Analysis of drugs in aquatic environment

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ABSTRACT

The occurrence, metabolism and toxicity of medicinally active drugs in the aquatic environment has been recognized as one of the emerging issues in environmental chemistry. In some investigations carried out in various countries like Spain, Greece, England, Canada, Italy, Austria, Brazil, Croatia, and the U.S., more than 100 compounds, pharmaceuticals and several drug metabolites, have been detected in the aquatic environment. Several drugs from various prescription classes have been found at concentrations up to the µg/l-level in influent and effluent samples and also in several surface waters located downstream from municipal sewage treatment plants. The present review is designed to collect the information about the various drug in aquatic environment and their analysis with respect to antipsychotics, anticancer, antibiotics and other commonly used drugs to provide the information for safe use of drugs and to avoid the toxicity of these drug to the environmental lives.

Key words: Aquatic environment, Toxicity, Active Drugs, Metabolites, Environmental hazards.

INTRODUCTION

In recent years, the occurrence and fate of pharmaceutically active compounds (PAC) in the aquatic environment has been recognized as one of the emerging issues in environmental chemistry. The disposal of unused medication via the toilet seems to be of minor importance but many of the pharmaceuticals applied in human medical care are not completely eliminated in the human body. Often they are excreted only slightly transformed or even unchanged mostly conjugated to polar molecules (e.g. as glucuronides) (Heberer, 2002). These conjugates can easily be cleaved during sewage treatment and the original pharmaceutically active compounds will then be released into the aquatic environment mostly by effluents from municipal sewage treatment plants (STPs). Several investigations have shown some evidence that substances of pharmaceutical origin are often not eliminated during waste water treatment and also not biodegraded in the environment (Ternes, 1998; Zwiener et al., 2000). Under recharge conditions, residues of PAC may also leach into groundwater aquifers. Thus, they have already been reported to occur in ground and drinking water samples from water works using bank filtration or artificial ground-water recharge downstream from municipal STPs (Heberer, 2002).

Concerns about the presence and possible harmful effects of active pharmaceuticals and personal care products in the environment, have arisen in recent years. Several studies have demonstrated adverse effects from longstanding, low-dose exposures in both aquatic and terrestrial wildlife, although human toxicity related to trace levels of pharmaceuticals in the water supply remains unknown (Strauch, 2011). It is now well-established that these
compounds are introduced into the environment, mainly through wastewater effluent from municipal treatment plants, hospital effluents and live- stock activities. Water effluents are then discharged into rivers, and sludge is spread on the soil as fertilizer, which means these compounds can reach all environmental compartments. There are several pathways influencing the occurrence of drugs in aquatic environment (Figure 1). Physicochemical analyses have confirmed the presence of drug residues and their metabolites in all the different compartments of the aquatic environment: wastewater, groundwater, surface water, and drinking water (Houeto et al. 2012). These analyses require highly specialized equipment, and the time and costs associated are also relatively high. The paper describes the detailed account of analysis of drugs in aquatic environment.

![Figure 1. Sources and pathways for the occurrence of pharmaceutical residues in the aquatic environment](image)

Besse et al. (2008) estimated the consumption of PAC and the excretion of some metabolites; they also calculated ratios of predicted environmental concentrations with respect to measured environmental concentrations (MECs) in France. In other research, they provided an overview of the occurrence of anti-cancer drugs in the aquatic environment by calculating PECs based on French consumption data (Besse et al. 2012). Carballo et al. (2008) calculated consumption and excretion rates of some PAC in Spain in 2003, Kasprzyk-Hordern et al. (2009) estimated the use of drugs in local communities, Baran et al. (2011) reported the use and occurrence of sulfonamides in different countries. These studies yielded interesting results and showed that, due to the large amount of use, more research (experimental and theoretical) is needed.

**Analysis of various drugs in aquatic environment**

Pharmaceuticals and personal care products (PPCPs) have been documented throughout the United States freshwaters but research has focused largely on lotic systems. Because PPCPs are designed to have a physiological effect, it is likely that they may also influence aquatic organisms. Thus, PPCPs may negatively impact aquatic ecosystems. The objectives of this research were to quantify PPCP abundance in near-shore habitats of southern Lake Michigan and identify factors related to PPCP abundance. Stratified sampling was conducted seasonally at four southern Lake Michigan sites. All sites and depths had measurable PPCP concentrations, with mean individual compound concentrations of acetaminophen (5.36 ng/L), caffeine (31.0 ng/L), carbamazepine (2.23 ng/L), cotinine (4.03 ng/L), gemfibrozil (7.03 ng/L), ibuprofen (7.88 ng/L), lincomycin (4.28 ng/L), naproxen (6.32 ng/L), Paraxanthine (1.7-dimethylxanthine; 46.2 ng/L), sulfadimethoxine (0.94 ng/L), sulfamethazine (0.92 ng/L), sulfamethoxazole (26.0 ng/L), sulfathiazole (0.92 ng/L), triclocarban (5.72 ng/L), trimethoprim (5.15 ng/L), and tyrosine (3.75 ng/L). Concentrations of PPCPs varied significantly among sampling times and locations (river mouth vs offshore), with statistical interactions between the main effects of site and time.
as well as time and location. Concentrations of PPCPs did not differ with site or depth. Temperature, total carbon, total dissolved solids, dissolved oxygen, and ammonium concentrations were related to total pharmaceutical concentrations. These data indicate that PPCPs are ubiquitous and persistent in southern Lake Michigan, potentially posing harmful effects to aquatic organisms (Ferguson et al., 2013).

**Antipsychotics**

In the past decade, there have been increasing concerns over the effects of pharmaceutical compounds in the aquatic environment, however very little is known about the effects of antidepressants such as the selective serotonin reuptake inhibitors (SSRIs). Many biological functions within invertebrates are under the control of serotonin, such as reproduction, metabolism, molting and behavior. The effects of serotonin and fluoxetine have recently been shown to alter the behavior of the marine amphipod, Echinogammarus marinus. It has been reported that fluoxetine and sertraline have a significant impact on the behavior and neurophysiology of this amphipod at environmentally relevant concentrations with effects observed after relatively short periods of time.

Doramectin (DOR), metronidazole (MET), florfenicol (FLO), and oxytetracycline (OXT) are among the most widely used veterinary drugs in animal husbandry or in aquaculture. Contamination of the environment by these pharmaceuticals has given cause for concern in recent years. Even though their toxicity has been thoroughly analyzed, knowledge of their ecotoxicity is still limited. Kołodziejska et al. (2013) investigated their aquatic toxicity using tests with marine bacteria (Vibrio fischeri), green algae (Scenedesmus vacuolatus), duckweed (Lemna minor) and crustaceans (Daphnia magna). All the Eco toxicological tests were supported by chemical analyses to confirm the exposure concentrations of the pharmaceuticals used in the toxicity experiments, since deviations from the nominal concentration can result in underestimation of biological effects. It was found that OXT and FLO have a stronger adverse effect on duckweed (EC50=3.26 and 2.96mgL(-1) respectively) and green algae (EC50=40.4 and 18.0mgL(-1)) than on bacteria (EC50=108 and 29.4mgL(-1)) and crustaceans (EC50=114 and 337mgL(-1)), whereas MET did not exhibit any adverse effect in the tested concentration range. For DOR a very low EC50 of 6.37×10(-5)mgL(-1) towards D. magna was determined, which is five orders of magnitude lower than values known for the toxic reference compound K2Cr2O7. The data show the strong influence of certain veterinary drugs on aquatic organisms and contribute to a sound assessment of the environmental hazards posed by commonly used pharmaceuticals.

González Alonso et al., (2010) investigated the presence of different psychoactive pharmaceuticals and metabolites in the main rivers of Madrid metropolitan area: Jarama, Manzanares, Guadarrama, Henares and Tajo. Sampling was done downstream of ten sewage treatment plants (STP) discharging into these rivers. Control points upstream of STPs discharge points were also sampled. Pharmaceutical compounds and metabolites for analysis were selected according to human consumption and prescription rates in Madrid, and the availability of valid techniques for detection. We observed residues of the antidepressants fluoxetine (80% of the sampling sites), citalopram (60%) and venlafaxine (100%), the anxiolytics nordiazepam (90%), oxazepam (80%) and 7-aminoflunitrazepam (10%) and the anticonvulsant carbamazepine (70%). Measured concentrations equalled or exceeded those reported for other geographical areas, although there is a pronounced lack of information for the anxiolytics and venlafaxine. This is of special concern given that Wyeth-Ayerst's venlafaxine, Effexor, was the 10th greatest selling pharmaceutical worldwide in 2006. We conclude that the origin of pharmaceutical pollution in the rivers of Madrid is mainly the discharge of sewage treatment plants in Madrid's metropolitan area and a comprehensive monitoring program should be implemented.

Letzel et al., (2010) investigated the occurrence and fate of ritalinic acid - the main human metabolite of the psychostimulant drug methylphenidate - in the aquatic environment, a HPLC-electrospray-MS/MS method for the quantification of ritalinic acid in wastewater, surface water and bank filtrate was developed. Carbamazepine known as very stable in the aquatic environment was analyzed as anthropogenic marker in parallel. Furthermore, the removal of ritalinic acid was studied in a sewage treatment plant using an activated sludge system during a field study and in lab-scale plants. In good agreement between lab-scale and field studies a low removal rate of 13% and 23%, respectively, was determined. As a consequence, the concentration of ritalinic acid in the wastewater effluents were in the range of <50-170 ngL(-1) which corresponds to a mean specific load per capita of 17.7 µgD(-1). Ritalinic acid has further been detected in German rivers at concentrations of 4-23 ngL(-1) and in bank filtrate samples in 100-850 m distance from the river up to 5 ngL(-1) demonstrating the widespread occurrence of this stable metabolite in the aquatic environment. A comparison to available sales data shows that a significant amount of methylphenidate applied can be found in waters as ritalinic acid.
Cytotoxic drugs

Cytostatic drugs have been widely used for chemotherapy for decades. However, many of them have been categorized as carcinogenic, mutagenic and teratogenic compounds, triggering widespread concerns about their occupational exposure and Eco toxicological risks to the environment. Past records have documented findings mainly on hospital effluents though little effort has been directed to household discharges. There is also a lack in physico-chemical data for forecasting the chemo dynamics of cytostatic in natural waters along with its human metabolites and environmental transformation products. In this light, obtaining comprehensive Eco toxicity data is becoming pressingly crucial to determine their actual impacts on the ecosystem. Literature review also reveals urinary excretion as a major contributor to various cytostatic residues appeared in the water cycle. As such, engaging urine source-separation as a part of control strategy holds a rosy prospect of addressing the “emerging” contamination issue. State-of-the-art treatment technologies should be incorporated to further remove cytostatic residues from the source-separating urine stream. The benefits, limitations and trends of development in this domain are covered for membrane bio-reactor, reverse/forward osmosis and advanced oxidation processes. Despite the respective seeming advantages of source separation and treatment technology, a combined strategy may cost-effectively prevent the cytostatic residues from seeping into the environment. However, the combination calls for further evaluation on the associated technological, social-economic and administrative issues at hand (Zhang et al., 2013).

Anti-tumor agents and their metabolites are largely excreted into effluent, along with other pharmaceuticals. In the past, investigations have focused on the input and analysis of pharmaceuticals in surface and ground water. The two oxazaphosphorine compounds, cyclophosphamide and ifosfamide are important cytostatic drugs used in the chemotherapy of cancer and in the treatment of autoimmune diseases. Their mechanism of action, involving metabolic activation and unspecific alkylation of nucleophilic compounds, accounts for Genotoxic and carcinogenic effects described in the literature and is reason for environmental concern. The anti-tumor agents cyclophosphamide (CP) and ifosfamide (IF) were not biodegraded in biodegradation tests. They were not eliminated in municipal sewage treatment plants. Degradation by photo chemically formed HO radicals may be of some relevance only in shallow, clear, and nitrate-rich water bodies but could be further exploited for elimination of these compounds by advanced oxidation processes, i.e. in a treatment of hospital waste water. Therefore, CP and IF are assumed to persist in the aquatic environment and to enter drinking water via surface water. The risk to humans from input of CP and IF into surface water is not known. The local and regional, i.e. nationwide predicted environmental concentration (PEC(local), PEC(regional)) of CP and IF was calculated for German surface water. Both compounds were measured in hospital effluents, and in the influent and effluent of a municipal treatment plant. Additionally, published concentrations in the effluent of sewage treatment plants and surface water were used for risk assessment. Excretion rates were taken into account. For a worst-case scenario, maximum possible ingestion of CP or IF by published concentrations in the effluent of sewage treatment plants and surface water were used for risk assessment. Drinking 2 L a day of unprocessed surface water over a life span of 70 years was calculated for adults. Elimination in drinking water processing was neglected, as no data is available. This intake was compared with intake during anti-cancer treatment. CP and IF are carcinogens. With respect to newborn and children, reduction of the emission of CP and IF into effluent and surface water is recommended at least as a precautionary measure. The collection of unused and outdated drugs is a suitable measure. Collection of patients' excreta as a measure of input reduction is not recommended. Data suitable for the assessment of the risk for newborn and children should be collected in order to perform a risk assessment for these groups. This can stimulate discussion and give new insights into risk assessment for pharmaceuticals in the environment. Our study showed that in the long term, effective risk management for the reduction of the input of CP and IF are recommendable (Kemmerer and Al-Ahmad, 2010).

Cytostatic agents are applied in cancer therapy and subsequently excreted into hospital wastewater. As these substances are known to be carcinogenic, mutagenic and toxic for reproduction, they should be removed from wastewater at their source of origin. Lenz et al., (2007) studied the fate and effects of the cancerostatic platinum compounds (CPC) cisplatin, carboplatin, oxaliplatin, 5-fluorouracil (5-FU) and the anthracyclines doxorubicin, daunorubicin and epirubicin were investigated in hospital wastewater. Wastewater from the in-patient treatment ward of a hospital in Vienna was collected and monitored for the occurrence of the selected drugs. Genotoxic effects of the oncologic wastewater were assessed before and after wastewater treatment followed by a risk assessment. Monitoring concentrations of the selected cytostatic in the oncologic wastewater were in line with calculated concentrations. Due to different mechanisms (adsorption, biodegradation) in the MBR-system 5-FU and the anthracyclines were removed < LOD, whereas CPC were removed by 60%. In parallel, Geno toxic effects could be reduced significantly by the MBR-system. The risk for humans, the aquatic and terrestrial environment by hospital wastewater containing cytostatic drugs was classified as small in a preliminary risk assessment.
Cytostatic drugs are used in cancer therapy. They can enter hospital wastewater due to excretion by patients undergoing chemotherapy. Little attention has been paid to these drugs in China even though their usage is high. The effluents of 21 hospitals of different size in Beijing, China, were investigated on 1-7 different days. Nine cytostatic compounds (methotrexate, azathioprine, doxorubicin, doxorubicinol, vincristine, ifosfamide, cyclophosphamide, etoposide, and procarbazine) were tested. Of the 65 effluent samples analyzed, the median concentrations for methotrexate, azathioprine, ifosfamide, cyclophosphamide and etoposide were 17, 15, 151, 100 and 42 ng/L, respectively. Doxorubicin, doxorubicinol, vincristine and procarbazine were not detected in this study. These results suggested that the hospital effluents are an important source of certain cytostatic drugs in aquatic environment (Yin et al., 2010).

Besse et al., (2012) reported in their study considers the implications and research needs arising from anticancer (also referred to as antineoplastic) drugs being released into the aquatic environment, for the entire therapeutic classes used: cytotoxic, cytostatic and endocrine therapy drugs. A categorization approach, based on French consumption amounts, allowed to highlight parent molecules and several metabolites on which further occurrence and ecotoxicological studies should be conducted. Investigations of consumption trends at a national and a local scale show an increase in the use of anticancer drugs between 2004 and 2008, thus leading to increased levels released in the environment. It therefore appears necessary to continue surveying their presence in surface waters and in wastewater treatment plant (WWTP) effluents. Furthermore, due to the rise of anticancer home treatments, most of the prescribed molecules are now available in town pharmacies. Consequently, hospital effluents are no longer the main expected entry route of anticancer drugs into the aquatic environment. Concerning Ecotoxicological risks, current knowledge remains insufficient to support a definitive conclusion. Risk posed by cytotoxic molecules is still not well documented and it is not possible to conclude on their long-term effects on non-target organisms. To date, Ecotoxicological effects have been assessed using standardized or in vitro assays. Such tests however may not be suitable for anticancer drugs, and further work should focus on full-life cycle or even multigenerational tests. Environmental significance (i.e. occurrence and effects) of cytostatic (protein kinases inhibitors and monoclonal antibodies), if any, is not documented. Protein kinases inhibitors, in particular, deserve further investigation due to their universal mode of action. Finally, concerning endocrine therapy drugs, molecules such as antiestrogen Tamoxifen and its active metabolites, could be of concern. Overall, to accurately assess the Ecotoxicological risk of anticancer drugs, we discuss the need to break away from tests on isolated molecules and to test effects of mixtures at the low ng.L(-1) range.

Martin et al., (2011) developed a method, based on solid-phase extraction prior to high-performance liquid chromatography-triple quadrupole mass spectrometry determination, was optimized and validated for the simultaneous determination of some (14) of the most widely used cytostatic drugs in river water, influent and effluent wastewater. Process efficiency was in the range between 41 and 99% in real samples, except for cytarabine (24%), docetaxel (17%) and methotrexate (30%), due to suppression effects; precision values were <11%, except for gemcitabine (up to 19%); and detection limits were in the range between 0.1 and 38 ng/L. Cytarabine, doxorubicin, etoposide, gemcitabine, ifosfamide and vinorelbine were found at concentration levels up to 14 ng/L in influent and effluent wastewater, showing an insignificant decrease during sewage treatment; cytarabine and gemcitabine were found in effluent wastewater and were also detected in river water associated with effluent discharges.

Although antibiotics have been used in large quantities for some decades, until recently the existence of these substances in the environment has received little notice. It is only in recent years that a more complex investigation of antibiotic substances has been undertaken in order to permit an assessment of the environmental risks they may pose. Within the last decade, an increasing number of studies covering antibiotic input, occurrence, fate and effects have been published. Antibiotics are one of the most important groups of pharmaceuticals. Antibiotic resistance is one of the major challenges for human medicine and veterinary medicine. However, there is still a lack of understanding and knowledge about sources, presence and significance of resistance of bacteria against antibiotics in the aquatic environment despite the numerous studies performed. This review summarizes this topic. It names important open questions and addresses some significant issues which must be tackled in the future for a better understanding of resistance related to antibiotics in the environment (Kümmerer, 2009).

Over the past few years, antibiotics have been considered emerging pollutants due to their continuous input and persistence in the aquatic ecosystem even at low concentrations. They have been detected worldwide in environmental matrices, indicating their ineffective removal from water and wastewater using conventional...
treatment methods. To prevent this contamination, several processes to degrade/remove antibiotics have been studied (Homem and Santos, 2011).

The mass flows of fluoroquinolone antibacterial agents (FQs) were investigated in the aqueous compartments of the Glatt Valley Watershed, a densely populated region in Switzerland. The major human-use FQs consumed in Switzerland, ciprofloxacin (CIP) and norfloxacin (NOR), were determined in municipal wastewater effluents and in the receiving surface water, the Glatt River. Individual concentrations in raw sewage and in final wastewater effluents ranged from 255 to 568 ng/L and from 36 to 106 ng/L, respectively. In the Glatt River, the FQs were present at concentrations below 19 ng/L. The removal of FQs from the water stream during wastewater treatment was between 79 and 87%. During the studied summer period, FQs in the dissolved fraction were significantly reduced downstream in the Glatt River (15-20 h residence time) (66% for CIP and 48% for NOR). Thus, after wastewater treatment, transport in rivers causes an additional decrease of residual levels of FQs in the aquatic environment. Refined predicted environmental concentrations for the study area compare favorably with the measured environmental concentrations (MEC) obtained in the monitoring study. Total measured FQ concentrations occurring in the examined aquatic compartments of the Glatt Valley Watershed were related to acute ecotoxicity data from the literature. The risk quotients obtained (MEC/PNEC < 1) following the recommendations of the European guidelines or draft documents suggest a low probability for adverse effects of the occurring FQs, either on microbial activity in WWTPs or on algae, daphnia, and fish in surface waters (Golet et al., 2002).

Research has quite extensively studied the presence of antibiotics in the environment. As for other pharmaceuticals, it has been found that the concentrations of antibiotics measured in different countries are in the same range of concentrations in the different compartments such as sewage and surface water, respectively (Batt and Aga, 2005; Botitsi et al., 2007; Hernández et al., 2007; Chang et al., 2008; Peng et al., 2008; Duong et al., 2008; Martins et al., 2008). In general, concentrations were in the higher µg-per-litre range in hospital effluent, in the lower µg-per-litre range in municipal waste water, and in the higher and lower µg-per-litre range in different surface waters, ground water and sea water in a harbour (Xu et al., 2007). Losses of sulphonamide antibiotics from grassland to a brook after application of manure were strongly influenced by the weather conditions (Stoob et al., 2007). The compounds that have been analyzed up to now are from a number of different important classes of antibiotics. They include primarily macrolides, aminoglycosides, tetracyclines, sulphonamides and quinolones. Quinolones (ciprofloxacin most often analysed) and other pharmaceuticals have been detected in the effluents of hospitals (Hartmann et al., 1998; Brown et al., 2006; Thomas et al., 2007; Duong et al., 2008; Martins et al., 2008) up to a low µg-per-litre range.

The occurrence of ß-lactams, has not been covered frequently, despite the fact that ß-lactams account for by far the highest proportion of consumption (Färber, 2002; Christian et al., 2003). It is not clear whether they are not present in the aquatic environment because of the possible cleavage of the ß-lactam ring, whether this finding is due to the fact that they have not been analysed, or whether it is due to possible analytical short comings and difficulties. In one study ß-lactams were detected in the lower µg-per-litre range in hospital effluent and in the influent of a municipal STP (Christian et al., 2003). The concentrations found for ß-lactams are low compared to the ones expected from the extensive use of ß-lactams. Antibiotics have also rarely been found in drinking water (Ye et al., 2007).

The elimination of organic trace compounds in municipal wastewater was analysed at three German wastewater treatment plants. Additionally, the effects of advanced treatment, membrane filtration, adsorption and oxidation processes were investigated. To assess the ecotoxicity of effluents, a number of tools were used: substance-specific evaluation, case studies for combined effects and risk assessment on the basis of cumulative parameters. The results of the research projects revealed that aquatic environmental risks can be reduced significantly using advanced treatment technologies for wastewater treatment plants (Schwatter et al., 2007).

A large fraction of PAC pollution in water is composed of anti-inflammatory (AI) and analgesic (AN) drugs, which are rapidly excreted in urine. Ziylan and Ince, (2011) emphasized the occurrence of AI/AN wastes in sewage and fresh water bodies, their impacts on non-target organisms, and conversion or elimination by chemical, biochemical and physical treatment methods. The first part of the study is devoted to a critical review of most common AI/AN drugs and the relative efficiency of some selected sewage and drinking water treatment operations for their elimination/separation from aqueous systems. The second part focuses on pilot- or lab-scale applications of various advanced oxidation processes that are promising solutions to the ultimate degradation and/or conversion of such
medical residues in effluents of drinking water treatment plants (DWTPs) and wastewater treatment plants (WWTPs) to less harmful and non-toxic products.

In another study, occurrence of five non-steroidal anti-inflammatory drugs (salicylic acid, ibuprofen, naproxen, indomethacin and diclofenac) and three lipid regulators (bezafibrate, clofibric acid and gemfibrozil) was investigated in wastewater, sewage sludge, and river water of the urban section of the Pearl River at Guangzhou in South China. Behavior and fate of the pharmaceuticals during treatment in two sewage treatment plants (STPs) were also studied in depth by determining concentrations in the influents and effluents at major treatment units and the sewage sludge. Concentrations of the pharmaceuticals in the raw wastewater were mostly at ng L\(^{-1}\) levels except salicylic acid whose concentrations ranged from 9.6 to 23.3 µg L\(^{-1}\). No significant amount of the pharmaceuticals was detected in the suspended particulate matter of wastewater and sewage sludge. Salicylic acid, indomethacin, and naproxen were almost completely removed (≥ 99%); gemfibrozil, ibuprofen and bezafibrate were significantly removed (>75%), whereas diclofenac and clofibric acid were removed by 60-70% during treatment in the STPs. Generally, biodegradation was the governing process for elimination of the investigated pharmaceuticals. Anaerobic biodegradation was responsible for most of the removal of diclofenac whereas aerobic biodegradation also played an important role in elimination of the other pharmaceuticals except SA, which was nearly completely removed after the anoxic process. In the Pearl River, the pharmaceuticals were widely detected. Both the concentrations and detection frequency were higher in March 2008 than those in the other seasons, which may be ascribed mainly to less dilution caused by lower precipitation. Besides the STPs, urban canals directly connected with the Pearl River also may be important contributors to the pharmaceutical contamination in the river (Huang et al., 2011).

In another study it is reported that, In Spain, as in most of its neighbouring countries, there is an elevated use of pharmaceuticals for the treatment of cardiovascular diseases (which are extremely prevalent among the older adult population) and anti-inflammatory medications, which are obtainable over the counter without a medical prescription. This study therefore sought to determine to what degree pharmaceuticals with the highest regional prescription and/or use rates, such as cardiovascular and analgesic/anti-inflammatory/antipyretic medications, were present in the principal rivers (Jarama, Manzanares, Guadarrama, Henares and Tagus) and tap-water samples of the Madrid Region (MR). Samples were taken downstream the discharge of 10 of the most important region’s STPs and the most frequently used drugs in the region were analysed for. Of the 24 drugs analysed, 21 were detected at concentrations ranging from 2 ng L\(^{-1}\) to 18 µg L\(^{-1}\). The highest drug concentrations corresponded to ibuprofen, diclofenac, naproxen, atenolol, frusemide (furosemide), gemfibrozil and hydrochlorothiazide, and in most cases exceeded the amounts reported in the scientific literature. No traces of these groups of pharmaceuticals were detected in the drinking water analysed. On the basis of the high concentrations detected, we believe that an environmental surveillance system should be implemented to assess the continuous discharge of these pharmaceuticals and their possible Ecotoxicological effects. At the same time, efforts to raise the awareness of the public about responsible use and the proper disposal of such substances at purpose-designated collection points should be increased. Furthermore sewage treatment processes should be suitably adapted to increase the rates of removal of these drugs (Valcárcel et al., 2011).

The occurrence of the antihistamines cetirizine, acrivastine, fexofenadine, loratadine, desloratadine and ebastine in sewage treatment plants wastewaters and in recipient river waters was studied. The analytical procedure consisted of solid-phase extraction of the water samples followed by liquid chromatography separation and detection by a triple-quadrupole mass spectrometer in the multiple reaction mode. Antihistamines are poorly degraded/eliminated under the biological treatment processes applied in the wastewater treatment plants and, consequently, they are continuously being discharged along with other drugs to the aquatic environment (Kosonen and Kronberg, 2009).

In one research the four most abundantly used pharmaceuticals in Korea, namely acetaminophen, carbamazepine, cimetidine, and diltiazem, and six sulfonamide related antibiotics, including sulfamethoxazole, sulfachlorpyridazine, sulfathiazole, sulfamethazine, sulfadimethozone, and trimethoprim were examined for their acute aquatic toxicity employing a marine bacterium (Vibrio fischeri), a freshwater invertebrate (Daphnia magna), and the Japanese medaka fish (Oryzias latipes). In general, Daphnia was the most susceptible among the test organisms. The most acutely toxic among the chemicals tested in this study was diltiazem, with a median lethal concentration of 8.2 mg/L for D. magna. The resulting acute toxicity of these pharmaceuticals was reasonably predicted by physicochemical descriptors such as pH-dependent distribution coefficient and EHOMO-ELUMO gap. Predicted environmental concentrations (PECs) derived for the test pharmaceuticals in Korea ranged between 0.14 and 16.5 microg/L. Hazard quotients derived from PECs and predicted no effect concentrations (PNECs) for sulfamethoxazole and
Acetaminophen were 6.3 and 1.8, respectively, suggesting potential environmental concerns and a need for further investigation (Kim et al., 2007).

Acetaminophen (paracetamol) and acetylsalicylic acid (ASA) are the two most popular pain killers mainly sold as OTC drugs. In Germany, the total quantities of ASA sold per year have been estimated at 500 tons (Ternes, 2001). Nevertheless, other analgesics such as diclofenac or ibuprofen sold in Germany at annual quantities of approximately 75 and 180 tons, respectively (Ternes, 2001), have been recognized as being more important for the water-cycle. ASA was detected at a median concentration of only 0.22 g/l in sewage effluents in Germany (Ternes, 1998). In the same study, the median concentration of ASA in surface water samples was below the detection limits. The occurrence and behavior of carbamazepine (CBZ) was investigated in aquatic environment of Yangtze River Delta, East China. The water samples were enriched by solid-phase extraction and analyzed by high-performance liquid chromatography with diode array detector. The validation of the analytical method included linearity (0.1-1 mg/L), recovery studies, and determination of limits of quantification. Limits of quantification of CBZ in various aquatic samples were in the range of 0.1-0.2 µg/L. CBZ was detected in the Tongji University Intramural River, the Huangpu River, and the Suzhou River with the highest concentration of 1.090 ng/L, but not detected in the Nanhengyin River and the Caojia River. In sewage water samples, CBZ was not detected in one of the sewage treatment plants (STPs) but was detected in the raw influents and effluents at the other three selected STPs in Shanghai, with the concentrations ranging from 230 to 1,110 ng/L. CBZ was not completely eliminated after secondary treatment (Zhou et al., 2011).

CONCLUSION

As a huge quantity and variety of drugs and their metabolites are continuously discharged to rivers and the sea, the compounds should be considered as contaminants that may possess risks to the aquatic ecosystem. Further studies are urgently needed on the environmental fate of the various drugs and other pharmaceuticals in the aquatic environment. These studies should be concerned with the stability of the compounds, their transformation reactions and the identity of the transformation products, the distribution of drugs and their uptake and effects in organisms. On the basis of these studies, the possible environmental hazards of pharmaceuticals may be assessed.

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