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Occurrence, bioaccumulation and risk assessment of lipophilic pharmaceutically active compounds in the downstream rivers of sewage treatment plants

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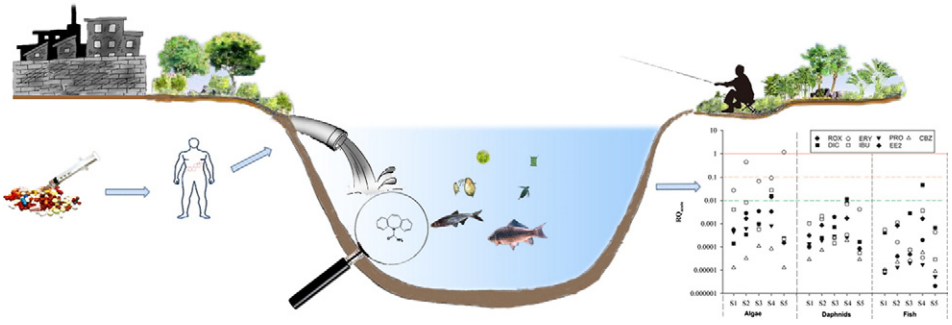
HIGHLIGHTS

- LPhACs were widely detected in the surface water and wild fish.
- Tissue distribution of ΣLPhACs was in general the liver > brain > gill > muscle in two wild fish.
- The bioaccumulation of LPhACs in wild fish was affected by exposure concentrations.
- Certain LPhACs posed high ecological risks to certain organisms in Nanjing's rivers.

GRAPHICAL ABSTRACT



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ABSTRACT

The occurrence, bioaccumulation and risk assessment of lipophilic pharmaceutically active compounds (LPhACs), such as antibiotics (roxithromycin, erythromycin and ketoconazole), anti-inflammatories (ibuprofen and diclofenac), β-blockers (propranolol), antiepileptics (carbamazepine) and steroid hormones (17α-ethinylestradiol), were investigated in the downstream rivers of sewage treatment plants in Nanjing, China. The results indicate that these LPhACs were widely detected in the surface water and fish samples, with the mean concentrations of the total LPhACs (ΣLPhACs) being in the range of 15.4 and 384.5 ng/L and 3.0 and 128.4 ng/g (wet weight), respectively. The bioaccumulation of the ΣLPhACs in wild fish tissues was generally in the order the liver > brain > gill > muscle. Among the target LPhACs, however, an interspecies difference in tissue distribution was evident for erythromycin. The bioaccumulation factors of LPhACs in the liver and brain, the two major targeted storage sites for toxicants, exhibited an obvious negative correlation with the aquatic concentrations ($P < 0.05$). Finally, risk quotients posed by pharmaceuticals were assessed by comprehensive and comparative methods for different aquatic organisms (algae, daphnids and fish). The overall relative order of susceptibility was estimated to be algae > daphnids > fish. However, the results indicate that diclofenac, ibuprofen and 17α-ethinylestradiol each posed chronic risks for high trophic level organisms (fish). In all of the risk assessments, erythromycin was found to be the most harmful for the most sensitive algae group. In this work, however, the total BAF and toxicological interactions of pharmaceuticals were not performed due to the lack of metabolite information and combined toxicity data, which represents a major hindrance to the effective risk assessment of pharmaceuticals.

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1. Introduction

The occurrence and fate of pharmaceutically active compounds (PhACs) in the aquatic environment has been recognized as one of the emerging issues in environmental chemistry (Heberer, 2002). From 2003 to 2011, the production of PhAC ingredients in China has doubled, and in 2011, approximately two million tons of PhACs were produced (Liu and Wong, 2013). Once used, PhACs are released into natural aquatic systems via different routes, such as wastewater effluent discharge, pharmaceutical effluent, agricultural runoff, or the improper disposal of unused drugs (Bu et al., 2013; Phillips et al., 2010). However, effluents from sewage treatment plants (STPs) have become the primary contributor of PhAC pollution in urban rivers because of the incomplete elimination of PhACs in STP facilities and an increasing population (Peng et al., 2008; Valdés et al., 2014). PhACs were found in surface water bodies with concentrations below the μg/L threshold for most of the reviewed cases in China (Liu and Wong, 2013).

However, PhACs are manufactured with the intent of providing beneficial effects for human/animal health, which are not necessarily the same for organisms subjected to episodic or continual lifecycle exposure. Fishes and other organisms downstream from STP effluent outfalls are chronically exposed to the complex mixtures of synthetic and biologically active pharmaceuticals, and a number of important physiological processes, such as development, reproduction and nervous system function, may be altered in aquatic organisms (Gelsleichter and Szabo, 2013; Glassmeyer et al., 2005; Pal et al., 2010). A range of experimental investigations has been performed during recent years with the aim of describing the hazards and risks of pharmaceuticals for the aquatic environment (Santos et al., 2007; Wang et al., 2010; Yan et al., 2013). However, environmental risks from chemicals are still often assessed substance-by-substance, neglecting any interaction effects in mixtures (i.e. parent compounds, metabolites and transformation products) (Backhaus and Faust, 2012; Vasquez et al., 2014). Ignoring possible mixture effects might run the risk of underestimating the actual impacts of pharmaceuticals in the environment, depending on the number of compounds involved, their concentrations and ecotoxicological profiles (Backhaus and Karlsson, 2014).

As a group of novel emerging contaminants, PhACs have varied physical–chemical behaviors, but some also exhibit the common property of lipophilicity. Like many pharmaceuticals, antibiotics (roxithromycin and erythromycin), anti-inflammatories (ibuprofen and diclofenac), antiepileptics (carbamazepine), antidepressants (sertraline and fluoxetine) and steroid hormones (17α-ethinylestradiol and 17β-estradiol) are relatively hydrophobic, enabling them the ability to partition into the lipid portion of organisms and bioaccumulate (Brozinski et al., 2012; Grabicova et al., 2014; Huang et al., 2013; Li et al., 2012). However, the bioaccumulation of these lipophilic pharmaceutically active compounds (LPhACs) in fish and other aquatic organisms has been reported in only a limited number of studies and their tissue distribution has not been well studied in the field. Larsson et al. (1999) provided the first report on the bioaccumulation in the bile of a lipophilic pharmaceutical, 17α-ethinylestradiol, whereas the test species, juvenile rainbow trout, were caged in a Swedish effluent-dominated river. Years later, 17α-ethinylestradiol was still detected in 50% of the wild fish samples caught downstream of the STP effluents, which averaged 1.6 ± 0.6 ng/g in males and 1.43 ± 0.96 ng/g wet weight (ww) in females (Al-Ansari et al., 2010). Grabicova et al. (2014) reported that antidepressants (i.e., sertraline, citalopram and venlafaxine) tend to accumulate in the brain and liver tissues of rainbow trout (*Oncorhynchus mykiss*), suggesting that analyses of concentrations in target tissues would be more informative in field studies. In a national study of German, only 2 pharmaceuticals (i.e., diphenhydramine and desmethylsertraline) of 17 pharmaceuticals were measured in fish fillet composites with concentrations ranging approximately from 0.01 to 3.0 ng/g ww (Subedi et al., 2012). The potential bioaccumulation for other LPhACs, e.g., the anti-inflammatory drugs diclofenac, naproxen and ibuprofen, and the antibiotic erythromycin, which can originate from wastewater, can be identified in the tissues of wild fish living in the recipient rivers, and their concentration in the bile was approximately >1000 times higher than the concentration found in the water (Brozinski et al., 2012; Gao et al., 2012a). The rationale is suggested that accumulation will also occur at low exposure concentrations, and if such a low exposure continues, eventually a steady state will be reached that may still yield a high BAF value if the compound depuration is slower than the rate of accumulation (Lombardo et al., 2014). From a regulatory perspective, physicochemical, toxicological and ecotoxicological information for these LPhACs needs to be evaluated in aquatic organisms.

The objectives of the present study were to investigate the occurrence of eight LPhACs in the surface water and to examine their bioaccumulation in the muscle, gill, liver and brain of wild fish species collected from the downstream rivers of five STPs in Nanjing, China. Moreover, the environmental implications of each individual component and the mixtures of detected LPhACs on different aquatic organisms (algae, daphnids and fish) were evaluated by employing the risk quotient method. The eight LPhACs investigated in this study include antibiotics roxithromycin (ROX), erythromycin (ERY) and ketoconazole (KCZ), anti-inflammatories ibuprofen (IBU) and diclofenac (DIC), β-blockers propranolol (PRO), antiepileptics carbamazepine (CBZ) and steroid hormones 17α-ethinylestradiol (EE2).

2. Materials and methods

2.1. Materials

Eight LPhACs were selected as target compounds because these compounds are hydrophobic, bioactive and/or frequently detected. Their basic physical and chemical information is listed in Table S1. The standards of ROX, ERY, KCZ, IBU, DIC, PRO, CBZ and EE2 were purchased from the laboratory of Dr. Ehrenstorfer (Augsburg, Germany). Erythromycin-^{13}C, d_3, carbamazepine-d_{10}, ibuprofen-d_3 and estrone-d_4 were obtained from Sigma-Aldrich (Flanders, New Jersey, USA).

2.2. Study area and sample collection

The study was conducted on urban rivers in Nanjing (China). Water and fish were sampled in four rivers: New Qinhuai River, Yunliang River, Jinchuan River and Yangtze River (Nanjing section), all of which receive discharge from industries and/or STP effluent. In addition, the four rivers were designated as areas of concern by Nanjing's city government in 2013. The basic information of each STP and the sampling locations are shown in Fig. 1. On the rivers, triplicate water samples were collected sequentially in dark amber glass bottles at sites 0.5, 1 and 1.5 km downstream of each STP outfall (S1, S2, S3, S4 and S5) in October 2013, according to the technical specification requirements for monitoring of surface water and waste water (SEPAC, 2003). Samples were transported to the laboratory in a cooler and filtered through 0.45 μm prewashed glass-fiber filters. Then, the samples were stored in the dark at 4 °C until the solid-phase extraction (within 48 h), and analyzed over a period of 4 days.

Fish were captured with hook and line in October 2013 from four sampling points: S1, S2, S3, and S4. Fish samples were unsuccessful at site S5 due to fast-flowing water and slippery riverbank of the Yangtze River. To collect a sufficient amount of fish, 3–5 anglers simultaneously fished at an approximate range of 0.5–1.5 km downstream of each STP outlet for 2 h. It should be noted that all fish samples were collected at the 1 km range, but the fish sampling sites are not accurately marked. After capture, the fish were anesthetized by immersion in tricaine methanesulfonate and sacrificed by rapid decapitation. The liver, brain, gill and muscle tissues were immediately excised and weighed. All tissues were washed with 0.15 M KCl, blotted with filter paper and stored in a portable liquid nitrogen tank.