ Spectinomycin Sulfonamides Cimethoprim Chinolones Chloramphenicole Gentamycin/Kanamycin/ Neomycin	Angulo et al., 2004; Hensel and Helmuth, 2005; Davis et al., 2007
Campylobacter spp.	Diarrhea, neural damage as a sequel	Ciprofloxacin Tetracyclines Doxycycline Erythromycin Trimethoprim Sulfamethoxazole	Luber et al., 2003; Angulo et al., 2004; Bae et al., 2005; Senok et al., 2007

C) Antiviral drugs

Oseltamivir, acyclovir, stavudin, and zidovudine are commonly used antiviral agents. Oseltamivir is the main antiviral agent for the treatment and prophylaxis of pandemic influenzas. Acyclovir is broadly used against herpes simplex virus infections and in the treatment of chickenpox. Another field of application of antiviral drugs is as agents used for the treatment of human immunodeficiency virus (HIV). At present, HIV- affected people are treated mainly with a triple combination antiretroviral therapy – highly active antiretroviral therapy (HAART) – by using a mixture of three antiretroviral classes, like protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and nucleoside reverse transcriptase inhibitors (NRTIs). With the help of these mixtures, it is possible to successfully suppress viral replication for long periods and to reduce the potential for the formation of resistant strains (Baggaley et al., 2010; Wu and Musto, 2011).

Consumption

Reliable data about the production and consumption of antiviral drugs that are used to control and treat pandemic influenzas, such as pig and bird flu and other viral diseases, are not available. In low- and middle-income countries, HIV, which is transmitted through unprotected sexual intercourse or the transfusion of contaminated blood and the sharing of contaminated needles, syringes, or other sharp instruments, is still one of the most dangerous and incurable viral diseases. WHO estimates that worldwide there are about 37 million people living with HIV infections, with approximately 95% of these living in low- and middle-income countries (World Health Organization, 2008, 2015b; Baggaley et al., 2010). Of these, about one-third (9.7 million people) have access to antiretroviral therapy and 1.6 million people are dying annually (World Health Organization, 2015b; United Nations Programme on HIV/AIDS (UNAIDS, 2013). In comparison, in 2009, it was documented that the pandemic influenza H1N1 caused about 12,500 deaths in the US (Shresta et al., 2011). The supply of antiretroviral drugs, especially in low- and middle-income countries, is very important and necessary. Nevertheless, the formation of antiviral drug-resistant strains can pose problems of high concern for the health of humans and other animals. Therefore, more investigation of the development of drug-resistant virus strains is required.

Environmental behavior and occurrence

To date, the environmental behavior and occurrence of antiviral drugs has not been studied sufficiently and controversial information about the degradation of these drugs in WWTPs and in the environment can be found. For instance, there are environmental concerns raised regarding the API oseltamivir, which is used for the treatment and prevention of pandemic influenza.

There is evidence that oseltamivir and its stable metabolites, such as oseltamivir carboxylate, are hardly degradable in normal WWTPs and that it is not degraded substantially by ultraviolet light radiation (Fick et al., 2007; Singer et al., 2007). Thus oseltamivir seems to be quite persistent in the environment and it seems to be hardly removable from water systems even through wastewater treatment. Its physicochemical properties include

high water solubility and it is not volatile as are most pharmaceuticals, but there is evidence that it can be slightly adsorbed by suspended particles, soils, or organic matter (Kümmerer, 2008; Straub, 2009). This persistence might lead to a release and an enrichment of oseltamivir in aquatic environments and favor the formation of drug-resistant virus strains in the environment (Fick et al., 2007; Singer et al., 2007).

The major concern regarding exposure to antivirals is the emergence of drug-resistant viral strains.

In German surface waters, for example, oseltamivir can be found at concentrations ranging from 0.1 to 1 µg/L (Fick et al., 2007; Kümmerer, 2008). There is evidence that this API is probably not as persistent in surface water as was suspected by Singer et al. (2007) and Fick et al. (2007). Straub (2009) and Bartels and von Tümpling Jr, (2008) revealed that in surface water oseltamivir can be degraded through a combination of indirect photolysis and a microorganism-induced biodegradation. There is evidence for the primary biodegradation of oseltamivir in sediments as well.

In addition, according to a monitoring study investigating the occurrence of antivirals in WWTP effluents and river waters in Germany, oseltamivir and other antivirals, such as acyclovir, abacavir, lamivudine, nevirapine, penciclovir, ribavirin, stavudine, and zidovudine, were found in raw wastewater as well. Abacavir, acyclovir, lamivudine, penciclovir, and stavudine concentrations were significantly reduced following wastewater treatment. However, this study did not investigate whether these compounds are degraded biologically by microorganisms or physically removed by adsorption to fecal sludge. In contrast, nevirapine, zidovudine, oseltamivir, and oseltamivir carboxylate concentrations stayed relatively constant, showing similar concentrations in raw wastewater influents and the effluents of WWTPs. So for the latter antivirals, bacterial biodegradation and/or adsorption to fecal sludge seems to be negligible. In river water from Hessian Ried, Germany, maximum concentrations of 0.19 µg/L for acyclovir and 0.17 µg/L for zidovudine were detected (Prasse et al., 2010). In general, knowledge of the environmental behavior, such as the photolytic and biological degradation of antiviral drugs used to treat influenza infections or immune deficiency diseases, are rare. In low- and middle-income countries there is a complete lack of information about the environmental concentrations of antivirals.

Toxicity

To date, the environmental impacts of antivirals on water organisms and aquatic ecosystems have not been comprehensively studied. However, for the API oseltamivir ethylester phosphate, which is available commercially as Tamiflu®, it has been shown that only surface water concentrations at mg/L levels can adversely affect the growth of algae after 96 hours of exposure (*Pseudokirchneriella subcapitata*) and the health of daphnia (*D. magna*) after 48 hours of exposure. A chronic daphnia (*D. magna*) reproduction test of 21 days and a fish early life stage test with *Danio rerio* of 32 days revealed that no toxic effects were observed at the highest tested concentrations (1 mg/L) of oseltamivir ethylester phosphate. Nevertheless, the chronic predicted no-effect concentration of this compound to *D. magna* and *D. rerio* of 0.1 mg/L was investigated (Straub, 2009). There are no proposals yet from the Ecotox Centre for testing other antiviral drugs (Ecotox Centre, 2015), but the chronic environmental standards (AA-EQS) for aquatic environments for the antivirals ribavirin, abacavir, and oseltamivir of 119, 95 and 100 µg/L have been investigated (Straub, 2009; FASS Vårdpersonal, 2014).

The major concern regarding exposure to antivirals is the emergence of drug-resistant viral strains. For example, HIV can replicate very quickly and it has specific mechanisms that are vulnerable to a high rate of mutation. The enzyme responsible for the replication of genetic information in HIV lacks a proofreading mechanism and, in addition, the virus can evolve and recombine at a high rate. These are the reasons why HIV achieves its considerable genetic diversity that enables the formation of strains resistant to antiretrovirals (Baggaley et al., 2010). In addition, the development of resistance to antiviral drugs in general is fostered in regions where there is widespread and unregulated access to antiretroviral medicaments. This is the case in sub-Saharan Africa and other regions that are characterized by war, extreme poverty, and inadequate infrastructure (Harries et al., 2001). Some empirically investigated instances of antiretroviral resistance in several low- and middle-income countries, categorized by drug class and country, are presented in Table 4 (Baggaley et al., 2010). According to this data, the highest resistance to the NRTIs – 11.6 or 12% – was observed in Africa and Thailand. In industrial countries, the occurrence and transmission of antiretroviral drug- resistant virus strains have become a major challenge as well. According to the study of Richman et al. (2004), conducted in the USA, it was estimated that 10 years after access to antiretroviral drugs 76% of the HIV-infected patients carried HIV strains resistant to one or more antiretroviral drugs.

Table 4: Abundance of antiretroviral resistance in low- and middle-income countries (Baggaley et al., 2010)

Region, country	Study	NRTI [%]	PI (primary mutations) [%]	NNRTI [%]
Asia				
India	Hira et al., 2004	6.5	2.5	NI
Korea	Chin et al., 2006	3.8	NI	3.8
China	Jiang et al., 2006	4.2		0
Thailand	Sukasem et al., 2007	12.4	0	0
Africa				
Nigeria	Ojesina et al., 2006	17	NI	NI
Mozambique	Parreira et al., 2006	11.6	NI	NI
Madagascar	Razafindratsimandresy et al., 2006	0	3.5	NI
Burkina Faso	Tebit et al., 2006	2.4	0	4.8
Ethiopia	Kassu et al., 2007	1.1	0	2.2
Latin America				
Brazil	Brindeiro et al., 2003	2.4	2.2	2.1
Argentina	Dilernia et al., 2007	1.4	1.4	2.1
Mexico	Viani et al., 2007	2.5	0	2.5
Russia and Eastern Europe				
Slovenia	Babič et al., 2006	3.9	0	0

NI = no information; NNRTI = non-nucleoside reverse transcriptase inhibitor (antiviral drug Class I); NRTI = nucleoside reverse transcriptase inhibitor (antiviral drug Class II); PI = protease inhibitor (antiviral drug Class III).

D) Beta-blockers

Betaxolol, carazolol, atenolol metoprolol, propranolol, and nadolol are common beta-blockers that are used worldwide.

Consumption

In general, beta-blockers are used to lower blood pressure for the treatment of hypertension and to prevent further attacks in patients who have suffered from heart attacks. Beta-blockers are competitive inhibitors of the beta-adrenergic receptors. The adrenergic system regulates several physiological functions. For example, it controls oxygen need and beating of the heart and it regulates the vasodilatation mechanisms of blood vessels and bronchodilation (Fent et al., 2006). In general, an increase in cardiovascular disease (CVD) burden is expected even in low- and middle-income countries that will stimulate the production and consumption of beta-blocker as well. In 2012, 17.5 million people died from CVDs worldwide and over three quarters of these deaths took place in low- and middle-income countries (World Health Organization, 2015a).

Environmental behavior and occurrence

It has been observed that beta-blockers, especially atenolol (Fent et al., 2006; Etter et al., 2015; Ecotox Centre, 2015), metoprolol (Fent et al., 2006; Bergmann et al., 2011; Ecotox Centre, 2015), propranolol (Fent et al., 2006; Bergmann et al., 2011), and nadolol (Bergmann et al., 2011), have the potential to accumulate in the environment, posing a risk to environmental health. Although beta-blocker have lipophilic characteristics – they should be able to pass the blood-brain barrier (Fent et al., 2006) – and the excretion rate of unchanged metoprolol and propranolol is quite low (not exceeding 10%; Ternes, 1998), these beta-blockers can be found in surface waters. For example, the metabolite of atenolol, atenolol acid, was found in urine samples in Durban, South Africa at concentrations ranging from 280 to 360 µg/L (unpublished data). In addition, effluents from a treatment plant that is connected to the effluents from around 90 bulk drug manufacturers in Hyderabad, India, showed an alarmingly high concentration of metoprolol of between 800 and 950 µg/L, which is an environmental risk level (Larsson et al., 2007). In hospital effluents from the Hangzhou metropolitan area and Linan County, southeast China, atenolol concentrations ranging from 0.05 to 0.3 µg/L were measured. The environmental concentration in the Qiantang River was determined to be below 0.02 µg/L (Chen et al., 2012).

In German surface water, maximum concentrations of propranolol, bisoprolol, and metoprolol of 0.59, 2.9, and 2.2 µg/L, respectively, were detected. Betaxolol and carazolol were found at lower levels of 0.028 µg/L and 0.11 µg/L (Ternes, 1998). In the Lyon area, France, comparable concentrations of bisoprolol, metoprolol, and propranolol of from 0.05 to 2.94 µg/L were measured as well (Miège et al., 2006).

Toxicity

The acute eco-toxicological effects of beta-blockers have not been extensively studied yet except for propranolol, which is observed to be the most toxic beta-blocker. The exposure of *Ceriodaphnia dubia* and *Daphnia magna* to propranolol showed EC50 (48 hour) values of 0.8 and 1.6 mg/L (Huggett et al., 2002; Ferrari et al., 2004), among phytoplankton. The EC50 (96 hour) of the cyanobacteria *Synechococcus leopolensis* was 668 µg/L (Ferrari et al., 2004). According to the data obtained, zoo- and phytoplankton seemed to be more sensitive to beta-blockers than benthos and fish (Fent et al., 2006). However, a chronic exposure of beta-blockers can cause impairments of reproduction and toxic effects to water organisms at environmentally relevant concentrations. For example, long-term exposure to 100 µg/L and 250 µg/L of propranolol caused significant impairments in reproduction to *Hyalella azteca* and *Ceriodaphnia dubia* (Huggett et al., 2002). To arrive at a conclusion about the eco-toxicity of beta-blockers is not yet possible as there is insufficient information, but their negative impact on environmental health is not negligible. According to the quality standards of the Ecotox Centre (2015), even concentrations of propranolol, metoprolol, and atenolol of about 12, 76, and 330µg/L, respectively, are posing acute risks to aquatic organisms given their proposed MAC-EQS values. Their chronic environmental standards (AA-EQS) are 0.16 µg/L, 64 µg/L, and 150 µg/L, respectively (Ecotox Centre, 2015).

E) Hormone preparations and oral contraceptives

Estrone (E_1), 17-beta-estradiole (E_2), and 17-alpha-ethinylestradiole (EE_2), used directly as active compounds or as the metabolized products of the prodrug mestranol by demethylation, belong to the most frequently found and reported hormone compounds in monitoring studies (Sumpter and Jobling, 1995; Ternes et al., 1999; Duong et al., 2010; Chávez et al., 2011; Ernst et al., 2012).

Consumption

Usually, hormone preparations and contraceptives are prescribed and broadly used as oral contraceptives. In some regions, they may be used as steroids to promote reproduction in or growth of livestock, as well (Fan et al., 2007). Global consumption data for these oral contraceptives has not been determined.

Environmental behavior and occurrence

Because of their occurrence in water samples and their high bioactive potential – they act as endocrine disruptors at concentrations of ng/L (Purdom et al., 1994) – these compounds have received noticeable public attention. Because of that they are partially measured and quantified in water systems, even in low- and middle-income countries. For instance, in influents of an activated sludge wastewater works in Darvill, Pietermaritzburg, South Africa, environmental concentrations (arithmetic mean values) of 84 ng E_1/L, 119 ng E_2/L, and 30 ng EE_2/L were measured. In effluents of a wastewater works in Darvill, concentrations of 23 ng E_1/L, 20 ng E_2/L, and 3 ng EE_2/L were measured. In the Umsunduzi River downstream of this wastewater works, concentrations of 8 ng E_1/L, 10 ng E_2/L, and 2 ng EE_2/L were found. Therefore, within this wastewater works, 72 ± 12% ng of E1, 78 ± 12% ng of E_2. and 90 ± 3% ng of EE_2 were eliminated, mainly through biodegradation, but partly through adsorption processes onto sludge particles (Silva et al., 2012; Manickum and John, 2014). Further investigations in the Tula Valley, Mexico, showed environmental concentrations of E_1 ranging from 10.3 to 77 ng/L and of E_2 from 0.2 to 13.1; the concentrations of EE_2 were below the limit of detection (Chávez et al., 2011). In influents of a Brazilian sewage water treatment plant in Penha, Rio de Janeiro, 40 ng E_1/L and 21 ng/L of and E_2 were determined. Of these, 67 to 83% of E_1 and 92 to 99.9% of E_2 were eliminated through the wastewater treatment (Ternes et al., 1999). In wastewater effluents of WWTPs in Italy and Canada, average concentrations of 9 and 3 ng/L of E_1 were measured, respectively. The E_2 concentration in the WWTP effluents in Italy was 1 ng/L and in Canada, 6 ng/L. An EE_2 concentration of 0.45 ng/L was found in the Italian WWTP effluents while in the Canadian ones it was 9 ng/L (Ying et al., 2002).

Although these oral contraceptives were found in water samples, according to their physicochemical properties they have the potential to adsorb to organic material and particles and for bioaccumulation as well. E_1, E_2, and EE_2 have relatively high log K_{ow} values of 3.42, 3.94, and 4.15, indicating their potential to bind to organic matter (Lai et

al., 2000). For example, concentrations of E_1 of 0.17 ng/g, of E_2 ranging from 0.22 to 2.48 ng/g, and of EE_2 ranging from 0.05 to 0.5 ng/g have been found in ocean sediments (Braga et al., 2005).

Toxicity

Within of the scope of the monitoring study of the IWW (Bergmann et al., 2011), EE_2 and E_2 are assigned to the list of high priority substances posing high risks to water organisms because of their high potential as endocrine disruptors (Purdom et al., 1994; Schultz et al., 2003).

These endocrine disruptors are well-known for reducing the fertility and causing feminization of males (Purdom et al., 1994). For example, after treating male rainbow trout with EE_2 concentrations of 10 and 100 ng EE_2/L, embryonic development was impaired by 50% if the sperm of the treated fish was used to fertilize the eggs of untreated rainbow trout. In addition, 1000 ng EE_2/L was deadly for all the test organisms (Schultz et al., 2003). In addition, the laboratory studies of Purdom et al. indicated that low concentrations, of up to 1 ng/L, of EE_2 are able to provoke feminization in male rainbow trout (Purdom et al., 1994). Converse results were found for mollusks. For example, Jobling et al. (2003) found that a 63 day exposure of *Potamopyrgus antipodarum* to about 25 ng EE_2/L stimulated embryo production, while concentrations of about 100 ng/L resulted in inhibiting this stimulation. For *Pimephales promelas*, embryo production was stimulated after the fish was exposed to a concentration of 1 ng EE_2/L and up for 3 weeks. However, exposure to concentrations of 100 ng/L caused spawning to cease. These alterations in reproduction relating to exposure to endocrine disruptive pharmaceuticals are mainly observed in vertebrates and mollusks. They are caused by the disruptors binding to and activating the estrogen receptors (Jobling et al., 2003; Schultz et al., 2003). Additionally, according to the quality values of the Ecotox Centre, chronic exposure to EE_2 of greater than 0.04 ng/L, to E_2 of greater than 0.4 ng/L, and to E_1 of greater than 3.6 ng/L will cause adverse effects to water organisms (Ecotox Centre, 2015).

F) Lipid regulators

The active metabolite clofibrate acid, formed by the transformation of the prodrugs etofibrate, etofyllin clofibrate, and clofibrate, and the active metabolites of the lipid regulators fenofibrate, bezafibrate, and gemifibrozil are found in wastewater, surface water and ground water samples (Fent et al., 2006; Vulliet and Cren-Olivé, 2011).

Consumption

Lipid regulators are applied to reduce cholesterol concentrations in blood plasma. They can be divided into two groups, statins and fibrates. Statins reduce cholesterol synthesis by inhibiting the 3-hydroxymethylglutaril coenzyme A (HMG-CoA) reductase. This decrease in intracellular cholesterol induces the expression of low-density-lipoprotein and consequently leads to resorption of LDL-cholesterol from the blood plasma (Laufs and Liao, 1998). Fibrates are used to decrease the concentrations of cholesterol and triglycerides in blood and they are observed to show anti-inflammatory effects as well (Staels et al., 1998; Fruchart et al., 1999). It is the fibrates that are of particular environmental concern.

Environmental behavior and occurrence

In the surface waters of 18 Brazilian rivers in Rio de Janeiro state, the main metabolites, fenofibric acid and clofibric acid, of the prodrugs fenofibrate, clofibrate, etofibrate, etofyllin clofibrate, and bezafibrate were measured at concentrations of from 0.09 to 0.35 µg/L (Stumpf et al., 1999). Lipid regulators are difficult to remove from wastewater. For instance, with wastewater treatment, from 34 to 51% of clofibric acid and from 46 to 69% of gemifibrozil can be eliminated, thus they have a potential to enrich aquatic environments (Petrovič et al., 2003). In German surface waters, the maximum measured environmental concentration (MEC_{max}) of bezafibrate was above 1 µg/L and the main metabolite (clofibrine acid) of the prodrugs etofibrate, etofyllin clofibrate, and clofibrate was found to be present at a similar level. The $MECs_{max}$ of mecfenobrate and gemifibrozil were likewise measured at the 0.1 µg/L level in German rivers (Bergmann et al., 2011).

Toxicity

In general, data about the toxicity of these lipid regulators are rare. According to the data that were available, the lipid regulator clofibrate seems to show LC_{50} values of from 7.7 to 39.7 mg/L. The fish *Gambusia holbrooki* was affected (LC_{50}) after a 96 hour exposure to 7.7 mg/L of clofibrate (Nunes et al., 2004). According to a water monitoring program for pharmaceuticals in Germany, bezafibrate, a substance classified as having moderate toxic potential for aquatic environments (Bergmann et al., 2011), was found in surface waters with a MEC_{max} above 1 µg/L. The main metabolite (clofibrine acid) of the prodrugs etofibrate, etofyllin clofibrate, and clofibrate was found at similar levels. The $MECs_{max}$ of mecfenobrate and gemifibrozil of 0.1 µg/L were observed in German rivers (Bergmann et al., 2011). Although data about the toxicity

of lipid regulators are rare, the proposed acute and chronic quality criteria values of the Ecotox Centre (2015), the MAC-EQS and AA-EQS, of bezafibrate are available. These values indicate that acute exposure to 76 µg/L and chronic exposure to 0.46 µg/L can cause significant adverse effects in water organisms.

G) Sedatives and antidepressants

Venlafaxin, fluoxetine, fluvoxamine, imipramine, and amitriptyline are commonly used antidepressants.

Consumption

Although there is a lack of information about the supply of antidepressants and the treatment of mental disorders in low- and middle-income countries, the amount used for the treatment of neuropsychiatric disorders will increase over time. This is especially so as there are cheaper generic sedatives and antidepressants now available in low- and middle-income countries, so availability and consumption in these countries will rise as well (Patel, 2007). Patel (2007) showed that mental disorders account for 11 % of all the diseases occurring in low- and middle-income countries. The antidepressant fluoxetine, which was found in the environment, is showing its effect by inhibiting the re-uptake of serotonin. As a result of this inhibition, the serotonin level in the pre-synaptic nerve cleft is increasing, causing a reduction of depression (Fent et al., 2006).

Environmental behavior and occurrence

Even in industrial countries, the occurrence of these pharmaceuticals has not been well studied and there is a lack of data about their eco-toxicological relevance and their potential for geo- and bioaccumulation (Brooks et al., 2003).

In low- and middle-income countries, there is even less data available about the environmental concentrations of antidepressants than there is in high-income countries. The effluents of the huge drug manufacturing area in Patancheru, India, (a major production site of generic drugs) contained the globally highest ever measured amounts of pharmaceuticals (the antibiotic-fluoroquinolone) in industrial effluents – up to 31,000 µg/L (Larsson et al., 2007). There, the antidepressant agent citalopram was measured at concentrations ranging from 770 to 840 µg/L. As a result, it has to be considered that drug factories, especially in low- and middle-income countries, can act as relevant pollution sources for pharmaceuticals as well.

In the context of the IWW water monitoring study of German water systems (Bergmann et al., 2011), no measured environmental concentrations were available for several antidepressant agents, such as alprazolam, amitriptyline, citalopram, fluvoxamine, imipramine, etc. Fluoxetine is one of the most commonly used and investigated antidepressants (Reddy et al., 2007). A concentration of 0.0012 µg/L was detected in river water in the USA (Kolpin et al., 2002) and a concentration of 0.099 µg/L was found in river water in Canada (Metcalfe et al., 2003).

Toxicity

It has been found that these selective serotonin re-uptake inhibitors can elicit endocrine effects in vertebrates as well as invertebrates. Studies with zebrafish showed adverse effects on egg viability at test concentrations of the antidepressant mianserin of 250 µg/L after an exposure of 14 days (van der Ven et al., 2006). With invertebrates, fluvoxamine showed contrary effects. For instance, fluvoxamine at concentrations about 0.032 µg/L, lead to a stimulation of spawning in zebra mussels (Fong, 1998). Furthermore, for some organisms fluoxetine seems to be highly acutely toxic; the EC50 values of a concentration of fluoxetine of 24 µg/L for algae was observed by Brooks et al. (2003). According to the proposed chronic environmental quality standards (AA-EQS), the long-term environmental concentration of the sedative fluoxetine should not exceed 0.012 µg/L (Umweltbundesamt, 2012), that for fluvoxamine should not exceed 0.1 µg/L (FASS Vårdpersonal, 2014), and that for venlafaxine should not exceed 4.8 µg/L (FASS Vårdpersonal, 2014).

H) Anticonvulsants

Carbamazepine, diazepam, and promidone are anti-epileptic drugs that are found in the environment worldwide.

Consumption

In 2007, the following predicted sale volumes of carbamazepine in low- and middle-income countries were estimated: India, 115.5 tonne in total or 102 mg per capita; Brazil, 30.4 tonne in total or 160 mg per capita; Pakistan, 24.9 tonne in total or 151 mg per capita; Russia, 21.3 tonne in total or 151 mg per capita; South Africa, 16.2 tonne in total or 368 mg per capita; Egypt, 15.1 tonne in total or 188 mg per capita; Argentina, 11.8 tonne in total or 293 mg per capita; China, 11.8 tonne in total or 8.8 mg

per capita; Hungary, 11.7 tonne in total or 1175 mg per capita; and Romania, 10.6 tonne in total or 476 mg per capita. In comparison, in high-income countries the figures were: Germany, 72 tonne in total or 874 mg per capita; UK, 51.2 tonne in total or 842 mg per capita; and France, 31.4 tonne in total of 493 mg per capita (Zhang and Geißen, 2010; Barzel, 2013). Anticonvulsants affect the central nervous system by lowering neuronal activity (Fent et al., 2006). The neuronal activity can be decreased by enhancing γ-aminobutyric acid (GABA)-ergic inhibition (diazepam), by blocking the neuronal and glial uptake of GABA, and by fostering an increase of the synaptic GABA concentration through inhibition of GABA-aminotransferase. It can also be decreased by inhibition of the voltage-dependent calcium ions into neurons (Czapinski et al., 2005; Fent et al., 2006).

Environmental behavior and occurrence

Carbamazepine is one of the most abundant pharmaceuticals found in the effluents of STPs or in surface water, although only 1 or 2% of carbamazepine is excreted unchanged by humans (Ternes, 1998; Ferrari et al., 2003). Nevertheless, carbamazepine occurs broadly in aquatic environments mainly because of its high water solubility (carbamazepine has a water solubility of 112 mg/L (Ferrari et al., 2003) while diazepam has a water solubility of 50 mg/L (Yalkowsky and Dannenfelser, 1992)) and its high resistance to biodegradation. For instance, even in STPs almost no elimination of this pharmaceutical is observed. Results show that sometimes the effluents of STPs contained even more carbamazepine than the influents. This can be explained by the transformation of carbamazepine glucuronides and other conjugates to the parent compound during the enzymatic processes during the wastewater treatment (Gros et al., 2010). Other data showed that less than 10% carbamazepine is eliminated in STPs (Zhang and Geißen, 2010).

In the Pearl River system in China, an MEC_{max} of 43.1 ng/L was found for carbamazepine (Zhao et al., 2010). In Indian river waters, the MEC_{max} of carbamazepine was 128 ng/L (Ramaswamy et al., 2011). In North America (Canada and the USA), the environmental average concentrations of carbamazepine ranged from 2.5 to 166 ng/L, and the MEC_{max} was 1500 ng/L (Cunningham et al., 2010). In Europe, the average carbamazepine concentrations of between 1.1 and 410 ng/L were identified in surface waters and the MEC_{max} was 7100 ng/L (Cunningham et al., 2010).

Toxicity

There is significant evidence that anti-epileptic agents can have adverse effects on water organisms. For instance, Pascoe et al. showed that a concentration of anti-epileptic agents of 0.010 mg/L inhibited polyp regeneration in the cnidarian *Hydra vulgaris* (Pascoe et al., 2003). However, for several other organisms the effect concentrations are outside the range of environmental concentrations. For instance, a motility test of *Daphnia magna* showed EC_{50} (48 hour) values of around 13.8 mg/L after exposure to carbamazepine (Ferrari et al., 2003). Some fish species seem to be relatively sensitive to carbamazepine. It was found that the LC_{50} (24 hour) for *Cyprinus carpio* was 50.70 mg/L (Malarvizhi et al., 2012). In rainbow trout and common carps, a concentration of carbamazepine of 1000 mg/L caused significant adverse effects to the liver, The malfunctions caused by exposure to the pharmaceuticals diclofenac and metoprolol were more pronounced than those caused by carbamazepine and clofibrate (Schwaiger et al., 2004). During a comprehensive sediment study, the midge *Chironomus riparius* was found to be very sensitive to carbamazepine showing EC_{10} values of 0.07–0.21 mg/kg dry weight. In contrast, other species, such as the oligochaete *Lumbriculus variegatus* and the freshwater snail *Potamopyrgus antipodarum*, were not affected at the tested concentrations (0.625–10 mg/kg dry weight *L. variegatus*; 0.4–250 mg/L *P. antipodarum*; Oetken et al., 2005). In summary, apart from some specific organisms, carbamazepine is characterized as low acute toxic to aquatic organisms (Oetken et al., 2005). Along these lines, the proposed acute environmental quality standard (MAC-EQS) of the Ecotox Centre for carbamazepine of 2.550 mg/L is relatively high (Ecotox Centre, 2015). Nevertheless, the exposure of aquatic ecosystems to carbamazepine in the long term can have adverse effects on water organisms as well and this is indicated by the low chronic environmental standard of 0.0005 mg/L.

I) Cytostatic cancer therapeutics

Cyclophosphamide, ifosfamide, methotrexate, cisplatin, 5-fluorouracil, etoposide, doxorubicin, and doxorubicinol are agents often used in the chemotherapy treatment of cancer. These therapeutics work by impairing cell proliferation, particularly of fast growing tumor cells (Fent et al., 2006; Matthies, 2008).

Consumption

Some cytostatics, such as cyclophosphamide and ifosfamide, reduce the growth and inhibit the division of tumor cells and other fast growing cells through the alkylation of DNA. According to the IMS Institute (IMS Institute for Healthcare Informatics, 2012), anticancer drugs lead the market with sales of US$83–88 billion. Since generics of several of these pharmaceuticals are available, the spending on medicines in the so-called 'pharmerging' countries (Russia, Brazil, China, and India) has increased. The IMS Institute (IMS Institute for Healthcare Informatics, 2012) has shown that of 22 new anticancer drugs, between 18% and 46% were available in China, India, Brazil, and Russia (ascending order of availability).

Environmental behavior and occurrence

In aquatic environmental samples, the cytostatics cyclophosfamide, ifosfamid, and methotrexate seem to be the most representative ones. Yin et al. (2010) conducted the first monitoring study of cytostatic drugs in hospital effluents in China (Beijing). They detected the highest concentrations of cyclophosfamide, ifosfamide, and methotrexate – ranging from 4 to 10,647 ng/L – with cyclophosfamide and ifosfamide being found most frequently. Methotrexate, etoposide, and azathioprine were less abundant at maximal measured concentrations of 4689, 380, and 38 ng/L, respectively. They are mostly found in the effluents of hospitals at low levels – between ng/L to µg/L. This was certainly the case in the effluents of German hospitals (Heberer, 2002). In the surface water of a lake in Switzerland, they were found at concentrations ranging from 0.05 to 0.17 ng/L. However, in general, there is a dearth of data about the occurrence of cytostatic agents, especially in surface waters or sediments (Heberer, 2002; Buerge et al., 2006; Zounková et al., 2007; Yin et al., 2010).

According to the investigations of Buerge et al. (2006), cytostatic drugs seem to have persistent characteristics. For example, under dark conditions the half-life of cyclophosphamide was 80 days and that of ifosfamide was 620 days. The transformation of cytostatics by photo-oxidation cannot be excluded, though this process seems to be relevant only in regions of clear, shallow water. Experiments with active sludge revealed that no transformation of cytostatics was observed within 24 hours at test concentrations of about 100 ng/L.

Toxicity

The concentrations measured in the aquatic environment are several orders of magnitude lower than the concentrations posing risk (showing acute toxic effects) to aquatic organisms (Yin et al., 2010). Although they are used as anticancer drugs to treat bronchial, breast, and ovarian cancer, lymphomas and leukemia or to treat auto-immune diseases, they are able to promote cancer at certain concentrations. They are well-known for their mutagenic and embryo-toxic characteristics and for inhibiting cell proliferation (Heberer, 2002; Buerge et al., 2006; Yin et al., 2010). For instance, exposure of the ciliate *Tetrahymena pyriformis* to methotrexate showed an EC_{50} (48 hour) value of 45 mg/L (Henschel et al., 1997). Disorders in fish embryo development were observed at concentrations around 85 mg/L (EC_{50}, 48 hour; Henschel et al., 1997). Zounková et al. (2007) conducted a comprehensive toxicity study using five cytostatics (cyclophosfamide, cisplatin, 5-fluorouracil, doxorubicin, and etoposide). They found that cisplatin and 5-fluorouracil were the most toxic to the bacteria *Pseudomonas putida* and the algae *Pseudokirchneriella subcapitata*, showing LOECs between 0.01 and 1 mg/L. Cyclophosfamide showed values of between 500 and 1000 mg/L (Zounková et al., 2007). Although the concentrations of the cytostatics found in the environment are lower than the concentrations that are causing adverse effects to water organisms, their occurrence and their impact on the environment and on water organism should not be ignored. The use of these agents is still increasing given the constant improvements in living standards and the increase in the number of cancer patients worldwide. These compounds are known to have high bioactive potential and we lack information about their chronic toxicity and the environmental distribution pattern of these agents (Buerge et al., 2006; Zounková et al., 2007; Yin et al., 2010). The chronic environmental standard found for the cytostatic cancer drug doxorubicin is 0.01 mg/L (FASS Vårdpersonal, 2014), that for ifosfamide is 2 mg/L (Bergmann et al., 2011), and that for cyclophosphamide is 20 mg/L (Bergmann et al., 2011).

J) X-ray contrast medium

Iopamidol, iobitridol, iomeprol, iopromide, iohexol, diatrizoate, and ioxithalamic acid are a selection of iodinated x-ray contrast media which are broadly used.

Consumption

These agents are used frequently and with high doses (up to 200 g per person (Steger-Hartmann et al., 1999)

as diagnostic agents, especially in hospitals (for computed tomography or x-ray images and magnetic resonance imaging or radiological surgeries). These media improve the contrast between organs or vessels and tissues during x-ray radiography and facilitate visualization and observation of morphological alterations on organ tissues (Steger-Hartmann et al., 1999; Heberer, 2002; Bergmann et al., 2011; Ernst et al., 2012). These agents can be differentiated into ionic (diatrizoate, iothalamic acid, and ioxithalamic acid) and non-ionic (iopamidol, iopromide and iomeproll) contrast media (Ternes and Hirsch, 2000). In all countries with a developed health care system – mainly in emerging and developed countries – the residuals of x-ray contrast media can be found in wastewaters, effluents of STPs, surface water, and ground water.

Environmental behavior and occurrence

X-ray contrast media are specifically designed to be stable against chemical and biological degradation and, because of this, x-ray contrast media are not metabolized after uptake by humans. They are excreted as the parent compound, primarily in urine. This stability of the x-ray contrast media enables it to maintain the efficiency of the diagnostic analysis following application of the x-ray contrast media. Additionally, given their stability, the formation of toxic transformation products is avoided (Ternes and Hirsch, 2000; Kümmerer, 2009b).

Accordingly, these agents are negligibly, or not at all, degraded by bacterial processes or adsorbed to sewage sludge during wastewater treatment or when exposed in surface waters. This is because of their high persistence, high water solubility, and their low lipophilicity (for instance, iopromide has a K_{ow} of $4.7*10^{-3}$; Steger-Hartmann et al., 1999). It has been found in raw domestic wastewater in Atlanta, South Africa, that the maximal concentration of iopromide was 0.09 µg/L. In the VUNA project (Eawag: The Swiss Federal Institute of Aquatic Science and Technology and eThekwini Water and Sanitation (EWS), 2013) a concentration of 97 µg/L iobitridol was found in urine samples in Durban, South Africa. In Gaobeidian, China, effluents of a STP contained about 2 µg/L iopamidol (middle value), 1.5 µg/L diatrizoate, and about 0.2–0.3 µg/L iopromide and iohexol. Analogous values, with magnitudes of µg/L, were found in industrial countries such as Germany and Switzerland (Ternes and Hirsch, 2000; Buerge et al., 2006; Ernst et al., 2012). In addition, in WWTPs in Hesse, Germany, no degradation of x-ray contrast media was observed (Ternes and Hirsch, 2000). Because of that, x-ray contrast media are well-known for their high persistence in aquatic systems (Heberer, 2002; Kümmerer, 2008).

Toxicity

Steger-Hartmann et al. (1999) conducted a comprehensive study on the eco-toxicological behavior of the x-ray contrast medium iopromide. They discovered that iopromide presented no acute toxic effects to the bacteria *Vibrio fisheri*, *Pseudomonas putida*, the algae *Scenedesmus subspicatus*, the crustacean *Daphnia magna*, or the fish *Danio rerio* and *Leuciscus idus* at the highest test concentration of 1 g/L. In addition, *Daphnia magna* showed no chronic toxic effects after long-term exposure to 1 g iopromide/L. Toxicity tests with mammals, which were conducted during the development of the pharmaceutical iopromide, showed no adverse effects on reproduction or any genotoxic effect (Schöbel and Günzel, 1993). According to the environmental risk assessment study of Steger-Hartmann et al. (1999), x-ray contrast media, like iopromide, do not pose any risk to the aquatic environment. Given their high persistence, however, and the lack of knowledge of their ability to cause sublethal effects (Ternes and Hirsch, 2000), environmental assessments are still required. Nevertheless, the chronic environmental standard of 1000 µg/L for the x-ray contrast media iohexol (Bergmann et al., 2011) and iomeprol (FASS Vårdpersonal, 2014) have been proposed.

Input pathways of pharmaceuticals

The possible entry pathways of APIs are outlined in Figure 11. For example, APIs can be released into the environment directly at pharmaceutical production plants, mainly through the release of industrial wastewater effluents. The APIs of pharmaceuticals for veterinary purposes – to treat animal diseases or as food additives to promote growth at aquaculture farms (Cabello, 2006) or animal husbandries – can enter the environment via excretion (Sarmah et al., 2006). In addition, after human uptake, the excreted pharmaceuticals from private households or hospitals can enter the municipal wastewater system via urine or feces, with most of the APIs excreted unchanged (Holm et al., 1995; Hirsch et al., 1999; Duong et al., 2008; Kümmerer, 2009b). If industrial or municipal wastewaters are processed by STPs, the non-degradable APIs are released into the surface water (Gros et al., 2007; Togola and Budzinski, 2008; Voigt and Bruggemann, 2008; Ernst et al., 2012; Köck-Schulmeyer et al., 2013). If no WWTPs are available, which is more likely to be the case

in low- and middle-income countries, all the APIs from these wastewaters are directly released into the surface water (Rehman et al., 2015). If sewage sludge or excreta from animals is used as manure in agriculture or the contaminated surface water is used for irrigation, which is often the case in low- and middle-income countries (Heeb et al., 2012; Rehman et al., 2015), APIs can further accumulate in the soil. Alternatively, they can enter surface waters as surface runoff after rain events or they can leach into groundwater aquifers (Rehman et al., 2015). If unused medicaments are flushed down the toilet (this pathway is not presented in Figure 11) they are released into the municipal wastewater system (Kümmerer, 2009b). If expired or unused pharmaceuticals are disposed of as domestic waste in landfills they could leach into groundwater systems as well (Holm et al., 1995; Heberer, 2002).

Given their persistence, their continuous consumption, and the large amounts used, many APIs have the potential to remain and to accumulate in the environment.

As a result, given their persistence (even after wastewater treatment), their continuous consumption, and the large amounts used, many APIs have the potential to remain and to accumulate in the environment (Gros et al., 2007; Togola and Budzinski, 2008; Voigt and Bruggemann, 2008; Zhang et al., 2008; Fatta-Kassinos et al., 2011; Ernst et al., 2012; Kirrolia and Nehra, 2012; Köck-Schulmeyer et al., 2013). In general, the excretion of pharmaceuticals by humans or other animals and the use of contaminated sewage sludge and feces of animals as manure are the main inputs of pharmaceuticals' into the environment. Pharmaceuticals' loads in industrial effluents can be very high as well. However, in general, industrial pollution is very local.

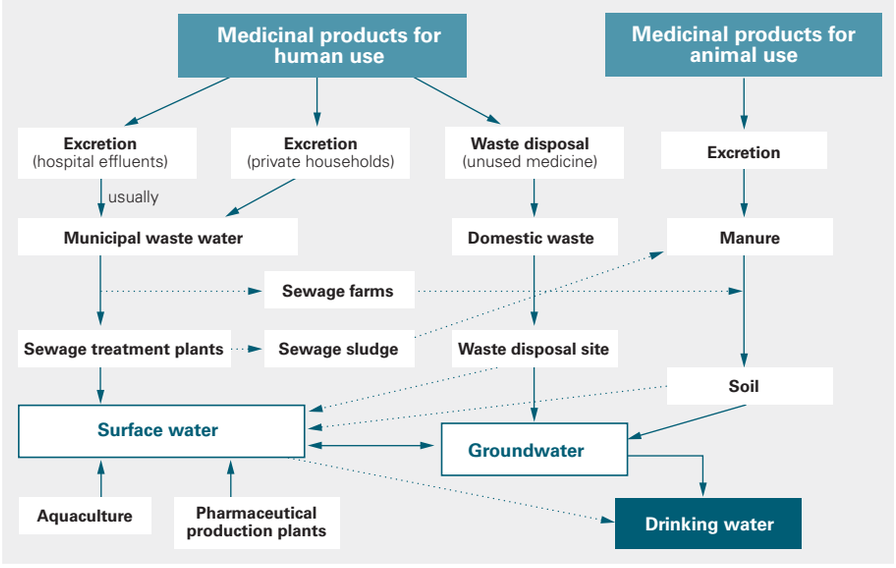

***Figure 11**: Entry routes for human and veterinary pharmaceuticals into the aquatic environment (Heberer, 2002)*

Use of pharmaceuticals and pollution trends and impacts

Data availability

Currently, there is a scarcity of data about the production, sales, and consumption of pharmaceuticals. There are almost no comprehensive systematic data available, especially, for the non-OECD countries. Where such data about pharmaceuticals have been compiled using marketing survey studies and industry intelligence, mostly only the urban regions were covered and small-scale and retail enterprises were left out. In addition, there is a lack of transparency about these data and limited public access (Dickens, 2011). The Institute for Healthcare Informatics (IMS Institute), a leading pharmaceutical consulting company, and the consulting company PricewaterhouseCoopers AG (PWC) are focusing on collecting data about pharmaceuticals. They are endeavoring to forecast future behavior changes in pharmaceutical sales and production from a global perspective. But mostly these data are not publicly available or the data about specific pharmaceuticals has to be purchased (IMS Institute for Healthcare Informatics, 2012; PricewaterhouseCoopers, 2012).

Future trends and hot spots

The data introduced by PricewaterhouseCoopers (Figure 12; PricewaterhouseCoopers, 2012; and the IMS Institute (Figure 13) are in accordance with each other. Both are showing an increasing trend in global spending on pharmaceuticals. IMS Institute is showing an increase of from US$658 billion to $1,205 billion from 2006 to 2016, while PWC predicts an increase from US$1,084 billion in 2011 to US$1,571 billion in 2020. Both predict a declining trend for the spending in the EU, while the spending in Canada and Japan will remain almost constant in future. In addition, there will be increased spending on pharmaceuticals in the USA and, especially, in the pharmerging countries – China, Brazil, Russia, and India – and the fast followers – Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan, and Vietnam. According to the IMS Institute, pharmerging countries are defined as those with more than US$1 billion in absolute spending growth between 2012 and 2016 and with a gross domestic product per capita of less than $25,000 at purchasing power parity. These criteria essentially define low- and middle-income countries. Between 2011 and 2016, sales of pharmaceuticals in the pharmerging countries are calculated to increase from US$191 billion to US$362 billion, according to the IMS Institute data. The PWC data indicate a possible increase from

US$205 billion to US$500 billion between 2011 and 2020 (IMS Institute for Healthcare Informatics, 2012; PricewaterhouseCoopers, 2012). These increases in spending will arise for several reasons. Since the economic crisis of 2007, there has been a shift of the industry from high-income countries to low- and middle-income ones (United Nations Environment Programme, 2013c), which will lead to an increase in sales of pharmaceutical products in these countries. Furthermore, PWC and the IMS Institut forecast that the production of generics will increase extensively in pharmerging countries. This process will be stimulated given that the patents of several widely used pharmaceuticals are due to expire. Consequently, there will be a increased manufacture of, and spending on, cheaper generics taking place mainly in low- and middle-income countries. The IMS Institute showed that the increase in spending on pharmaceuticals in pharmerging countries is mainly the result of the increased production of generic drugs. Besides the shift of the pharmaceutical production and the added production of generics in low- and middle-income countries, demographic changes can have effects on the spending on medicines as well. For instance, the global extended life expectancy and the one-child policy in China are promoting the aging population phenomena, leading to an increase in the average age of a population, even in low- and middle-income countries. In addition, the increasing growth rate of the world's population, especially in low- and middle-income countries, will further increase the demand for pharmaceuticals worldwide (The World Bank Group, 2001). Moreover, the middle class will expand worldwide resulting in improved living standards, infrastructure, and development in general. The percentage of the population having an income ranging from US$6000 to US$30,000 purchasing power parity is predicted to further increase (PricewaterhouseCoopers, 2012). The conclusion to be drawn is that this increase in demand, improvement in living standards, and the enhanced production of pharmaceuticals in low- and middle-income countries will improve health care systems. These changes, in turn, will increase the availability of pharmaceuticals in these countries, which will lead to an intensification of the release of pharmaceuticals into the environment though production processes and excretion by humans or animals following their use (IMS Institute for Healthcare Informatics, 2012; PricewaterhouseCoopers, 2012).

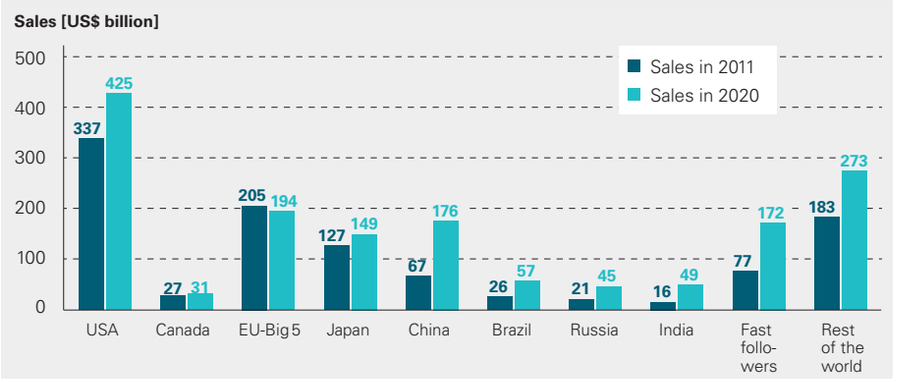

Figure 12: *Sales of pharmaceuticals in US$ billion at constant exchange rates in several countries (PricewaterhouseCoopers, 2012). Total sales in 2011 were US$1,084 billion and in 2020 are predicted to be US$1,571 billion. The EU Big 5 are France, Germany, Italy, Spain, and the UK. The fast followers include Argentina, Egypt, Indonesia, Mexico, Pakistan, Poland, Romania, South Africa, Thailand, Turkey, Ukraine, Venezuela and Vietnam.*

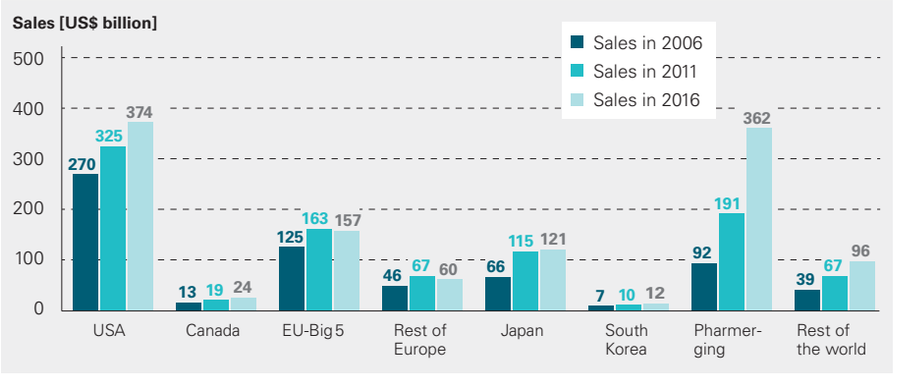

Figure 13: *Sales of pharmaceuticals in US$ billion with variable exchange rates in several countries (IMS Institute for Healthcare Informatics, 2012). Total sales in 2006 were US$658 billion, in 2011 US$956 billion, and in 2016 are predicted to be US$1,205 billion. The EU Big 5 are France, Germany, Italy, Spain and the UK. The pharmerging countries are China, Brazil, Russia, India, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan, and Vietnam.*

Pharmaceuticals for veterinary treatment

Currently, there is almost no information available about the consumption patterns and amounts of pharmaceuticals – antibiotics, anti-inflammatory drugs, or steroids – used for animal treatment. Nowadays, the use of pharmaceuticals to treat diseases in animal husbandry and aqua-farming is inevitable (Sarmah et al., 2006). Each year, high volumes of these drugs are used in veterinary treatments, especially since these pharmaceuticals are relatively cheap. They are traded worldwide and many of these agents are available as generic drugs. Looking at the volume of chicken, cattle, and pig meat produced in each region may give some indirect insights about those regions where environmental and human health is endangered as a result of the increased exposure to veterinary pharmaceuticals. These agents are released through excretion into the environment without any treatment and leach and accumulate in soils and drinking water reservoirs. According to the data on meat production from FAOSTAT (Food and Agriculture Organization, 2013)

and illustrated in Figure 14, the demand for veterinary pharmaceuticals in low- and middle-income countries is highest in China, followed by Brazil, Russia, Mexico, Argentina, Vietnam, and India (in descending order). By considering the tonnes of chicken, cattle, and pig meat produced per 1000 ha of arable land, which is shown in Figure 15, the highest meat production areas in low- and middle-income countries are Djibouti, Malaysia, Lebanon, St. Lucia, Jordan, Colombia, Costa Rica, Seychelles, Jamaica, Kiribati, Occupied Palestinian Territory, Ecuador, Dominican Republic, Samoa, and China (in descending order).

Given the high meat production, especially in these regions, continuous monitoring of the movement of veterinary drugs into the environmental compartments is strongly recommended. However, other regions may be adversely exposed to veterinary pharmaceuticals as well. This cannot be specified more precisely given the data available and with the resolution of the data obtained. One example where environmental health was endangered after exposure of the environment to veterinary pharmaceuticals occurred in two regions, in India and in Pakistan. There, the vulture population declined drastically because of renal failure caused by ingesting the carcasses of diclofenac-treated animals (Oaks et al., 2004).

Moreover, in a cooperative, interdisciplinary project involving the German Federal Environmental Agency, the IWW Water Centre and adelphi (Weber et al., 2014), worldwide data on the maximum environmental concentrations (MEC_{max}) measured were compiled. This

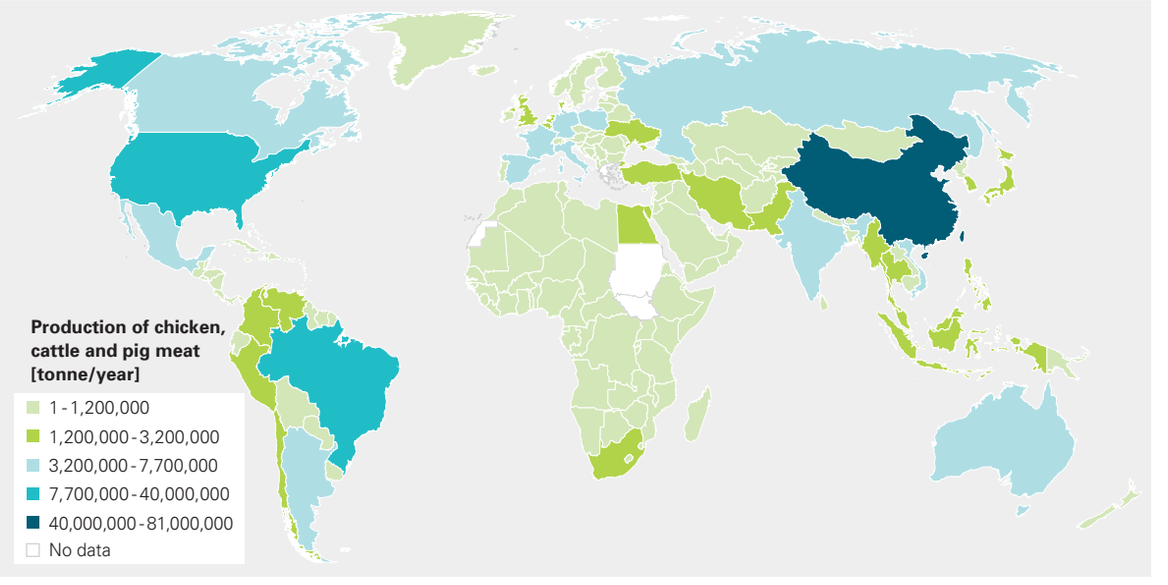

Figure 14: *Summary of the amount of chicken, cattle, and pig meat produced on average between 2006 and 2010. The range is from 1 to 81 million tonne of meat/year (Food and Agriculture Organization, 2013)*

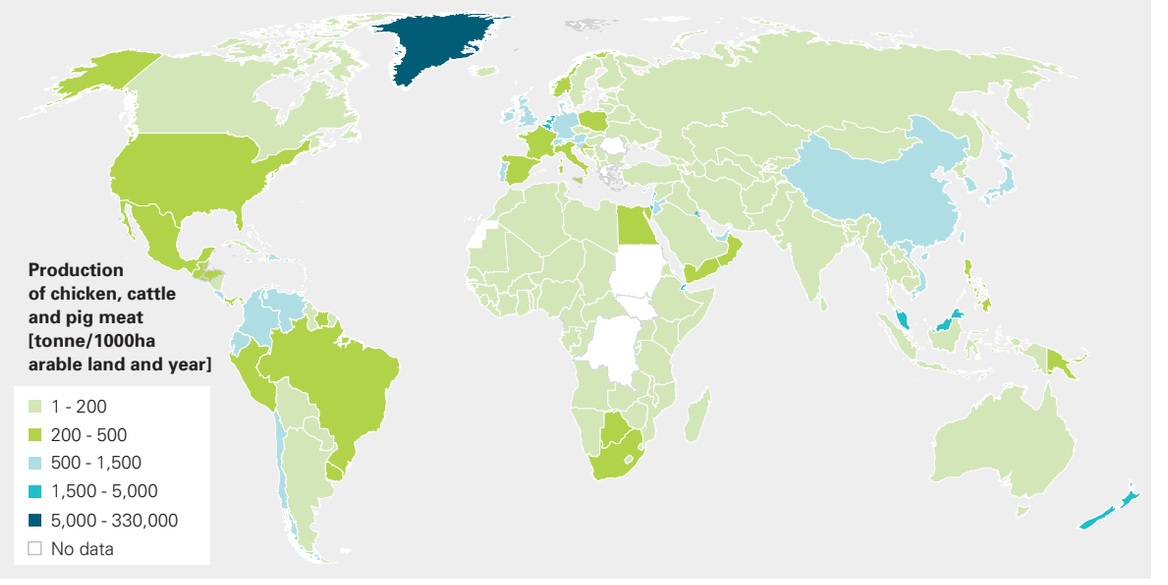

Figure 15: *Summary of the average amount of chicken, cattle, and pig meat produced per 1000 ha of arable land between 2006 and 2010. The range is from 1 to 33 thousand tonne of meat/1000 ha of arable land/year (Food and Agriculture Organization, 2013)*

was undertaken to indicate high risk areas where pharmaceuticals released into the environment may affect human and environmental health. One, not yet finished, example of a collection of measured environmental concentrations is shown in Figure 16 (Weber et al., 2014). According to previous data, the $MECs_{max}$ of diclofenac were measured in low- and middle-income countries like Ukraine, Greece, Pakistan, and Côte d'Ivoire, where concentrations greater than 1 µg/L were detected. In Brazil, Costa Rica, South Africa, Jordan, China, and Malaysia, concentrations ranging from 0.1 to 1 µg/L were found. These values indicate that even in low- and middle-income countries the monitoring of environmental concentrations of pharmaceuticals is highly relevant. This monitoring is relevant, first because of the high concentrations found in these regions and second because of the lack of data on this issue, especially in low- and middle-income countries.

To get a better overview of the global distribution of pharmaceutical industries, the locations of pharmaceutical companies, associations, and pharmaceutical production places were identified using Google Maps and illustrated in Figure 17. These data, although they have to be treated with caution, indicate that high levels of activity are suspected in the low- and middle-income countries of north and west Latin America, west, east and south Africa, India, east and west China, and Indonesia.

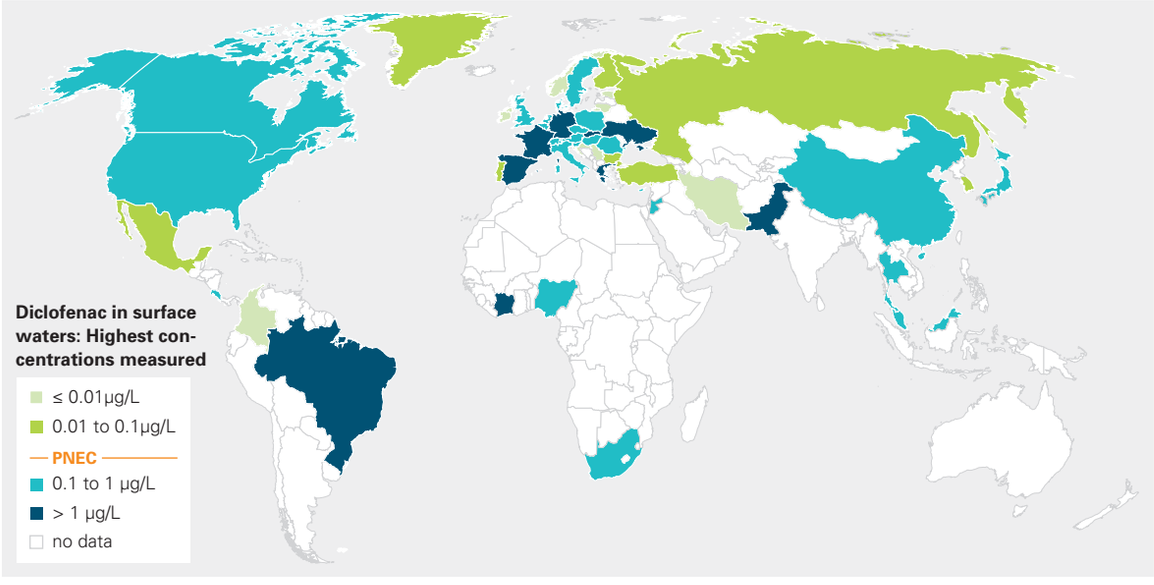

Figure 16: *Environmental concentrations of the analgesic diclofenac in different UN regions; (Weber et al., 2014)*

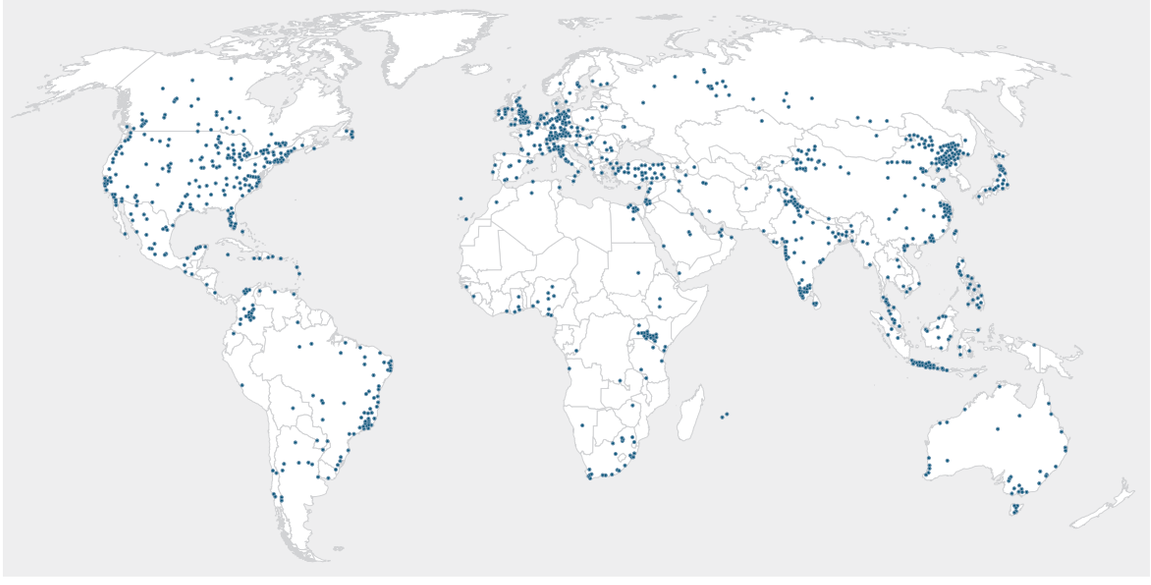

Figure 17: *Google map of places connected with pharmaceuticals and pharmaceutical companies*

Issues of special concern

In general, the excretion of pharmaceuticals used for the treatment of human and veterinary diseases is supposed to be the main pathway for the release of pharmaceuticals into the environment. However, it has to be considered that, especially in low- and middle-income countries the effluents of pharmaceutical manufactories can be relevant point sources of APIs. These latter also show the highest environmental concentrations worldwide. In these regions, there is little or no legislation for sound waste management. There are no regulations governing the maximum concentrations of APIs that are allowed to be present in the effluents of industries and WWTPs. There are no monitoring programs for checking the occurrence of APIs in drinking water and river systems. Often the inspections, if available, are failing and the use of sustainable and environmentally-friendly methods is not guaranteed. The legacies of obsolete, closed factories and the use of landfills for disposal pose risks to environmental and human health. If pharmaceuticals are produced for the global market, as in an example from Brazil, an internationally shared responsibility for producing more environmentally-friendly APIs is necessary.

Diclofenac endangers vulture population in India and Pakistan

As already mentioned in chapters above, one prime example where exposure to pharmaceuticals has had disastrous consequences to environmental health is presented in the Indian and Pakistani regions, where several vulture populations were endangered because of the anti-inflammatory agent diclofenac. Oaks et al. (2004) determined that the renal failure found in vultures was directly correlated with the diclofenac residues found in carcasses of veterinary treated livestock. This indicates that although most of the pharmaceuticals are supposed to be polar and, therefore, should be excreted easily from the body, some of them show the potential for bioaccumulation within the food web system. This results in an enrichment of these compounds per trophic level, posing risk to environmental health, especially to the end consumers of the food web, the raptors and other predators.

Pharmaceutical manufacturing in India

Another example is that pharmaceuticals are not only released into the environment primarily through the excreta of medically treated humans and animals but also by inappropriate disposal of expired medicines – by flushing them down the toilet. In addition, wastewater effluents of manufacturing plants can channel large volumes of pharmaceuticals into aquatic systems. APIs can leach into soils and water aquifers at dumping sites close to production facilities (Larsson, 2010). For instance, Larsson et al. (2007) investigated the effluents of the WWTP in Patancheru near Hyderabad, India. Patancheru Enviro Tech Ltd. (PETL) is posing a risk to environmental and human health. PETL is treating the waste of approximately 90 bulk drug manufacturers. Each day, about 150 trucks of wastewater are delivered to PETL representing a volume of about 1500 m^3. This WWTP is able to deplete about 77% of the organic material contained in the industrial wastewater (measured as the biological and chemical oxygen demands) and about 50% of the total dissolved solids and total suspended solids. The efficiency and the capacity of PETL is not high enough to treat the volume of wastewater received. Larsson et al. (2007) ranked the top 11 APIs found in the effluents of the WWTP. These effluents contained the highest concentrations of APIs measured in any effluent worldwide. For example, the maximum concentrations of the antibiotics ciprofloxacin, and enrofloxycin (fluoroquinolone group) were found to be about 31,000 and 900 µg/L. The beta-blocker metoprolol was measured at concentrations up to 950 µg/L.

The concentrations of ciprofloxacin are so high that the maximum therapeutic dose for humans would be exceeded by ingesting 1 L of this water. The concentration is three to four times higher than that which was toxic to the water plant *Lemna minor* and the cyanobacteria *Microcystis aeruginosa*. An additional problem arises through the inappropriate dumping of untreated wastewater (Gurunadha Rao et al., 2001; Larsson et al., 2007). In two lakes in this area, which are not connected to the effluents of PETL, high amounts of ciprofloxacin – up to 6.5 mg/L – were found. These high concentrations may result from leakages of untreated wastewater from the dumping sites (Larsson, 2010). Many of these APIs (mostly generics), which are produced in Patancheru, are distributed worldwide and included in products sold by other pharmaceutical companies in industrial countries as well. Aside from these findings in India, elevated concentrations of APIs in effluents were found in the effluents of other drug companies in China and Brazil as well (Li et al., 2008a; Deschamps et al., 2012).

Pharmaceutical manufacturing in China

The Shanghai Environmental Department has compiled a blacklist of 721 companies. Of these, 374 companies are not applying approved environmental procedures or are failing inspections. It was found that 159 companies were contravening the water pollution prevention rules (Chi-

naCSR, 2010). For instance, Li et al. (2008a) found concentrations up to 920 mg/L of oxytetracycline (OTC) in influents and 19.5 mg/L in effluents of a WWTP in North China in Hebei Province. This tetracycline derivate is an antibiotic mainly used for aquaculture and livestock to promote growth. In the surface water of the Xiao River downstream of the WWTP, a maximum concentration of OTC of 712 µg/L was detected. In 2007, about 117 pharmaceutical production plants were forced to close down their facilities until they had improved significantly their facilities and made them more environmentally friendly (China Daily, 2007). According to the Blacksmith Institute's The World's Worst Toxic Pollution Problems: Report 2011, obsolete factories (of both pharmaceutical and other industrial manufacturers) are posing risks to human and environmental health. This is because often, especially in low- and middle-income countries, there is no capacity to remove these legacy structures or nobody feels responsible for their removal (Blacksmith Institute and Green Cross, 2011).

Pharmaceutical manufacturing in Brazil

Deschamps et al. (2012) revealed that pharmaceutical companies in the state of Minas Gerais, Brazil, release their water into the environment without any treatment. At present, there is no legislation in Brazil that controls exposure of the environment to micro-pollutants and pharmaceuticals. (Even in high-income countries there are no critical values implemented for pharmaceuticals in the environment). Moreover, it was brought to light that several companies do not rigorously manage their waste disposal as untreated waste was dumped in landfills and garbage dumps. Primarily, the Brazilian companies are producing commodities for domestic use in contrast to the industrial park area in Patancheru, India, where APIs for the domestic and the global market are produced (Larsson et al., 2007; Deschamps et al., 2012).

Best practices

The impact of pharmaceuticals released into the environment is an emerging issue, especially since general environmental consciousness is rising and better techniques for measuring environmental concentrations have been developed. More attention is being paid to this topic. At the moment, there are several initiatives and programs running with a focus on reducing the emission of pharmaceuticals into the environment and monitoring pharmaceuticals in WWTP effluents, surface water, and drinking water. However, to assess the risks these compounds pose to the environment, especially in low-and middle-income countries, more efforts are required. Examples, some theoretical and others already implemented, of how to reduce the impacts of pharmaceuticals on the environment, which are feasible for low- and middle-income countries, are mentioned below.

Implemented examples

Changes in regulations

Fortunately, during the last decade since the convening of the Johannesburg Plan of Implementation (United Nations, 2002) and Agenda 21 (United Nations, 1992), more commitments to ensure the sound management of chemicals and hazardous wastes have been made. These should enforce more sustainable development and protect human and environmental health. The goal of this implementation is to ensure that, by the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on environmental and human health, using transparent science-based risk assessment approaches and risk management procedures to support developing countries in strengthening their capacity for sound management of chemicals and hazardous wastes by providing technical and financial assistance (United Nations, 2013). In China, around 100 pharmaceutical production factories were forced to close because of severe pollution issues. To continue operations they must significantly improve the quality of their operations and put more effort into working more sustainably and in a more environmentally-friendly way. In addition, in developing countries, environmental consciousness is slowly growing. In Nigeria and Senegal, industrial wastewaters are starting to be controlled. In most low- and middle-income countries parameters like chemical or biological oxygen demand, heavy metals, pathogens, total suspended solids, pH, conductivity, nutrients, and dissolved oxygen are quantified, but information about the occurrence of pharmaceuticals in wastewaters is lacking (Institut sénégalais de Normalisation (ISN), 2001; Ngwuluka et al., 2011). However, initiatives to assess the state of wastewater management conducted by pharmaceutical industries in Nigeria have been undertaken (Ngwuluka et al., 2011). A survey showed that of 34 pharmaceutical businesses in Nigeria, 31 did poorly in managing the disposal of their waste. About one-third of the pharmaceutical businesses were releasing their wastewaters into the environment without any treatment. Some companies were found to be burying their pharmaceutical wastes near their premises ignoring the fact that these agents can leach into water aquifers or threaten environmental health. Surveys like

this are helping to localize weaknesses in regulation or of the authorities. They are helping to identify those regions where the released chemicals are reaching high levels (in the air, soils, and water), and posing risks to environmental and human health. Furthermore, they can help link the pharmaceutical industries with the environmental agencies helping to reduce environmental pollution from industrial facilities that are acting as point sources. This could be beneficial for the industry as well. It will encourage them to develop techniques to further improve their efficiency of production and sustainability. It will help to improve the working conditions of their employees by reducing hazardous emissions in the work place or the occurrence of occupational accidents. In addition, preventing the release of toxicants into the environment is much cheaper than the remediation of contaminated sites (Blacksmith Institute and Green Cross, 2013). Furthermore, such surveys are providing information about which companies require further support and more education in wastewater management. The focus should not be to punish companies with poor results, but, rather, to help them develop strategies and find methods to support the sound production and management of chemicals.

More transparency

As previously mentioned, Larsson and Fick (2009) investigated the origin of pharmaceutical products marketed in Sweden. They came to the conclusion that about one-third of the 242 pharmaceuticals that were available in the Swedish market were produced and delivered from a pharmaceutical production plant in India which releases high amounts of hazardous APIs – mainly antibiotics – into the environment (Larsson et al., 2007). Because of the lack of data about pharmaceutical production and the stages of the supply chain, investigations like these are necessary to obtain more insights into the processes involved in pharmaceutical production and their supply chains. More transparency in the production chain would be helpful in reducing the chemical pollution caused by the pharmaceutical production facilities. Another possibility for assessing the risk pharmaceuticals pose for the environment is to predict the concentrations of APIs in river systems or effluents.

Predictions of pharmaceutical concentrations in sewage treatment plant effluents

Even in high-income countries, there is a dearth of information about the occurrence and biodegradation of several pharmaceuticals in industrial wastewaters (Heberer, 2002), such as antiviral agents (Prasse et al., 2010), sedatives (Brooks et al., 2003), or cytostatic cancer therapeutics (Buerge et al., 2006; Zounková et al., 2007; Yin et al., 2010). Zhang and Geißen (Zhang and Geißen, 2010) modeled the carbamazepine concentration found in the effluents of WWTPs treating human excreta in 68 countries. Although their approximations are a really good approach for calculating concentrations of APIs in wastewater effluents, it has to be considered that for their models, they used values such as:

- Consumption of carbamazepine (represented by the sales volumes of carbamazepine per country in 2007)
- Water consumption
- Disposal rate
- Excretion rate
- Removal efficiency for carbamazepine through wastewater treatment.

These values are not always available for every region and for every substance. Furthermore, the rates of degradation of different groups of APIs and individual pharmaceuticals can vary considerably depending on their physicochemical differences or the different wastewater treatment techniques. This makes it complicated to model the concentrations of APIs in effluents.

Zhang and Geißen estimated that in the low- and middle-income countries – Pakistan, Singapore, Tunisia, Turkey, and South Africa – the predicted concentrations of carbamazepine in WWTP effluents resulting from human excretion ranged from 942 to 1736 ng/L (Zhang and Geißen, 2010). Data like this can help to find risk areas where pharmaceuticals may be released into the environment at high levels, to spot regions where more monitoring would be required, and identify the need for more comprehensive data about toxicants. Consequently, their model is not easily applicable for every substance. For highly persistent chemicals, like carbamazepine, which have elimination rates below 10%, or other substances with stable elimination rates, the concentrations in the effluents can be calculated more accurately (Zhang et al., 2008; Zhang and Geißen, 2010). In contrast, the concentrations of APIs in the effluents of WWTPs cannot be calculated if the efficiency of removal of the WWTPs or the sewage pipes for the different agents vary a lot, it is very difficult to calculate the amount of diclofenac released through WWTPs (or to predict its environmental concentration in surface waters) since its elimination rates range from zero to 70 or 80% in the effluents of STPs (Zhang et al., 2008). Another difficulty is that the production, sales, or consumption data for APIs, especially in low- and middle-income countries, are

currently not readily available to the public. Some consulting groups are selling data about sales and production volumes of pharmaceuticals, but these are quite expensive.

Theoretical examples

Changes in legislation

Today, there is less reliable data available about the production and sales of individual pharmaceuticals, particularly for public access (Larsson and Fick, 2009; Zhang and Geißen, 2010). Following the expansion of international trade and the associated complex production chains – covering every step from purchasing raw materials to packaging the end product offered to the consumer – it is even more difficult to obtain information about the real origin of a product. To assess the amount of pharmaceuticals that can be released into the environment and to identify the risks these chemicals pose to environmental and human health, the production and the sales figures need to be more transparent. In addition to more information about the pharmaceuticals for human use, more information about the amounts of veterinary pharmaceuticals produced, sold, and consumed are required as well. This is particularly so if they are used on a large scale – as in livestock and aquaculture for the treatment of diseases or promotion of growth. Production and sales of pharmaceuticals, which are known to show significant adverse effects on water organisms and which are persistent as well, should be reduced wherever comparable and more environmentally-friendly substitutes for these APIs are available. In future, initiatives like the Kiev Protocol on Pollutant Release and Transfer Registers (part of the Aarhus Convention) will help generate more insights about the production and trade of waste and other hazardous material (United Nations Economic Commission for Europe, 2014). The objective of this protocol is to improve public access to information by implementing international pollutant release and transfer registers. It is an open global initiative, so all states can participate in the protocol. At present, apart from Switzerland, Iceland, French Guiana, Ukraine, Georgia, Armenia, Tajikistan, Republic of Moldova, the former Yugoslav Republic of Macedonia, Albania, Montenegro, Bosnia and Herzegovina, and Serbia, mostly EU countries have joined this protocol. Hence, at present there is no information available from most of the low- and middle-income countries. Although there is a change going on and more restrictions and guidelines are being implemented in low- and middle-income countries (China Daily, 2007), the production facilities and the legislation governing waste disposal need to be adapted to the standards of the industrial countries.

More investigations in ecotoxicology

Although there are already a number of investigations on the eco-toxicological potential of pharmaceuticals, the total impact of most of the APIs on the environment and their distribution among biota, water, and soil is still not well understood (Ternes, 1998; Brooks et al., 2003; Oetken et al., 2005; Fent et al., 2006; Kümmerer, 2008). This is especially so for the consequences of chronic emissions of APIs into the environment, the synergetic effect of several APIs (Cleuvers, 2004; Jones et al., 2005; Schwarzenbach et al., 2006), and the exposure of non-target organisms – bacteria, plants, invertebrates (worms and snails), and vertebrates (fish and birds) – which are often unclear (Oetken et al., 2005). Mostly, initiatives were taken to monitor and reduce exposure to pharmaceuticals only after significant adverse effects on environmental and animal health – impairment of reproduction, malformations of mental, physiological, and morphological development, and even species extinction – were noticed (Oaks et al., 2004). Through more detailed investigations of the eco-toxicological potential, the impacts of pharmaceuticals on the environment could be estimated in advance, before the APIs are produced and released into the environment. To achieve that, more comprehensive toxicity tests are required during the development phase of new pharmaceuticals. Often pharmaceuticals are tested in the short term on basic test organisms – zebrafish, daphnia, algae, and rats and mice. But the toxic effects to other plants or invertebrates and vertebrates, like birds, snails, worms, insects, and amphibians, which are essential for ecosystems, remain unclear. In addition, it is important to focus on gaining a better understanding about the presence and impacts of pharmaceuticals in the environment in the long term. This will aid in better understanding the effects within complete ecosystems and the food web. In addition, the implementation of toxicity tests, risk assessments, and modeling approaches are useful tools for predicting the impact of pharmaceuticals on the environment.

Risk assessment

From the risk assessment approaches, valuable information about the toxic potential of different APIs can be investigated. This helps to estimate their risk to the environment. For instance, examination of the toxic potential of APIs on water organisms, expressed as acute quality criterion values (MAC-EQS) and chronic quality criterion values (AA-EQS), delivers information about the acute and chronic concentrations of different APIs that are provoking adverse effects on water organisms (Ecotox Centre, 2015). APIs which are posing a high risk at low chronic concentrations in higher-income countries, for example 17-alpha-ethinylestradiol, 17-beta-

estradiol, azithromycin, clarithromycin, carbamazepine, and diclofenac (with AA-EQS ranging from 0.037 ng/L to 0.5 µg/L) should be monitored in low- and middle-income countries as well.

More information for physicians, prescribers, and customers

Often the interest groups – the physicians, prescribers, and customers – are well informed about the side effects of pharmaceuticals, but on the packaging or package inserts there is no information available about the ecotoxicological potential and persistence in the environment or about the origin of the APIs. An optional, adequate, and consistent labeling or certification system with pictograms could give information to the provider and the consumer about the ranking of sustainability of the production processes. (For instance, were environmentally-friendly techniques, standards, and controls implemented? Were the APIs produced in domestic or non-domestic facilities? Was the waste disposed of appropriately? Is there information about persistence in the environment and risks to water organisms?) With this information, consumers can make their own decisions; whether they are willing to pay more for a certified environmentally-friendlier product or if they prefer to buy an unlabeled or a cheaper one, which may be produced under less controlled and less environmentally-friendly conditions. Unfortunately at this time, the latter is more often the case in low- and middle-income countries than in higher-income countries (Larsson and Fick, 2009). Larsson and Fick (2009) showed that of 242 pharmaceuticals on the Swedish market, about 123 (51%) products originated from manufacturers located in India. And of these, 74 (31%) were produced in the highly industrial region near Hyderabad, where large amounts of pharmaceutical waste are being dumped into river systems following inefficient wastewater treatment or are being deposited inappropriately in landfills where they could leak into aquifers (Larsson et al., 2007; Larsson, 2010).

More education in the veterinary sector

Besides providing more information for physicians, prescribers, and customers, the farmers involved in raising livestock animals and aquaculture farming in low- and middle-income countries should be better educated about using veterinary medicines as well. This may be of especially high relevance for growing markets like the raising of fish, crustaceans, and mollusks. From 1950 to 2008, fish production through aquaculture increased from less than 1 million tonne to 52.5 million tonne. This represents around 37% of the estimated annual global fish production of 142.3 million tonne (Food and Agriculture Organization, 2010). The production of fish is dominated by the Asian region. Of the 52.5 million tonne of fish produced through aquaculture, 88.8% were produced in Asia (China accounts for 62.3%), while 4.5% was produced in Europe, 3.3% in Latin America, and 1.8% in Africa. Farmers need to be taught about the consequences to the environment that result from using large amounts of pharmaceuticals and how they can reduce the volume of veterinary pharmaceuticals used for animal treatment and growth promotion. They should also be shown that there are alternative therapies available for treating animal diseases and for avoiding parasitic or bacterial infestations of animals. For instance, Romero et al. (2012) introduced some alternative therapies. These included using probiotic microorganisms, essential oils containing antimicrobial components, or bacteriophages as ways of preventing infections by pathogens. One recent headline indicates that more education and stronger legislation and controls are desperately needed in low- and middle-income countries, especially China. There, thousands of dead ducks and the carcasses of around 16,000 pigs were found floating in the Jiapingtang River, which supplies drinking water to the megacity Shanghai. From local reports, it is suspected that the dead animals may have originated from animal husbandries in neighboring Zhejiang province (BBC, 2013; Richard, 2013). The animals probably died of bacterial or viral infections and afterwards they were disposed of inappropriately in the river. Given the large number of dead animals, the question of whether the livestock in this region is kept under tolerable and environmentally-friendly conditions can be raised.