

Occurrence and distribution of pharmaceuticals in raw, finished, and drinking water from seven large river basins in China

Jia Lv, Lan Zhang, Yongyan Chen, Bixiong Ye, Jiayi Han and Ning Jin

ABSTRACT

The occurrence of pharmaceuticals in the drinking water is a growing concern in China. In this study, we determined the concentration and distribution of 59 selected pharmaceuticals in raw, finished, and tap water samples from 79 drinking water treatment plants (DWTPs) in 15 cities, encompassing seven large river basins in China, using solid-phase extraction pretreatment and ultra-high-performance liquid chromatography–tandem mass spectrometry analysis. Forty-seven pharmaceuticals were detected in raw water samples, with detection rates of 1.27–96.20% and average concentrations of 0.09–128.87 ng/L. Forty-three pharmaceuticals were detected in finished water samples, with detection rates of 1.27–96.20% and average concentrations of 0.07–59.17 ng/L. Forty-two pharmaceuticals were detected in tap water samples, with detection rates of 1.27–94.94% and average concentrations of 0.07–58.43 ng/L. Purification methods implemented by DWTPs are capable of removing some pharmaceuticals from water treatment systems; however, low concentrations of pharmaceuticals were detected in drinking water, raising concerns about the possible human health implications of long-term exposure to low-dose pharmaceuticals. The detection and quantification of pharmaceuticals in municipal water samples presented in this study represent the most extensive analysis of commonly used pharmaceuticals and personal care products located in Chinese river basins.

Key words | China, drinking water, pharmaceuticals, ultra-high-performance–liquid chromatography–tandem mass spectrometry (UPLC–MS/MS)

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INTRODUCTION

In recent years, concerns regarding the occurrence of pharmaceuticals in the drinking water in China have escalated. To date, more than 3,000 pharmaceuticals and personal care products (PPCPs), including antibiotics, analgesics, antipyretics, nervous system drugs, and mental disorder drugs, have been used throughout the world for the medical treatment of both humans and animals (Liu & Wong 2013). Pharmaceuticals enter aquatic environments mainly through effluents from sewage treatment plants (STPs), treated effluents from industries and hospital services, untreated household effluents, and effluents from livestock

farms (Zhang *et al.* 2015). Effluents from STPs are a predominant source of pharmaceuticals in the aquatic environment, and the limited removal efficiency of pharmaceuticals from STPs largely results in contamination of aquatic environments (Simazaki *et al.* 2008).

The occurrence of pharmaceuticals in surface and groundwater has been well documented in the USA, Canada, Australia, France, Italy, Finland, Poland, Switzerland, Spain (Calamari *et al.* 2003; Vieno *et al.* 2007; Watkinson *et al.* 2009; Alder *et al.* 2010; Ontario Ministry of the Environment 2010; Vulliet *et al.* 2011; Carmona *et al.*

2014; Bradley *et al.* 2016; Kot-Wasik *et al.* 2016). In surface water and groundwater, pharmaceuticals are typically found at concentrations of parts-per-trillion (ng/L) to parts-per-billion ($\mu\text{g/L}$). Studies on the occurrence of pharmaceuticals in surface water and groundwater in China were initiated in the past 10 years, including various fresh water environments in China (Zhao *et al.* 2016). For most reviewed cases in China, pharmaceuticals were generally found at concentrations less than parts-per-billion, including studies on the occurrence of pharmaceuticals in the Yangtze River, the Pearl River, the Haihe River, Taihu Lake, Dianchi Lake, and groundwater in Beijing and Jiangnan Plain of central China.

Incomplete removal during water treatment processes results in contaminated drinking water (Simazaki *et al.* 2008). Human exposure to pharmaceuticals may have serious adverse health impacts, and the long-term effects of human exposure to pharmaceuticals are unknown (Boxall *et al.* 2012; Ashbolt *et al.* 2013; Wang *et al.* 2016). Data on the concentrations of pharmaceuticals in drinking water are available for some developed countries, such as the USA, Canada, Spain, Finland, and Germany, but relevant information in developing countries is limited (Ternes *et al.* 2002; Boyd *et al.* 2003; Vieno *et al.* 2007; Benotti *et al.* 2008; Ontario Ministry of the Environment 2010; Carmona *et al.* 2014). Pharmaceuticals have been reported in the drinking water of some cities in China, such as Beijing, Guangzhou, and Macao, but few studies have determined pharmaceutical concentrations in raw water, finished water, and tap water in China. Thus, it is necessary to explore the occurrence and fate of PPCPs in the drinking water of China (Yiruhan *et al.* 2010; Cai *et al.* 2015).

We employed a rapid method, based on USEPA Method 1694, to simultaneously detect multiclass pharmaceuticals in drinking water, using solid-phase extraction (SPE) pretreatment and ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) analysis. SPE is a ubiquitous pretreatment technique, commonly employed for purification and preconcentration of trace-level analytes in complex sample matrices. Specifically, we selected Oasis hydrophilic-lipophilic balance (HLB) cartridges for the SPE method, which are composed of a hydrophilic-lipophilic balanced copolymer structure. These cartridges are designed to reduce the number of steps required for sample

extraction via the water-wettable capability of the sorbent, offering simpler protocols with high analyte retention over the complete pH range (0–14) (Afonso-Olivares *et al.* 2017). In addition, UPLC-MS/MS is the preferred analytical technique for pharmaceutical and personal care product analysis in water matrices due to the high precision and sensitivity of tandem mass spectrometry, as well as the ability to quantify multiple compounds simultaneously via multiple reaction monitoring (MRM) (Al-Qaim *et al.* 2012; Petrovic 2014).

In this study, 59 pharmaceuticals were selected as the target analytes in our analysis, including six penicillins, four cephalosporins, five macrolides, 15 sulfonamides, 10 fluoroquinolones, two other antibiotics, and 17 other pharmaceuticals. In addition, we aimed to determine the concentration and distribution of the 59 select pharmaceuticals in raw water, finished water, and tap water originating from 10 different river basins of China.

METHODS

Chemicals and standards

We detected 59 pharmaceuticals of 19 different classes (see Supplemental Material, Table S1, available with the online version of this paper). The following isotopically labeled compounds were used as internal standards for UPLC-MS/MS analysis: D₅-fluoxetine, D₃-cotinine, ¹³C₃-¹⁵N-ciprofloxacin, ¹³C₆-sulfamethazine, D₆-thiabendazole, D₈-sarafloxacin, ¹³C₃-caffeine, ¹³C₃-trimethoprim, D₃-acetaminophen, ¹³C-D₃-erythromycin, D₃-lincomycin, D₅-cephalexin, and ¹³C₆-sulfamethoxazole. Detailed information about target analyte standards and internal standards is listed in Supplemental Material, Table S1.

The following reagents were utilized in the sample analyses, as described where relevant in the subsequent method sections. Methanol and formic acid were of LC/MS grade and purchased from Fisher Scientific (New York, USA). Analytical grade phosphoric acid, potassium phosphate monobasic, ethylene diamine tetraacetic acid disodium salt (EDTA-2Na) and ascorbic acid were purchased from Sino-pharm Chemical Reagent Beijing Co., Ltd (Beijing, China). Ultrapure water (18 M Ω cm) was supplied by a Milli-Q

unit (Millipore, MA, USA). Stock solutions of individual pharmaceuticals and internal standards were prepared in methanol and stored at -20°C in the dark. Mixtures of standards at different concentrations were obtained by serial dilution with a methanol/water solution (10:90, v/v) prior to use and stored at 4°C .

Study area and sample collection

Water samples were collected from September 2016 to December 2016 in sunny weather condition, including raw water (the water from rivers, lakes, and reservoirs and groundwater), finished water, and tap water from 79 drinking water treatment plants (DWTPs) in 15 cities in seven large river basins in China. The cities of Yibin, Wuhan, and Shanghai are in the upper, middle, and lower reaches of Yangtze River Basin, respectively. Lanzhou and Jinan are in the upper and lower reaches of Yellow River Basin, respectively. Guangzhou, Mudanjiang, Huainan, Shenyang, and Kuerle are in Pearl River, Songhua River, Huaihe River, Liaohe River, and Northwest Rivers Basins, respectively. Additionally, Wuxi, Kunming, Chaohu, Chongqing,

and Danjiangkou were selected from Taihu Lake, Dianchi Lake, Chaohu Lake, Three Gorges Reservoir, and Danjiangkou Reservoir Basins, which are the key lake and reservoir watershed areas in China and belong to the Yangtze River Basin. The sampling cities and large river basins are shown in Figure 1.

According to the water distribution in each city, the following DWTPs were selected: 10 DWTPs each in Shanghai and Guangzhou, nine in Huainan, three each in Wuxi, Jinan, and Danjiangkou, one in Kuerle, and five each in the other eight cities. For each sample type, a 2,000 mL water sample was collected. In total, 237 water samples were collected and analyzed, including 79 raw water samples, 79 finished water samples, and 79 tap water samples. Water samples were collected manually by qualified personnel in 2,000 mL amber glass bottles with screw caps. The amber glass bottles were washed with water, methanol, and ultrapure water, and dried prior to sample collection. A total of 30 mg of ascorbic acid was added for each liter of water as a pharmaceutical preservative. The water samples were maintained in the dark at $<4^{\circ}\text{C}$ at the time of collection and upon reception at the laboratory.



Figure 1 | Sampling locations, including cities and seven large river basins. A, Yangtze River Basin; B, Yellow River Basin; C, Pearl River Basin; D, Songhua River Basin; E, Huaihe River; F, Liaohe River Basin; G, Northwest Rivers Basin.

Sample extraction

Target analytes were extracted from the water samples using SPE. One liter of water samples were acidified to pH 2.0–2.5 with phosphoric acid and potassium phosphate monobasic. The samples were spiked with isotopically labeled internal standards, at a concentration of 20 ng/L, and 500 mg of EDTA-2Na were added.

The water samples were loaded on the automated SPE system at an approximate rate of 5 mL/min (Visiprep-DL 24-Ports SPE Vacuum Manifold, Supelco, USA). Oasis HLB cartridges (6 mL, 200 mg of sorbent, Waters, USA) were used for sample pretreatment. The cartridges were conditioned with 10 mL of methanol and 10 mL of ultrapure water prior to sample loading. After sample loading, the cartridges were rinsed with 10 mL of ultrapure water, dried for 10 min under vacuum and eluted with 10 mL of methanol. The eluates were concentrated to near dryness under a gentle stream of nitrogen in a 30 °C water bath and reconstituted in 1 mL of water/methanol (95/5; v/v). The concentrated extracts were then analyzed by UPLC–MS/MS.

UPLC–MS/MS analysis

A UPLC system (ACQUITY UPLC, Waters, USA) equipped with a Waters ACQUITY UPLC HSS T3 column (100 mm × 2.1 mm and 1.8 µm particle size) was used to separate the analytes (see Supplemental Material, Table S2, available online). The column temperature was 40 °C, the injection volume was 10 µL, and the flow rate was 0.35 mL/min. The mobile phases consisted of water with 0.1% (v/v) formic acid (A) and methanol (B), and the following elution program was employed: 95% (A) to 80% (A) from 0 to 3 min, 80% to 70% (A) from 3 to 6 min, 70% to 60% (A) from 6 to 10 min, 60% to 30% (A) from 10 to 12 min, 30% to 5% (A) from 12 to 15 min, and then 95% (A) from 15 to 15.5 min. Finally, the column was re-equilibrated for 2.5 min before the next injection, for a total run time of 18 min.

A Waters TQ-S micro triple quadrupole mass spectrometer (Waters Technologies, USA) equipped with an electrospray ion source was used for the analysis of the pharmaceuticals (see Supplemental Material, Table S2 and Figure S1, available online). MRM mode was used for quantitative analysis, and

all pharmaceuticals were measured in positive ion mode. The source temperature was 120 °C, the desolvation temperature was 350 °C, the desolvation gas flow was 650 L/h, the collision gas flow was 50 L/h, and the capillary voltage was 2.0 kV.

Method performance and quality assurance

The determination of linearity, limit of detection (LOD) and limit of quantification (LOQ), recovery and precision were used to validate the method. Calibration curves were generated using mixtures of standards (IS) at concentrations from 0.05 to 100 µg/L and isotopically labeled internal standards at a concentration of 20 µg/L. Good linearity was observed, with correlation coefficients greater than 0.99 (see Supplemental Material, Table S3, available online).

The analytes were identified by their retention times, two characteristic ion transitions and specific ion ratios (deviation <20% with respect to analytical standard ratios). Spiked ultrapure water with various concentrations was extracted and analyzed to determine the LOD and LOQ. The LOD and LOQ were defined as the lowest concentrations that gave signal-to-noise ratios greater than 3 and 10, respectively (see Supplemental Material, Table S3).

Percent recovery and precision were determined using ultrapure water and spiked matrix samples (raw water and finished water) at three concentrations (5, 10, and 40 ng/L) and the IS solution (20 ng/L). Six replicates of each concentration were used to evaluate the analyte recovery during sample pretreatment and UPLC–MS/MS analysis. The recoveries were expressed as the average of six replicates. The recoveries and precision varied with the natures of the analytes (see Supplemental Material, Table S4, available online), and an acceptable result was generated (U.S. EPA 2007).

RESULTS

Pharmaceuticals in raw water samples

A total of 47 of the 59 compounds were identified in raw water samples, with detection rates ranging from 1.27 to 96.20%, and the average concentrations ranged from 0.09 ng/L to 128.87 ng/L (see Supplemental Material, Table S5, available with the online version of this paper).

The concentrations of pharmaceuticals in raw water samples from different river basins are shown in Figure 2. Penicillin compounds were found in the highest concentration in the upper reaches of the Yellow River Basin (116.07 ng/L) and were also found in relatively high

concentrations in the upper and lower reaches of the Yangtze River Basin (26.59 ng/L and 38.20 ng/L, respectively), Pearl River Basin (42.66 ng/L), Huaihe River Basin (39.38 ng/L), Dianchi Lake Basin (29.50 ng/L), and Three Gorges Reservoir (46.20 ng/L), where the predominant

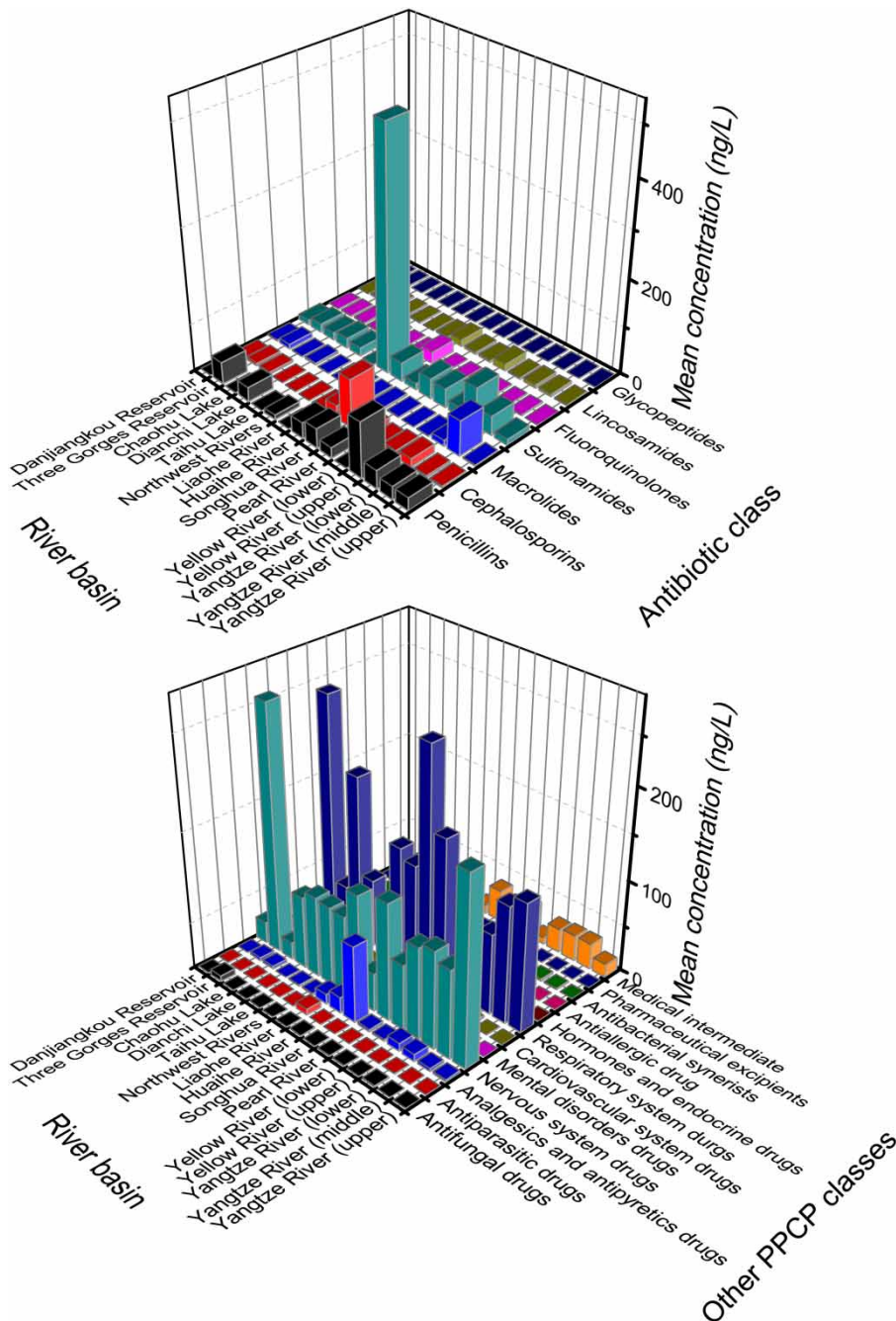


Figure 2 | Average concentrations of antibiotics and other pharmaceutical classes in raw water samples. The average concentration of one pharmaceutical class is the sum of the average concentration of all pharmaceuticals belonging to the class.

compounds were ampicillin and penicillin V (lower reaches of the Yangtze River Basin and upper reaches of the Yellow River Basin). Cephalosporins and penicillins were found in relatively high concentrations (102.05 ng/L and 40.67 ng/L, respectively) in the Songhua River Basin, and the predominant compounds were penicillin V, cefradine, and cephalexin. Sulfonamides had relatively high average concentration in the lower reaches of the Yellow River Basin (40.17 ng/L), the lower and middle reaches of the Yangtze River Basin (81.15 ng/L and 40.54 ng/L, respectively), Pearl River Basin (22.10 ng/L), Huaihe River Basin (33.11 ng/L), Taihu Lake Basin (17.65 ng/L), and Chaohu Lake Basin (15.47 ng/L), where the predominant compounds were sulfamethoxazole, sulfanilamide (the lower reaches of the Yangtze River Basin), and sulfamethazine (Pearl River Basin). Overall, sulfonamides had the highest average concentration (505.52 ng/L) in the Liaohe River Basin, and the predominant compounds were sulfanilamide, sulfadiazine, and sulfathiazole. Macrolides were also found at relatively high concentrations (73.28 ng/L) in the middle reaches of the Yangtze River Basin. Caffeine and codeine were present at relatively high concentrations in the upper reaches of the Yangtze River Basin (202.06 ng/L and 138.82 ng/L, respectively), Songhua River Basin (41.01 ng/L and 249.97 ng/L, respectively), and the Three Gorges Reservoir (196.33 ng/L and 251.76 ng/L, respectively). Finally, acetaminophen was also present at relatively high concentrations in the Songhua River Basin (82.82 ng/L).

Pharmaceuticals in finished water samples

A total of 43 of the 59 compounds were detected in finished water, with detection rates ranging from 1.27 to 96.20%, and average concentrations ranging from 0.07 ng/L to 59.17 ng/L (see Supplemental Material, Table S5). The pharmaceutical concentrations of finished water samples collected from different river basins are shown in Figure 3. Penicillin compounds were detected in relatively high average concentrations in finished water collected from the upper reaches of the Yangtze River Basin (11.15 ng/L), the upper reaches of the Yellow River Basin (47.88 ng/L), Pearl River Basin (21.87 ng/L), Huaihe River Basin (17.90 ng/L), Liaohe River Basin (10.61 ng/L), Three Gorges River Basin (9.62 ng/L), Chaohu Lake Basin (6.94 ng/L), and

Taihu Lake Basin (5.23 ng/L), where the predominant compounds were ampicillin (Yangtze River, Yellow River, Pearl River, Huaihe River, Three Gorges River, and Taihu Lake) and penicillin V (Yellow River, Huaihe River, and Chaohu Lake). Sulfonamides were detected in relatively high average concentrations in the lower reaches of the Yangtze River Basin (61.88 ng/L), the lower reaches of the Yellow River Basin (5.99 ng/L), Songhua River Basin (7.11 ng/L), Huaihe River Basin (21.59 ng/L), and Liaohe River Basin (9.55 ng/L), where the predominant compounds were sulfapyridine, sulfamethoxazole (Yellow and Songhua River Basins), sulfachloropyridazine, and sulfanilamide, respectively. The concentrations of antibiotics in finished water samples in the middle reaches of the Yangtze River Basin, Northwest Rivers Basin, Danjiangkou Reservoir, and Dianchi Lake Basin were relatively low. Macrolides were detected at a relatively high average concentration (10.54 ng/L) in the Songhua River Basin, and the predominant compound was roxithromycin.

Pharmaceuticals in tap water samples

A total of 42 compounds were determined in tap water samples, with detection rates ranging from 1.27% to 94.94% and the average concentrations ranging from 0.07 ng/L to 58.43 ng/L (see Supplemental Material, Table S5). The antibiotics such as ampicillin, penicillin V, roxithromycin, sulfamethoxazole, sulfanilamide, and oxolinic acid had relatively high detection rates, ranging from 13.92% to 65.82%, and the average concentrations ranged from 0.77 ng/L to 20.28 ng/L. Sulfapyridine and enrofloxacin had relatively high average concentrations (18.09 ng/L and 16.23 ng/L, respectively), and the detection rates were 7.59% and 6.33%, respectively. For the other pharmaceutical classes, caffeine, codeine, dimethylxanthine, and cotinine were detected at relatively high concentrations (42.05 ng/L, 74.68 ng/L, 7.32 ng/L, and 36.71 ng/L, respectively) and detection rates (94.94%, 74.68%, 36.71%, and 36.71%, respectively). In Spain, the median concentrations of caffeine, cotinine, and carbamazepine in drinking water were 30.0 ng/L, 25.0 ng/L, and 4.0 ng/L, respectively (Carmona *et al.* 2014). In this study, the median concentrations of caffeine, cotinine, and carbamazepine were 21.2 ng/L, 55.2 ng/L, and 0.5 ng/L, respectively. By

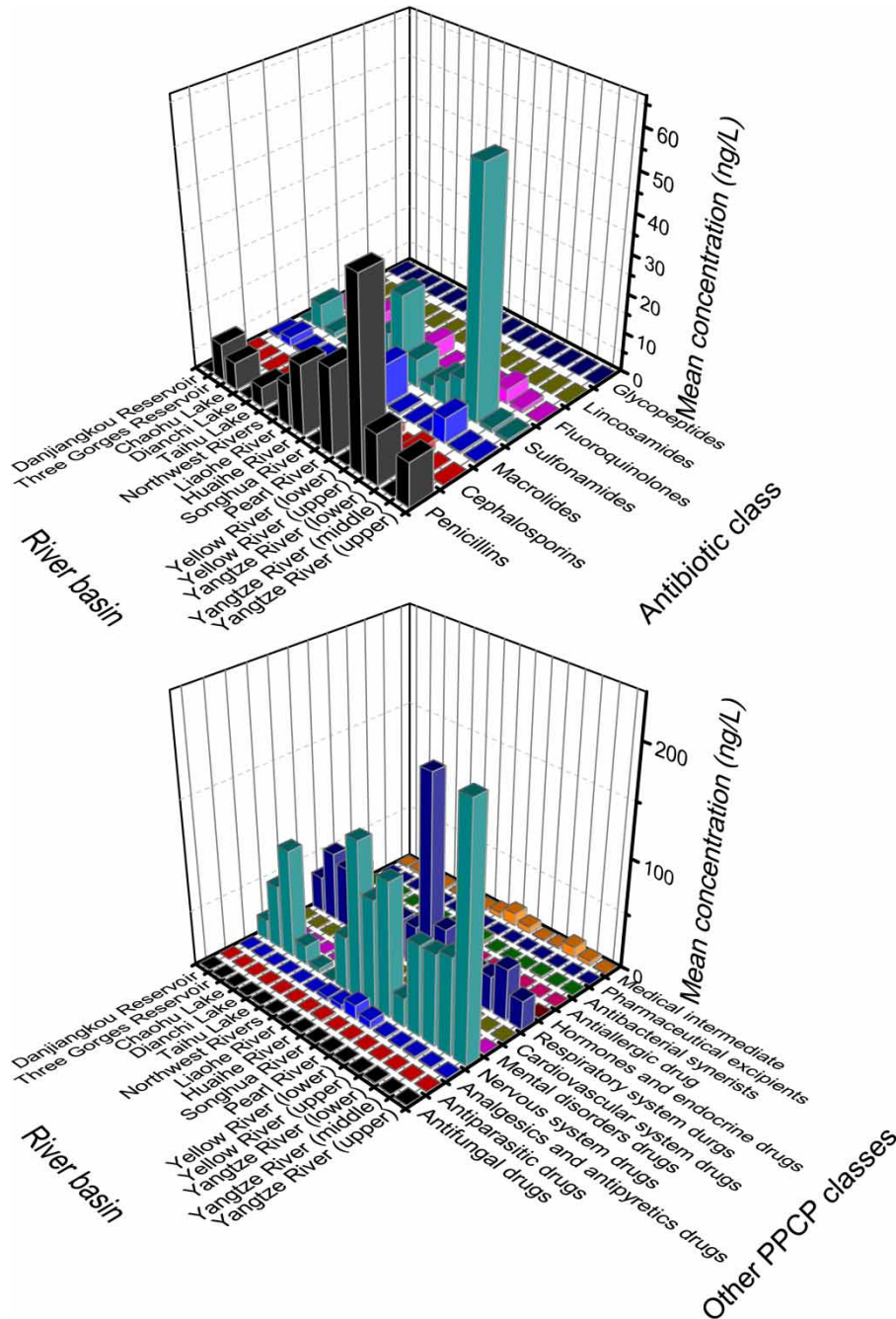


Figure 3 | Average concentrations of antibiotics and other pharmaceutical classes in finished water samples.

comparison, the median concentrations of caffeine and carbamazepine in drinking water were lower than those in Spain, while the median concentration of cotinine was more than double that measured in Spain. The spatial distribution of the pharmaceutical concentration levels in tap

water samples from different river basins is shown in Figure 4. The concentration distribution of most pharmaceuticals is similar to that of the finished water samples, except enrofloxacin which is detected in the highest concentration in Chaohu Lake (70.09 ng/L).

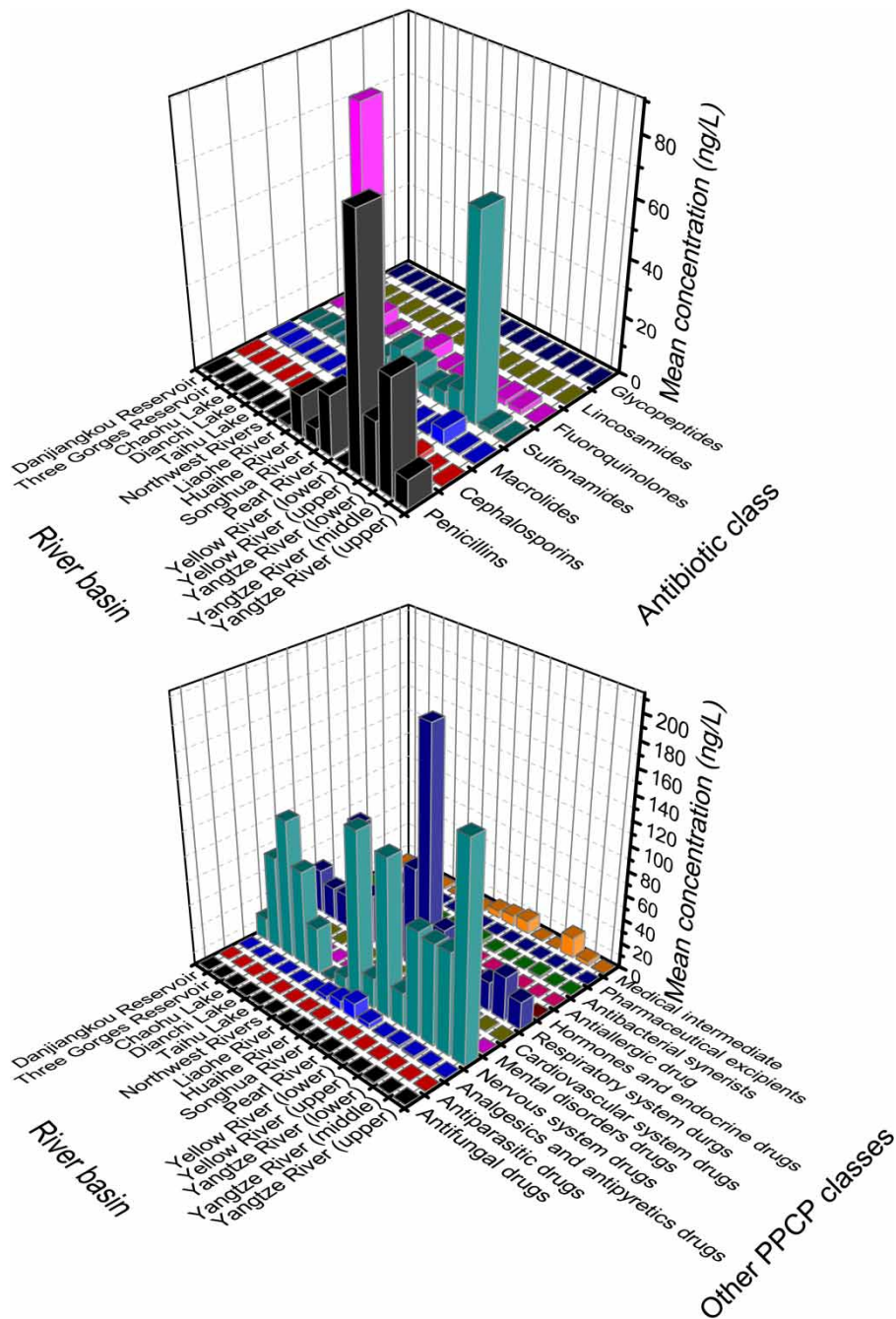


Figure 4 | Average concentrations of antibiotics and other pharmaceutical classes in tap water samples.

Removal efficiency of pharmaceuticals in DWTPs

Samples were collected from 79 DWTPs with different treatment schemes, and the details are listed in Table 1. The average removal efficiency of each pharmaceutical from

water treatment processes is shown in Figure 5. The result shows that purification methods during water treatment have a positive effect on the removal of some pharmaceuticals. Seventeen antibiotics, including two penicillins, three cephalosporins, two macrolides, nine sulfonamides, one

Table 1 | Summary of treatment schematics of 79 drinking water treatment plants and the number of facilities with each treatment schematic

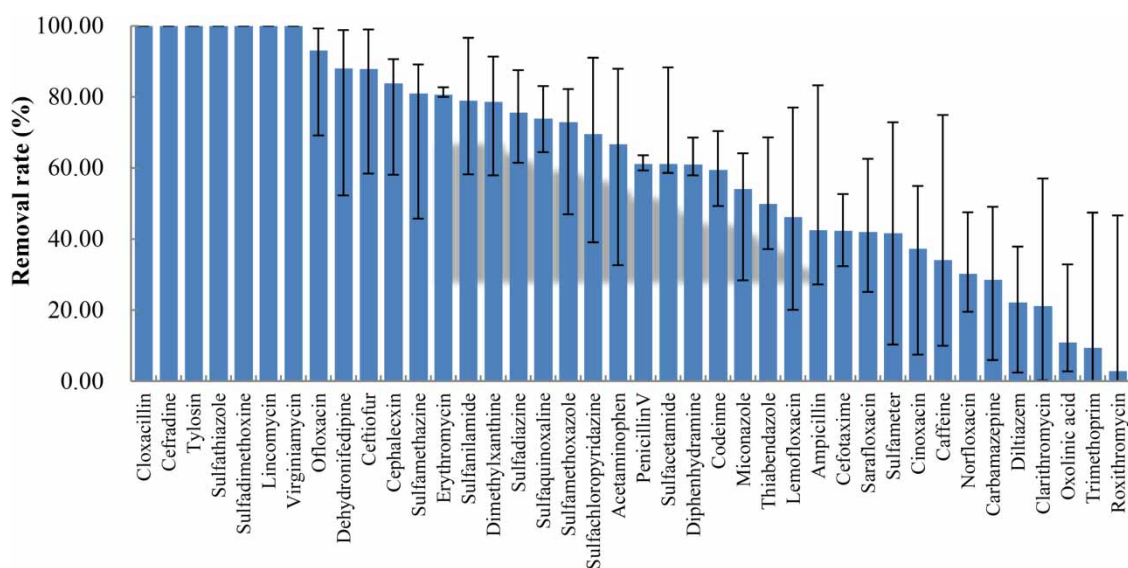
Treatment processes	Facilities
Coagulation–sedimentation–filtration–disinfection	57
Biological pretreatment–coagulation–sedimentation–filtration–disinfection	2
Coagulation–sedimentation–filtration–ozonation and activated carbon–membrane–disinfection	2
Coagulation–sedimentation–filtration–ozonation and activated carbon–disinfection	5
Coagulation–sedimentation–filtration–iron and manganese treatment–disinfection	1
Filtration–disinfection	2
Sedimentation–disinfection	1
Disinfection	7
Sedimentation	2

fluoroquinolones, lincomycin, and virginiamycin, as well as seven other pharmaceuticals, had average removal rates above 50%, and eight pharmaceuticals had average removal rates above 90%. Some pharmaceuticals were also detected in the effluents at concentrations equal to the concentrations in the influents, indicating removal rates of 0%. The average removal efficiencies of caffeine, carbamazepine, erythromycin, and sulfamethoxazole were 34.1%,

28.7%, 80.7%, and 72.9%, respectively. According to previous studies, the removal efficiencies were 61.3% for caffeine, 20.0–88.9% for carbamazepine, >81.2% for erythromycin, and >48.0% for sulfamethoxazole (Vieno *et al.* 2007; Benotti *et al.* 2008; Carmona *et al.* 2014; Cai *et al.* 2015). Although these compounds have different removal efficiencies in these studies, a similar positive removal effect is seen.

DISCUSSION

Five penicillins, four cephalosporins, five macrolides, 11 sulfonamides, seven fluoroquinolones, two other antibiotics, and 13 other pharmaceuticals were detected in raw water samples. Generally, the concentrations of all selected pharmaceuticals were at the nanogram per liter level in raw water samples. Of penicillins detected in raw water samples, ampicillin was detected with the highest detection rate (54.43%). The concentration levels ranged from 1.61 ng/L to 162.28 ng/L, with an average concentration of 27.72 ng/L. Of the four cephalosporins, cephalexin was detected with the highest detection rate (39.24%). The concentration levels ranged from 0.99 ng/L to 72.13 ng/L, with an average concentration of 10.44 ng/L. Of the five macrolides,

**Figure 5** | Removal efficiency of 40 target pharmaceuticals detected in raw water samples with positive removal rates in the DWTPs. Results of the bar graph showed a maximum, average and minimum removal rate of each pharmaceutical. Removal rates (% elimination) were calculated by dividing the concentration difference for each pharmaceutical before and after treatment steps by the concentration of the pharmaceutical in raw water.

roxithromycin was detected with the highest detection rate (78.48%) but with relatively low concentrations (0.06 ng/L to 6.88 ng/L). A similar result was found in a study of eight DWTPs in France, in which the roxithromycin concentration was 6 ng/L (Vulliet *et al.* 2011). Erythromycin was found at relatively high concentrations (2.34 ng/L to 78.71 ng/L), with an average concentration of 26.31 ng/L, but it was only detected in samples collected from the middle and lower reaches of the Yangtze River Basin. Compared to the average erythromycin concentrations found in surface water near Gdańsk, Poland (2.7 ng/L), the erythromycin concentrations in the Yangtze River Basin were considerably higher. Sulfonamides detected in the raw water samples were significantly higher than that of the other classes of antibiotics. Sulfamethoxazole had the highest detection rate (91.14%) and was found at concentrations ranging from 0.42 ng/L to 49.20 ng/L, with an average concentration of 11.56 ng/L. Sulfadiazine and sulfamethazine were also prevalent, with concentrations ranging from 0.05 ng/L to 85.31 ng/L and 0.03 ng/L to 75.03 ng/L, respectively. Sulfamethoxazole and sulfamethazine were also detected in surface water in Canada, with the concentrations of 284 ng/L and 34 ng/L, respectively (Ontario Ministry of the Environment 2010). Of the seven fluoroquinolones, flumequine was detected with the highest detection rate (36.71%) but at relatively low concentrations (0.02–2.34 ng/L). Ofloxacin was only detected in samples from the Huaihe River Basin, the lower reaches of the Yellow River and lower reaches of the Yangtze River Basin, with relatively high concentrations (0.39–35.10 ng/L). Caffeine, dimethylxanthine, codeine, acetaminophen, and cotinine were also found at relatively high concentrations and detection rates.

Five penicillin compounds were detected in finished water. Ampicillin had the highest detection rate (15.19%), and its concentration ranged from 5.14 ng/L to 33.14 ng/L, with an average concentration of 10.48 ng/L. Three cephalosporin compounds were detected in finished water samples with relatively lower detection rate, ranging from 1.27% to 3.80%. The concentrations ranged from 0.90 ng/L to 1.68 ng/L. Four macrolides were detected in finished water samples. Roxithromycin had the highest detection rate (67.09%) and a relatively low average concentration (1.33 ng/L). Erythromycin was detected in finished water

samples from the lower reaches of the Yangtze River Basin, with an average concentration of 5.07 ng/L, and the concentrations were similar to the average concentration (3.4 ng/L) measured in finished water in Poland (Vieno *et al.* 2007). Ten sulfonamides were detected in finished water samples. Sulfamethoxazole had the highest detection rate (44.30%), and its concentration ranged from 0.04 ng/L to 19.98 ng/L, with an average concentration of 3.13 ng/L. The concentration of sulfamethoxazole was higher than that in finished water from eight DWTPs in France (concentration range of not detected to 0.8 ng/L) (Vulliet *et al.* 2011). Eight fluoroquinolones were detected at relatively low concentrations (0.07–2.79 ng/L). Thirteen other pharmaceuticals were also detected, including caffeine, codeine, dimethylxanthine, and cotinine, at relatively high concentrations (41.02 ng/L, 52.28 ng/L, 5.31 ng/L, and 59.17 ng/L, respectively) and detection rates (96.2%, 78.48%, 59.49%, and 41.77%, respectively). In addition, the median, average, and maximum concentrations for carbamazepine, fluoxetine, and caffeine were 0.67 ng/L, 2.1 ng/L, and 23.56 ng/L median concentrations, respectively; 1.22 ng/L, 2.08 ng/L, and 41.02 ng/L average concentrations, respectively; and 6.16 ng/L, 2.08 ng/L, and 576.02 ng/L maximum concentrations, respectively. In comparison, the median concentration of carbamazepine in finished water samples in Canada was lower at 0.21 ng/L, and the highest concentration was 601 ng/L, which was considerably higher (Boyd *et al.* 2003; Ontario Ministry of the Environment 2010). In the USA, the median concentrations of carbamazepine and fluoxetine in finished water samples were 6 ng/L and 0.11 ng/L, respectively, and the highest concentrations were 18 ng/L and 0.82 ng/L, respectively (Benotti *et al.* 2008). In Poland, the average concentrations of caffeine and carbamazepine in finished water were 49.3 ng/L and 3.4 ng/L, and the highest concentrations were 158.7 ng/L and 6.0 ng/L, respectively (Vieno *et al.* 2007). In France, the maximum concentration of carbamazepine in finished water samples was 21.8 ng/L (Vulliet *et al.* 2011).

The concentrations of all detected pharmaceuticals in tap water samples were at the nanogram per liter level. Wang *et al.* (2016) investigated the presence of antibiotics in drinking water and their contribution to antibiotic exposure of school children in Shanghai. The results indicated that drinking water contaminated by antibiotics in Shanghai played a limited role in the total antibiotic

exposure in children. However, as a low-dose antibiotic exposure risk factor, antibiotic contamination of drinking water led to the long-term exposure of children to low-dose antibiotics. It is noteworthy that current studies on the potential health hazards of antibiotics are based on antibiotic use or relevant high-dose exposure. Moreover, most studies have focused on the short-term effects of high-dose antibiotic exposures. Because a significant difference exists between the two kinds of exposure modes (i.e., short-term exposure to high-dose antibiotics and long-term exposure to low-dose antibiotics), more studies are needed to clarify the effects of the latter's exposure mode on human health.

In summary, PPCPs were detected in all watersheds, treatment facilities, and municipal tap water samples investigated in this study. Some concentrations were particularly high across the three water sample types and various locations in China, such as for ampicillin, penicillin V, roxithromycin, sulfamethoxazole, sulfanilamide, caffeine, cotinine, and carbamazepine. Moreover, some pharmaceuticals were detected in concentrations higher than those typically found in other countries. While removal rates for pharmaceuticals, via different water treatment methods, were promising, the issue of long-term low-dose exposure to pharmaceuticals remains. This study provides important and thorough data regarding the prevalence of these 59 compounds in drinking water systems; yet, further study of the long-term health risks, as well as the development of more efficient water treatment techniques, is still needed.

CONCLUSIONS

The method chosen for the identification and quantification of pharmaceuticals in water samples, which involved solid-phase extraction coupled with ultra-high-performance liquid chromatography–tandem mass spectrometry (SPE–UPLC–MS/MS), provided appropriate linearity, LODs, LOQs, recoveries, and precision. This analysis method was developed based on EPA Method 1694, and commonly used pharmaceuticals in China were selected as the target analytes. This study represents the most extensive investigation of pharmaceuticals in tap water and finished water in Chinese river basins. Of the 59 selected PPCPs, 47, 43, and 42 of these compounds were detected in raw, finished,

and tap water samples, respectively. The concentrations of pharmaceuticals were in the nanogram per liter range. Among the detected antibiotics, ampicillin, penicillin V, roxithromycin, sulfamethoxazole, sulfanilamide, and oxolinic acid were predominant in finished water and tap water samples. Among the other pharmaceuticals, caffeine, codeine, dimethylxanthine, and cotinine were predominant in finished water and tap water samples, at relatively high concentrations. The concentrations of most pharmaceuticals detected in finished water and tap water were lower than those in raw water, indicating positive removal efficiency during water treatment. However, incomplete removal of pharmaceuticals during water treatment led to contamination of drinking water. This contamination is concerning, even at low concentrations, since the consequential health effects are not fully understood. This study provides important information regarding the occurrence and distribution of these substances in raw, finished, and tap water in seven different water basins of China. Certainly, further investigation on the fate of pharmaceuticals in DWTPs is needed. Furthermore, studies on the health effects as well as thorough health risk assessments are needed for long-term exposure to low-dose pharmaceuticals in drinking water.

CONFLICTS OF INTEREST

The authors declare no competing financial interest.

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REFERENCES

- Afonso-Olivares, C., Čadková, T., Sosa-Ferrera, Z., Santana-Rodríguez, J. & Nováková, L. 2017 Simplified solid-phase extraction procedure combined with liquid chromatography tandem-mass spectrometry for multiresidue assessment of pharmaceutical compounds in environmental liquid samples. *J. Chromatogr. A* **1487**, 54–63.
- Alder, A. C., Schaffner, C., Majewsky, M., Klasmeier, J. & Fenner, K. 2010 Fate of β -blocker human pharmaceuticals in surface water: comparison of measured and simulated concentrations in the Glatt Valley Watershed, Switzerland. *Water Res.* **44**, 936–948.
- Al-Qaim, F. F., Abdullah, M. P. & Othman, M. R. 2012 Analysis of different therapeutic classes using liquid chromatography-mass spectrometry in aquatic environment: a review. *Int. J. Pharm. Pharm. Sci.* **4** (4), 3–11.
- Ashbolt, N. J., Amézquita, A., Backhaus, T., Borriello, P., Brandt, K. K., Collignon, P., Coors, A., Finley, R., Gaze, W. H. & Heberer, T. 2013 Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environ. Health Perspect.* **121**, 993–1001.
- Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D. & Snyder, S. A. 2008 Pharmaceuticals and endocrine disrupting compounds in US drinking water. *Environ. Sci. Technol.* **43**, 597–603.
- Boxall, A. B. A., Rudd, M. A., Brooks, B. W., Caldwell, D. J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J. P. & Verslycke, T. 2012 Pharmaceuticals and personal care products in the environment: what are the big questions? *Environ. Health Perspect.* **120**, 1221–1229.
- Boyd, G. R., Reemtsma, H., Grimm, D. A. & Mitra, S. 2003 Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *Sci. Total Environ.* **311**, 135–149.
- Bradley, P. M., Journey, C. A., Button, D. T., Carlisle, D. M., Clark, J. M., Mahler, B. J., Nakagaki, N., Qi, S. L., Waite, I. R. & VanMetre, P. C. 2016 Metformin and other pharmaceuticals widespread in wadeable streams of the southeastern United States. *Environ. Sci. Technol. Lett.* **3**, 243–249.
- Cai, M. Q., Wang, R., Feng, L. & Zhang, L. Q. 2015 Determination of selected pharmaceuticals in tap water and drinking water treatment plant by high-performance liquid chromatography-triple quadrupole mass spectrometer in Beijing, China. *Environ. Sci. Pollut. Res.* **22**, 1854–1867.
- Calamari, D., Zuccato, E., Castiglioni, S., Bagnati, R. & Fanelli, R. 2003 Strategic survey of therapeutic drugs in the rivers Po and Lambro in northern Italy. *Environ. Sci. Technol.* **37**, 1241–1248.
- Carmona, E., Andreu, V. & Picó, Y. 2014 Occurrence of acidic pharmaceuticals and personal care products in Turia River Basin: from waste to drinking water. *Sci. Total Environ.* **484**, 53–63.
- Kot-Wasik, A., Jakimska, A. & Śliwka-Kaszyńska, M. 2016 Occurrence and seasonal variations of 25 pharmaceutical residues in wastewater and drinking water treatment plants. *Environ. Monit. Assess.* **188** (661), 1–13.
- Liu, J. L. & Wong, M. H. 2013 Pharmaceuticals and personal care products (PPCPs): a review on environmental contamination in China. *Environ. Int.* **59**, 208–224.
- Ontario Ministry of the Environment 2010 *Survey of the Occurrence of Pharmaceuticals and Other Emerging Contaminants in Untreated Source and Finished Drinking Water in Ontario*. Ontario Ministry of the Environment, Ontario, Canada.
- Petrovic, M. 2014 Methodological challenges of multi-residue analysis of pharmaceuticals in environmental samples. *Trends. Environ. Analyt. Chem.* **1**, e25–e33.
- Simazaki, D., Fujiwara, J., Manabe, S., Matsuda, M., Asami, M. & Kunikane, S. 2008 Removal of selected pharmaceuticals by chlorination, coagulation-sedimentation and powdered activated carbon treatment. *Water Sci. Technol.* **58** (5), 1129–1135.
- Ternes, T. A., Meisenheimer, M., McDowell, D., Sacher, F., Brauch, H. J., Haist-Gulde, B., Preuss, G., Wilme, U. & Zulei-Seibert, N. 2002 Removal of pharmaceuticals during drinking water treatment. *Environ. Sci. Technol.* **36**, 3855–3863.
- U.S. Environmental Protection Agency 2007 *Method 1694: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment and Biosolids by HPLC/MS/MS*. Environmental Protection Agency, Office of Water, WDC, USA.
- Vieno, N. M., Härkki, H., Tuhkanen, T. & Kronberg, L. 2007 Occurrence of pharmaceuticals in river water and their elimination in a pilot-scale drinking water treatment plant. *Environ. Sci. Technol.* **41**, 5077–5084.
- Vulliet, E., Cren-Olivé, C. & Grenier-Loustalot, M. -F. 2011 Occurrence of pharmaceuticals and hormones in drinking water treated from surface waters. *Environ. Chem. Lett.* **9**, 103–114.
- Wang, H. X., Wang, N., Wang, B., Zhao, Q., Fang, H., Fu, C. W., Tang, C. X., Jiang, F., Zhou, Y., Chen, Y. & Jiang, Q. W. 2016 Antibiotics in drinking water in Shanghai and their

- contribution to antibiotic exposure of school children. *Environ. Sci. Technol.* **50**, 2692–2699.
- Watkinson, A. J., Murby, E. J., Kolpin, D. W. & Costanzo, S. D. 2009 The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. *Sci. Total Environ.* **407** (8), 2711–2723.
- Yiruhan, W. Q. J., Mo, C. H., Li, Y. W., Gao, P., Tai, Y. P., Zhang, Y., Ruan, Z. L. & Xu, J. W. 2010 Determination of four fluoroquinolone antibiotics in tap water in Guangzhou and Macao. *Environ. Pollut.* **158**, 2350–2358.
- Zhang, Q. Q., Ying, G. G., Pan, C. G., Liu, Y. S. & Zhao, J. L. 2015 Comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. *Environ. Sci. Technol.* **49**, 6772–6782.
- Zhao, W. T., Guo, Y., Lu, S. G., Yan, P. P. & Sui, Q. 2016 Recent advances in pharmaceuticals and personal care products in the surface water and sediments in China. *Front. Environ. Sci. Eng.* **10** (6), 29–40.

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