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Antibiotics in the surface water and sediment from the tributaries of the Xiaoqing River, China: occurrence, distribution and risk assessment

Wenping Dong[a], Miaowei Ci[b,c], Xianshou Yan[d,e], Yongqiang Wang[b], Guodong Zhang[f], Wenfeng Xu[g], Xingang Gao[h], Kang Xie[i], Weiliang Wang[b,c,*]

[a]*Shandong Academy of Environmental Science Co., Ltd., Jinan 250013, China, email: yueyan224@163.com*
[b]*College of Geography and Environment, Shandong Normal University, Jinan 250358, China, Tel. +86 15990905868; email: sunboyhood@163.com (W. Wang), 115914848@qq.com (M. Ci), yqwang0_0@163.com (Y. Wang)*
[c]*Institute of Environment and Ecology, Shandong Normal University, Jinan 250358, China*
[d]*Heze Zhongkecheng Sewage Purification Co., Ltd., Heze 274000, China, email: yanxianshou2018@163.com*
[e]*BeiJing Enterprises Water Group Limited, Beijing 100000, China*
[f]*College of Natural Resources and Environment, Northwest A&F University, Xianyang 712100, China, email: 947596309@qq.com*
[g]*Shandong Think-eee Environmental Technology Co., Ltd., Jinan 250101, China, email: michael.xu@think-eee.cn*
[h]*Qingdao Jiaming Measurement and Control Technology Co., Ltd., Qingdao 266000, China, email: 13006525021@163.com*
[i]*School of Civil Engineering and Architecture, University of Jinan, Jinan 250022, China, email: sdxiekang@126.com*

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ABSTRACT

Antibiotic residues are being highlighted around the world as emerging concerns in aquatic environments. Here, the occurrence of antibiotics in tributaries of the Xiaoqing River, China, as well as the spatial and temporal distributions, were reported. The total concentrations of 19 antibiotics in surface water and sediments ranged from 8.20–809.07 ng L^{-1} and from 39.57–2,151.64 μg kg^{-1} dry weight (dw), respectively. Among all detected antibiotics, ofloxacin showed the highest concentration and detection frequency in both surface water (283.83 ng L^{-1}, 100%) and sediment (1,827.18 μg kg^{-1} dw, 100%). The pollution levels of antibiotics in different seasons were in the following order: dry season > normal season > wet season, except for clarithromycin, sulfadiazine, sulfamerazine and sulfaquinoxaline. Domestic, aquaculture and livestock wastewater might be the main pollution sources of antibiotics in the tributaries of the Xiaoqing River. Moreover, the Pearson correlation coefficient showed significantly positive correlations between antibiotics and heavy metals (such as Cu, Zn and Pb), indicating that there may be a combination of contaminants. The environmental risk assessment indicated a high environmental risk of ofloxacin, clarithromycin, roxithromycin and sulfamethoxazole.

Keywords: Antibiotics; Xiaoqing River; Surface water; Sediment; Risk assessment

1. Introduction

In recent decades, antibiotics have been widely used in the treatment of human infectious diseases and the protection of animal health [1,2]. Simultaneously, the side effects of antibiotics have gradually emerged, such as killing beneficial cells, inducing the production of antibiotic resistance genes and spreading bacterial resistance [3,4]. China is the largest producer and user of antibiotics in the world based on market sales data [5]. More than 53 thousand tons of antibiotics were discharged into the aquatic environment following various wastewater treatments in 2013 [6]. The level of antibiotic residues in the aquatic environment in

* Corresponding author.

China is relatively high on the global scale [7]. The massive overuse of antibiotics and the neglect of antibiotic emissions pose great threats to the environment and human beings [8–10].

The discharge of antibiotics from multiple sources (e.g., sewage treatment plants and domestic and/or aquaculture wastewater) causes antibiotic contamination [11,12]. After entering the aquatic environment, antibiotics undergo a variety of migration and transformation processes, such as dilution, deposition, adsorption and degradation [13]. Various antibiotic residues detected in water, sediment and soil may have toxic effects on aquatic organisms [14,15]. Long-term exposure to antibiotics can change the structure and function of microbial communities and increase the bioaccumulation in algae and fish [16–18]. Moreover, heavy metals, another important pollutant in rivers and lakes, may have synergistic or antagonistic effects when combined with antibiotics [19,20].

The Xiaoqing River basin is located in the northwest plain of Shandong Province. The total length of the river is 237 km, and the controlled area of the basin is 10,336 km^2 (6.5% of the total area of Shandong Province). The population density of cities in the basin is relatively high (699 people km^{-2}), and the level of agriculture is developed. As the main artificial river accepting sewage in the basin, the Xiaoqing River originates in Jinan, passes through Binzhou, Zibo, Dongying and Weifang, and eventually enters Laizhou Bay. Li et al. [21] found that macrolide antibiotics and trimethoprim were widely detected in surface waters in the Xiaoqing River. The results of Zhang et al. [22] showed that the Xiaoqing River is the main source of pollution loading in Laizhou Bay. However, with increasingly strict environmental protection requirements, the direct discharge of sewage into the mainstream of the Xiaoqing River has been gradually banned. Many potential sources of pollution in tributaries of the Xiaoqing River may contribute to more antibiotic contamination.

Four groups of target antibiotics, quinolones (QNs), macrolides (MLs), tetracyclines (TCs) and sulfonamides (SAs), were investigated in tributaries of the Xiaoqing River, as was trimethoprim (TMP). These are the most commonly used antibiotics in human and veterinary medicine in China and are widely present in surface water and sediments [22–24]. The objectives of the present study were not only to investigate the occurrence and distribution of antibiotics in water and sediment in the tributaries of the Xiaoqing River but also to clarify the relationship between antibiotics and heavy metals. Risk quotients (RQs) were used to evaluate the environmental risk of each antibiotic. This work can provide a reliable reference for antibiotic inventories and promote our understanding of antibiotic environmental processes and fates, as well as improve water quality and water resource management in the Xiaoqing River basin.

2. Materials and methods

2.1. Chemicals and reagents

The selection of the 19 antibiotics was based on their high detection frequencies in other lakes and rivers and their high consumption. Five quinolones (QNs), including enoxacin (ENX), ofloxacin (OFX), norfloxacin (NOR), ciprofloxacin (CIP) and enrofloxacin (EFX); three tetracyclines (TCs), including oxytetracycline (OTC), tetracycline (TC) and chlortetracycline (CTC); two macrolides (MLs), including clarithromycin (CTM) and roxithromycin (RTM); and seven sulfonamides (SAs), including sulfadiazine (SDZ), sulfathiazole (STZ), sulfamerazine (SMA), sulfachloropyridazine (SCP), sulfadimethoxypyrimidine (SDX), sulfamethoxazole (SMX) and sulfaquinoxaline (SQX); and trimethoprim (TMP), were purchased from Dr. Ehrenstorfer-Schafers (Augsburg, Germany). Azithromycin (AZM) was purchased from the Fluorochem Company (British). The isotope-labelled internal standards sulfamethoxazole-D_4 (SMX-D_4), ciprofloxacin-D_8 (CIP-D_8), trimethoprim-$^{13}C_3$ (TMP-$^{13}C_3$), erythromycin-^{13}C-D_3 (ERM-^{13}C-D_3) and demethylaureomycin (DMC) were purchased from Dr. Ehrenstorfer-Schafers (Augsburg, Germany). Individual antibiotic standard stock solutions with concentrations up to 1,000 mg L^{-1} were prepared in methanol and stored in the dark at −20°C before use. Mixed working solutions with different concentrations were prepared by diluting the stock solutions before each analytical process.

High-performance liquid chromatography-grade methanol and acetonitrile were obtained from Sigma-Aldrich (St. Louis, MO, USA), and formic acid was purchased from Tianjin Chemical Reagents Company (Tianjin, China). Na_2EDTA, ammonia, hydrochloric acid and other chemicals used were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China).

2.2. Study area and sample collection

Surface water (in February, May and August) and sediment (in August) samples were collected from the tributaries of the Xiaoqing River in 2017. The sampling points were located mainly at the intersection of the significant tributaries, the urban section in Xiaoqing River basin, and the vicinity of industry, aquaculture and hospitals (Fig. 1). Detailed information about the sampling sites is shown in Supplementary Material Table S1. Water samples (1 L) were collected by a stainless steel water sampler and stored in brown glass bottles washed with methanol and ultrapure water. Methanol (10 mL) was added to inhibit the growth of microorganisms and returned to the laboratory for storage at 0°C–4°C. Sediments (0–20 cm) were collected by a grab bucket, wrapped in aluminium foil and then put into Ziplock bags. After being transported back to the laboratory, the sediments were frozen and dried and stored at –20°C for subsequent experiments.

2.3. Sample extraction and analysis

The surface water samples (1 L) were filtered through glass microfibre filters (0.45 μm) (Tianjin, 0.45 μm, USA origin membranes) to remove suspended particles. Na_2EDTA (0.5 g) and 100 ng internal standard were added to the samples, and the pH was adjusted to 3 ± 0.5 with hydrochloric acid. The antibiotics were concentrated through solid-phase extraction (SPE) by an Oasis HLB cartridge (500 mg, 6 mL). The following steps were performed according to

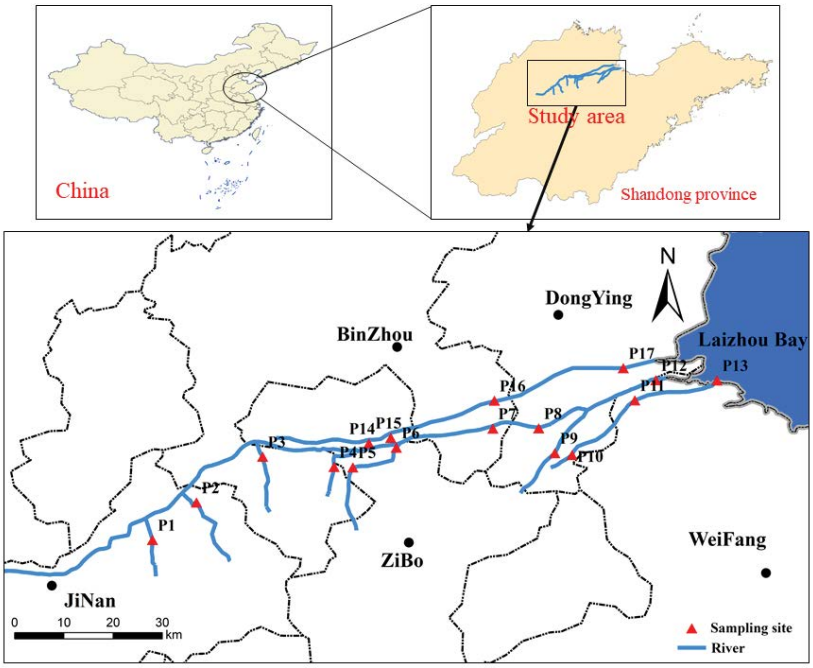

Fig. 1. Sampling sites in Xiaoqing River, Shandong, China.

our previous study [25]. The antibiotics in sediments (2 g, freeze-dried, containing 100 ng internal standard) were extracted by oscillation (200 rpm, 15 min), ultrasound (40 Hz, 10 min) and centrifugation (8,000 rpm, 5 min), with 15 mL EDTA-Mcilvaine buffer and 15 mL acetonitrile added. This extraction was repeated two more times. The supernatant was decanted into a round bottom flask for rotary evaporation. The residual liquid was redissolved in ultrapure water to 500 mL. The SAX cartridge (6 mL, 500 mg) and Waters Oasis HLB (6 mL, 500 mg) cartridge were connected in series to extract antibiotics from the solution. Then, the HLB column was washed with 5 mL of deionized water. The following treatment procedure was the same as that for the water sample treatment.

The analysis of the antibiotics was performed by high-performance liquid chromatography-tandem mass spectrometry (Agilent LC1100-641OB, USA) equipped with a UPLC BEH-C18 column (50 mm × 2.1 mm, 1.7 μm). The mobile phases were A (0.3% formic acid and 0.1% ammonium formated in ultrapure water) and B (acetonitrile:-methanol = 1:1), and the column was maintained at 40°C during the sample analysis. The flow rate was 0.3 mL min^{-1}, and the injection quantity was 10 μL. The separation of the antibiotics was achieved with a gradient program as follows: 95% A~5% B was maintained for 3 min at first and then linearly changed to 12% A~88% B within 30 min. Mass spectrometric analyses were equipped with an electrospray ionization source in the positive mode (ESI+) to analyze the antibiotics, and the quantification of each target antibiotic was performed in the multiple reaction monitoring modes (MRM). More mass spectrometry conditions are described in Supplementary Material Table S2. The total amounts of different metals (Table S3), such as Cu, Pb, Zn, and Cr, were analyzed using inductively coupled plasma–mass spectrometry (ICP–MS, Optima, 2,000 DV, Perkin Elmer, USA).

2.4. Quality assurance and quality control

A 9-point multicomponent internal standard calibration curve presented a good linear relationship ($R^2 > 0.99$) and was applied for the quantification of target antibiotics. The limits of detection (LODs) and quantification (LOQs) were determined as the concentration of analyte giving a signal-to-noise ratio of 3 and 10, respectively (Table S4). Duplicates, method blanks, and solvent blanks were used for quality control.

2.5. Environmental risk assessment

The risk quotient (RQ) was used to evaluate the ecological risk of antibiotics in the Xiaoqing River [11,26,27]. The RQ was calculated by the maximum measured environmental concentration (MEC) and the predicted no-effect concentration (PNEC). The formula is as follows:

$$RQ = \frac{MEC}{PNEC} \quad (1)$$

where the RQ values were classified into the following four risk levels: no risk (RQ < 0.01), low risk (0.01 < RQ < 0.1), medium risk (0.1 < RQ < 1), and high risk (RQ > 1).

3. Results and discussion

3.1. Occurrence of antibiotics in the tributaries of the Xiaoqing River

The concentrations of target antibiotics in the surface water and sediment are shown in Table 1. Seventeen of the

Table 1
Concentrations of target antibiotics in surface water and sediment

Antibiotics		Surface water (n = 17, ng L^{-1})				Sediment (n = 14, μg kg^{-1} dw)			
		Min.	Max.	Avg.	DF	Min.	Max.	Avg.	DF
QNs	ENX	ND	72.02	2.67	58.82%	ND	<LOQ	0.13	7.14%
	OFX	<LOQ	283.83	21.48	100%	4.05	1,827.18	171.34	100%
	NOR	ND	3.70	0.37	27.45%	ND	119.48	16.26	28.57%
	CIP	ND	<LOQ	0.02	1.96%	ND	50.23	10.08	71.43%
	EFX	ND	1.85	0.20	19.61%	ND	62.37	6.43	50%
TCs	OTC	ND	ND	0	0%	ND	20.67	4.62	35.71%
	TC	ND	ND	0	0%	ND	<LOQ	0.30	7.14%
	CTC	ND	141.80	4.45	19.61%	ND	51.10	7.86	21.43%
MLs	CTM	ND	37.11	5.32	86.27%	ND	0.98	0.13	42.86%
	AZM	ND	15.60	2.52	80.39%	ND	1.00	0.10	21.43%
	RTM	ND	71.94	14.57	96.08%	ND	1.88	0.76	85.71%
SAs	SDZ	ND	9.19	0.58	50.98%	ND	3.46	0.72	28.57%
	STZ	ND	<LOQ	0.08	15.69%	ND	ND	0	0%
	SMA	ND	5.76	0.35	31.37%	ND	ND	0	0%
	SCP	ND	0.83	0.19	49.02%	ND	<LOQ	0.07	35.71%
	SMX	ND	120.74	12.52	78.43%	ND	4.48	0.74	28.57%
	SDX	ND	16.65	1.99	58.82%	ND	0.44	0.26	85.71%
	SQX	ND	<LOQ	0.04	5.88%	ND	<LOQ	0.02	7.14%
	TMP	ND	25.26	4.17	72.55%	ND	1.96	0.40	71.43%

Min.: minimum concentration;
Max.: maximum concentration;
Avg.: average concentration;
DF: detection frequency;
ND: not detected.

19 antibiotics were detected in the surface water samples from 17 sampling sites, and 17 antibiotics were detected in 14 sediment sampling sites in the tributaries of the Xiaoqing River. Detailed data on the concentrations of antibiotics at each sampling site are available in Table S5.

3.1.1. Surface water

Among all analysed antibiotics, OFX was the most abundant antibiotic, with an average concentration of 21.48 ng L^{-1}, followed by RTM (14.57 ng L^{-1}) and SMX (12.52 ng L^{-1}) in surface water. OFX showed the highest detection frequency of 100%, and CTM, AZM, RTM, SMX and TMP were all detected with frequencies greater than 70%, indicating the wide use of human and animal antibiotics in the Xiaoqing River basin. In contrast, the detection of CIP and SQX was 1.96% and 5.88%, respectively, with the concentrations of both antibiotics being lower than the LOQs. There were two antibiotics (OTC and TC) that were not detected at any sites. Overall, the average concentrations ranged from 0.02 to 21.48 ng L^{-1} for QNs, ND to 4.45 ng L^{-1} for TCs, 2.52 to 14.57 ng L^{-1} for MLs, and 0.04 to 12.52 ng L^{-1} for SAs in the Xiaoqing River basin, making it less polluted than other river basins, such as the Liao River basin [28], Tai Lake [29] and Bohai Bay [12].

For QN detection, all five antibiotics were detected in water in the following order: OFX (100%) > ENX (58.85%) > NOR (27.45%) > EFX (19.61%) > CIP (1.96%). The difficulty in the biodegradation of OFX would be a possible reason for its long-term existence in the aquatic environment [27]. The average concentration of the five QNs ranged from 0.02 to 21.48 ng L^{-1}. It is worth noting that CIP had the lowest average concentration and detection frequency (0.02 ng L^{-1}, 1.96%) of the five QNs, despite being the most widely prescribed QN [30]. The biodegradation and photodegradation processes of CIP in the river may be a reason for its reduction [31]. The average concentration of the remaining QNs was lower than 1 ng L^{-1}, except for ENX (2.67 ng L^{-1}). TCs are the second most widely consumed antibiotic worldwide in human and veterinary medicines due to their low cost, ease of use and relatively minor side effects [32,33]. Among the three TCs, only CTC (4.45 ng L^{-1}) was detected in surface water, with a low detection frequency of 19.61%. OTC was not found at all sampling sites, although it is one of the most commonly used antibiotics in aquaculture in Southeast Asia [34,35]. This result differs from the Liao River, where the average concentration of OTC was higher than that of TC and CTC, indicating that there may be regional differences in drug use [28].

MLs are widely used to treat bacterial infections in animals and humans due to their antibacterial action and are stable in sewage during treatment [36,37]. The detection frequencies of MLs were relatively high (over 80%). As a new generation of macrolide antibiotics used in the medical

field, the antibacterial effect of RTM is 1~4 times stronger than that of erythromycin, making it widely detected in lakes and rivers [38,39]. The average concentration of CTM (5.32 ng L^{-1}) was lower than that of Tai Lake (503 ng L^{-1}), Chao Lake (46.7 ng L^{-1}), and Dongting Lake (7.8 ng L^{-1}) but higher than that of Michigan Lake (<3.1 ng L^{-1}) and Beibu Gulf (ranging from ND~0.72 ng L^{-1}) [40–42]. SAs were also found in water samples with an average concentration ranging from 0.04 to 12.52 ng L^{-1}. The average concentration of SMX was 12.52 ng L^{-1} and accounted for 79.5% of the SAs. The main reason may be its poor removal during conventional biological wastewater treatment [43,44]. For the rest of the SAs, the detection frequencies ranged from 5.88% to 58.82%, and the range of average concentrations (0.04~1.99 ng L^{-1}) was relatively low. TMP, as a sulfanilamide synergist, is often used in combination with SAs, resulting in a relatively high detection frequency (72.55%) [45].

3.1.2. Sediment

As shown in Table 1, all antibiotics, except for STZ and SMA, were detected in sediment samples, with average concentrations ranging from 0.02 to 171.34 μg kg^{-1} dw. In sediments, the concentrations of six major antibiotics were in the following order: OFX (171.34 μg kg^{-1} dw) > NOR (16.26 μg kg^{-1} dw) > CIP (10.08 μg kg^{-1} dw) > CTC (7.86 μg kg^{-1} dw) > EFX (6.43 μg kg^{-1} dw) > OTC (4.62 μg kg^{-1} dw). The concentrations of the remaining antibiotics were all lower than 1 μg kg^{-1} dw.

Of the QNs analysed, five QNs showed detection frequencies of 7.1% to 100% in sediments, with concentrations ranging from ND to 171.34 μg kg^{-1} dw. The maximum concentration of OFL was significantly higher (1,827.18 μg kg^{-1} dw, site P1) than that of the other QNs, which may be caused by point source pollution. Similar to surface water, the detection frequencies of OFX were highest among all the antibiotics in sediments, suggesting the wide use of OFX in the study area. CIP was found to have a higher concentration (10.08 μg kg^{-1} dw) and detection frequency (71.43%) in the sediment than in the surface water. Based on a previous study, CIP is difficult to biodegrade but is easily adsorbed by the sediment [46]. For TCs, the same phenomenon occurred. In sediments, the strong adsorption capacity of TCs for sediment may be the reason that three TCs were detected compared with surface water [14]. The concentrations of the three individual TCs were in the following order: CTC (7.86 μg kg^{-1} dw) > OTC (4.62 μg kg^{-1} dw) > TC (0.30 μg kg^{-1} dw). This result was consistent with previous studies placing the TCs on priority lists with high application and potential to spread in the environment and significance for the risk assessment; specifically, TC, OTC, and OTC ranked as 31, 28, and 16, respectively [47].

Compared with the antibiotics above, the contents of MLs and SAs in the sediment were relatively low (lower than 1 μg kg^{-1} dw). The concentrations of three MLs (0.10~0.76 μg kg^{-1} dw) in the Xiaoqing River were 2~4 orders of magnitude lower than those in other rivers in China, such as the Wangyang River (2581.8 μg kg^{-1} dw), Liao River (229.31 μg kg^{-1} dw), Ba River (50.90 μg kg^{-1} dw) and Huangpu River (24.6 μg kg^{-1} dw) [28,45,48,49]. Among the SAs, SDX was the most frequently detected antibiotic instead of SMX, while the average concentration was low (0.26 μg kg^{-1} dw). The low pseudo-partitioning coefficient and the dilution effect of water may be the reasons that SAs showed a low level of pollution [50]. The TMP in sediments maintained a detection rate similar to that in surface water.

3.2. Spatial and temporal distributions of antibiotics

Fig. 2 shows the seasonal distribution of different antibiotic groups (QNs, TCs, MLs, and SAs) as well as the TMP in surface water from the tributaries of the Xiaoqing River. The concentrations of antibiotics in each season were the average value of the sampling site in the whole season. The average annual precipitation in the Xiaoqing River basin is 639.7 mm, and the annual distribution of precipitation is unbalanced, which is affected by the temperate continental climate. As shown in Fig. 1, the pollution levels of target antibiotics decreased in the following order: dry season > normal season > wet season, which was similar to the pattern in the Hanjiang River [50] and Huangpu River [51]. This result was consistent with previous studies showing that the concentrations of antibiotics in rivers are generally higher during the dry season than during the wet season [52,53]. The QNs and MLs made up the majority of antibiotics (63.8%) in the dry season, which was also found in the normal season (67.6%) and wet season (76.8%), indicating extensive QN and ML pollution in the Xiaoqing River. The large population of the Xiaoqing River basin (11.5 million) is a major reason for the high proportion of these two groups of human antibiotics. Slight differences in the seasonal distributions of the five groups of antibiotics were found. The cumulative concentration of antibiotics decreased in the following order: QNs (50.52 ng L^{-1}) > MLs (37.93 ng L^{-1}) > SAs (33.08 ng L^{-1}) > TCs (9.83 ng L^{-1}) > TMP (7.21 ng L^{-1}) in the dry season; MLs (22.65 ng L^{-1}) > QNs (16.93 ng L^{-1}) > SAs (11.63 ng L^{-1}) > TMP (3.78 ng L^{-1}) > TCs (3.53 ng L^{-1}) in the normal season; and QNs (6.77 ng L^{-1}) > MLs (6.67 ng L^{-1}) > SAs (2.52 ng L^{-1}) > TCs (ND) > TMP (1.54 ng L^{-1}) in the wet season, which may be due to the different incidences of diseases in different seasons. Moreover, the average concentrations of CTM, SDZ, SMA and SQX were found to be higher in the normal season than in the dry season, suggesting that water dilution does not always reduce the concentration of antibiotics. The expansion of aquatic products and livestock and poultry farming during the wet season will increase the discharge of veterinary antibiotics, as well as the impact of runoff [25].

The spatial distribution of antibiotics is shown in Fig. 3. Wastewater from surrounding rural residents and industrial areas may be the main sources of antibiotic pollution, as well as some livestock and poultry aquaculture. In addition, the contribution of nearby hospitals and sewage treatment plants should not be ignored [54]. Sampling sites P1 and P2 are located in Jinan, the capital of Shandong Province, where the concentrations of antibiotics in sediments were measured in units of mg kg^{-1}. The presence of chicken and duck breeding (P4), beef cattle breeding (P5) and fish ponds (P6) around the sampling sites may be the main reasons for the occurrence of SAs

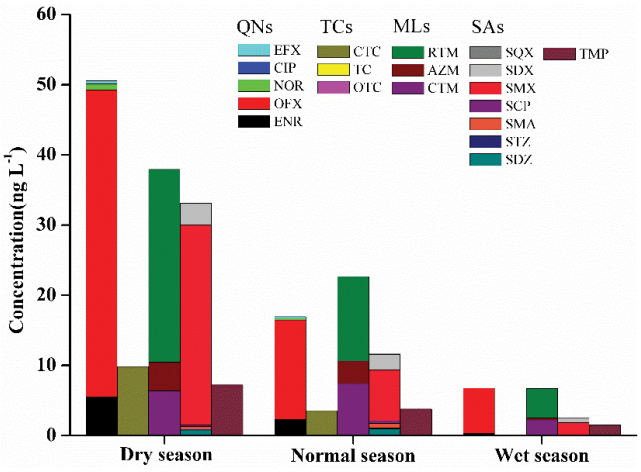

Fig. 2. Season distribution of target antibiotics.

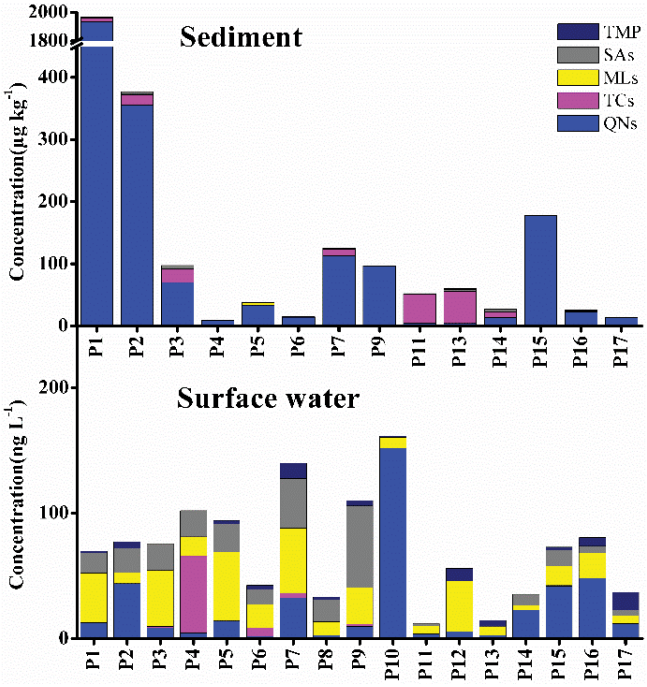

Fig. 3. Spatial distribution of antibiotics in surface water and sediments.

in water. The total concentration of antibiotics in the water was as high as 161.63 ng L^{-1} at sampling site P10, which has a large number of enterprises surrounding it. P9 is located in a tourist area, with aquaculture nearby, and the total concentration of antibiotics was 110.09 ng L^{-1}. The concentration of antibiotics at P15 (downstream of P14) was significantly higher than that at P14. The sewage treatment plant between the two sampling sites may be an important source of antibiotics. Agricultural runoff from the farmland around P11, P13 and P17 will also carry antibiotics into the river [25], and the total concentration of antibiotics ranged from 11.97 to 36.89 ng L^{-1} in the water and 13.79 to 60.63 μg kg^{-1} dw in the sediment at these sites. Compared with the above three sampling points, the concentration of antibiotics at P12 was relatively high. The reason may be that P12 is located in the mainstream of the Xiaoqing River and influenced by antibiotics from upstream (P7, P8 and P9).

3.3. Relationship between antibiotics and heavy metals

Heavy metals (As, Hg, Cr, Cu, Ni, Zn, Pb and Cd) are typical pollutants in aquatic environments. Sediments are the main storage medium of pollutants, especially heavy metals, in water bodies. Ninety-nine percent of heavy metals in water bodies can be stored in sediments in various forms [55]. Antibiotic residues in the environment mainly come from industrial discharge and medical and veterinary antibiotic residues. The combined contamination of heavy metals and antibiotics can greatly reduce the functional diversity and abundance of microorganisms [56]. The Pearson correlation coefficient between antibiotic concentration and heavy metals was calculated, as shown in Table 2. Hg and Ni were not correlated with the 17 selected antibiotics. A significant positive correlation was observed for ENX, OFX, TC and RTM with Cu and Pb. ENX, OFX, TC and RTM are human antibiotics, and domestic sewage discharge may be the common source. The functional groups (–OH, –COOH) and electron donors in these antibiotics can complexate with heavy metals, which may change the environmental behaviour and toxicity of pollutants in complex pollution systems. A positive correlation was observed for ENX, OFX, CIP, OTC, TC and SCP with Zn in the sediment. It is worth noting that in the field of medicine, Zn has been used as an antimicrobial for a long time [57]. Moreover, studies have shown a correlation between the presence of metals (Cu and Zn) in environmental samples and the concomitant presence of metal and antibiotic-resistant populations [58,59]. The positive correlations observed between SQX and Cr and between SCP and Cu, Zn and Cd suggest that livestock and poultry breeding wastewater may be their primary sources, and their environmental fates in the environment were similar. However, further research on the combination of antibiotic and heavy metal contamination is needed to test this explanation.

3.4. Environmental risk assessment

According to the PNEC estimation of algae in the literature (Table 2), the antibiotic risk coefficient in the surface water was calculated with the MECs to evaluate the environmental risk (as shown in Fig. 4). The RQ values indicate that more than half of the 13 antibiotics pose a moderate or high risk to the relevant aquatic organisms. Additionally, the environmental risk of antibiotics, except for CTM and SDZ, presents a significant seasonal pattern: dry season > normal season > wet season due to the seasonal difference in antibiotic concentration.

The OFX and CTM posed a high risk in over 80% of the water samples, with maximum RQs of up to 25.12 (dry season, P10) and 18.55 (normal season, P5), respectively. In addition to these two antibiotics, RTM, SMX and CIP presented a relatively high risk in different proportions ranging from 25% to 50% in all water samples. The same

Table 2
Pearson correlation coefficients (*r*) between antibiotics concentrations and heavy metals in sediment

Compound	As	Hg	Cr	Cu	Ni	Zn	Pb	Cd
ENX	–0.300	0.327	–0.043	0.757**	–0.080	0.609*	0.815**	0.141
OFX	–0.337	0.322	–0.018	0.752**	–0.100	0.660*	0.792**	0.190
NOR	–0.473	0.358	–0.128	0.481	–0.125	0.481	0.321	0.352
CIP	–0.394	0.263	0.265	0.308	–0.173	0.617*	0.109	0.556*
EFX	–0.353	0.157	–0.103	0.041	–0.086	0.105	–0.192	0.396
OTC	–0.125	0.300	0.230	0.615*	–0.188	0.582*	0.562*	0.580*
TC	–0.300	0.327	–0.043	0.757**	–0.080	0.609*	0.815**	0.141
CTC	–0.235	–0.109	–0.161	–0.323	–0.129	–0.432	–0.156	–0.393
CTM	–0.058	0.191	–0.119	0.321	–0.133	0.002	0.233	0.027
AZM	–0.050	0.055	–0.095	0.217	–0.097	–0.057	0.135	0.003
RTM	–0.417	0.362	0.132	0.731**	–0.196	0.529	0.686**	0.479
SDZ	–0.279	0.069	–0.116	0.052	–0.138	–0.169	0.014	0.166
SCP	–0.457	0.226	0.190	0.537*	–0.193	0.675**	0.450	0.729**
SMX	0.329	–0.001	–0.160	0.192	–0.160	0.042	0.265	0.164
SDX	0.330	0.112	0.161	0.013	0.256	0.250	–0.107	0.116
SQX	0.252	0.016	0.998**	–0.023	–0.075	0.402	–0.095	0.459
TMP	–0.252	0.194	–0.121	0.438	–0.188	0.236	0.510	–0.190

*$p < 0.05$;
**$p < 0.01$.

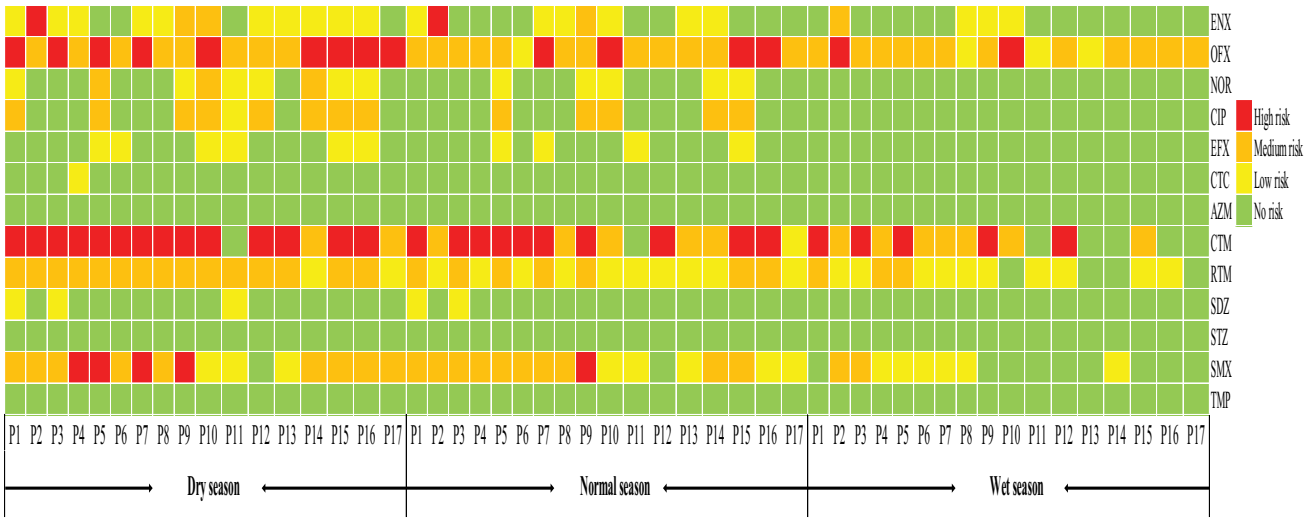

Fig. 4. Risk quotients of the antibiotics in dry, normal and wet season in surface water.

phenomenon occurs in surface water in Laizhou Bay, where the OFX, CTM, ENX and SMX levels pose relatively high ecological risks [22]. The RQ values for TMP as well as AZM and STZ were all less than 0.01 in the dry, normal and wet seasons, suggesting that these antibiotics are unlikely to pose environmental risks. Previous studies have shown that TMP greatly contributes to ecological risks for daphnids in river water in Zhuhai city [69]. Overall, the continued release of these antibiotics (low concentrations and high levels of PNECs) will lead to the accumulation of antibiotics in sediments and the generation of antibiotic resistance genes, which will still be toxic to aquatic organisms [7,70]. Among the different sampling sites, the high environmental risk presented by multiple antibiotics was observed in three seasons at P2-P5 and P14-P16, which are close to aquaculture and livestock farming, sewage treatment plants and hospitals. However, the toxicity of a mixture of antibiotics needs to be clarified due to the presence of synergistic and/or antagonistic effects.

4. Conclusion

This study investigated the occurrence, distribution and environmental risk of 19 antibiotics in surface water

and sediment from tributaries of the Xiaoqing River, China, as well as the relationship between corresponding antibiotics and heavy metals. The results revealed that the QNs and MLs predominated in both the surface water and the sediment. Moreover, as a typical area with a large population and developed agriculture, there were many potential sources of antibiotics around the tributaries of the Xiaoqing River, suggesting that obvious differences in the spatial and temporal distributions of antibiotics were observed and that the combined contamination of antibiotics and heavy metals may exist. Antibiotics (such as OFX, CTM, ENX and SMX) posed a medium to high environmental risk, especially in the dry season.

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Supplementary information

Table S1
Information of sampling site locations

Sampling sites	Longitude	Latitude	Surrounding area
P1	117°18′06.390″	36°48′04.918″	Residents, farmland
P2	117°25′51.344″	36°54′40.874″	Residents, farms, hospital, industry
P3	117°37′32.437″	37°2′44.189″	Residents, farms, hospital
P4	117°50′08.750″	37°0′57.096″	Residential, industry
P5	117°53′27.859″	37°0′51.314″	Residents, beef cattle breeding plant
P6	118°1′08.821″	37°4′20.266″	Residents, farmland
P7	118°18′11.884″	37°7′41.441″	Residents, farmland
P8	118°26′17.549″	37°7′44.807″	Residents, farmland
P9	118°29′07.555″	37°3′22.781″	Tourist areas, aquaculture
P10	118°32′09.424″	37°3′02.434″	Residents, farmland, industry
P11	118°43′15.344″	37°12′40.321″	Residents, farmland
P12	118°46′57.389″	37°16′12.619″	Aquaculture, salt farms
P13	118°57′44.759″	37°16′11.053″	Residents, farmland
P14	117°54′45.940″	37°5′33.032″	Industry, sewage treatment plant
P15	118°0′10.094″	37°6′04.147″	Industry
P16	118°18′26.828″	37°12′36.964″	Residents, farmland
P17	118°41′12.828″	37°18′20.252″	Residents, farmland

Table S2
MS/MS parameters for antibiotics

Antibiotics	Precursor ion (m/z)	Product ion (m/z)	Fragmentor (V)	Collision energy (eV)
ENX	321	303*,234	100	20,20
OFX	362.2	318.1*,261	120	15,25
NOR	320	301.9*,233	100	20,20
CIP	332	314*,288	120	15,15
EFX	360	342*,315.9	120	22,15
OTC	461.2	444.2*,426.2	135	15,15
TC	445.2	427.3*,410.3	135	10,15
CTC	479.2	462.2*,444.2	135	15,20
AZM	749.6	591.5*,158	150	30,45
CTM	748	590*,158	150	15,20
RTM	837.5	679.3*,558.2	150	20,20
SDZ	251.1	155.9*,107.9	100	10,20
STZ	256	156*,108	120	15,15
SMA	265	172*,156	120	15,15
SCP	285	156*,108	100	15,20
SDX	311.1	156*,108	125	17,26
SMX	254	156*,147	120	15,20
SQX	301	207.8*,156	135	15,15
TMP	291.2	261.2*,230.1	200	25,20
CIP-D_8	340	322*,296	120	15,15
ERM-^{13}C-D_3	738	580*,161.9	160	10,10
DMC	464.9	429.9*,447.9	135	15,20
SMX-D_4	257.8	159.9*,112	100	13,13
TMP-$^{13}C_3$	294	233*,126	120	25,25

Table S3
Concentration of heavy metals in sediments (mg/kg)

Sampling sites	As	Hg	Cr	Cu	Ni	Zn	Pb	Cd
P1	4.28	0.267	96	57	0	272	53.2	0.323
P2	4.44	0.226	51	31	20	147	24.5	0.454
P3	6.12	0.090	67	32	0	134	33.8	0.529
P4	13.8	0.183	91	36	0	150	34.1	0.300
P5	8.04	0.051	72	34	31	123	31.5	0.247
P6	7.80	0.083	54	19	17	70	23.8	0.141
P7	12.0	0.139	945	26	13	224	24.8	0.505
P9	6.83	0.049	64	15	0	94	17.2	0.302
P11	4.95	0.079	49	14	0	62	26.1	0.044
P13	8.03	0.135	51	20	13	67	21.3	0.059
P14	18.4	0.051	62	18	0	75	24.7	0.094
P15	4.82	0.037	60	15	5	224	18.0	0.100
P16	9.07	0.451	94	31	0	113	30.5	0.159
P17	10.3	0.019	80	26	2,619	96	24.8	0.136

Table S4
Method validation parameters of the target antibiotics

Antibiotics	Surface water			Sediment		
	Recovery (%)	LOD (ng L^{-1})	LOQ (ng L^{-1})	Recovery (%)	LOD (ng L^{-1})	LOQ (ng L^{-1})
ENX	116.8 ± 17.2	0.2	0.72	88.21 ± 11.44	0.82	3.28
OFX	79.76 ± 3.08	0.31	1.04	121.60 ± 4.99	0.85	3.4
NOR	97.33 ± 9.40	0.39	1.3	88.78 ± 27.95	0.82	2.73
CIP	87.69 ± 2.30	1.05	3.5	78.63 ± 7.30	0.78	3.12
EFX	127 ± 9.17	0.33	1.1	75.24 ± 2.72	0.84	3.36
OTC	115 ± 10	3.21	10.65	82.69 ± 9.65	1.83	7.32
TC	96 ± 2	2.98	9.69	82.91 ± 11.64	1.43	5.7
CTC	87 ± 5	2.33	7.76	87.90 ± 9.45	1.5	6
AZM	133.4 ± 11.8	0.09	0.3	64 ± 5.1	0.04	0.2
CTM	107 ± 1.24	0.08	0.26	97.68 ± 1.34	0.07	0.25
RTM	211 ± 6.23	0.16	0.55	134 ± 4.43	0.1	0.34
SDZ	130 ± 11.90	0.08	0.27	87.24 ± 36.47	0.2	0.67
STZ	111 ± 5.81	0.35	1.35	97.74 ± 41.86	0.35	1.18
SMX	98.62 ± 7.01	0.2	0.66	134 ± 2.36	1.02	4.08
SCP	123.7 ± 0.4	0.09	0.2	119 ± 9.37	0.1	0.3
SDX	80.06 ± 1.74	0.11	0.37	121 ± 38.71	0.12	0.39
SMA	113 ± 0.68	0.13	0.45	115 ± 1.72	0.14	0.45
SQX	85.12 ± 2.25	0.37	1.23	156 ± 48.42	0.16	0.54
TMP	73.39 ± 13.50	0.21	0.73	108 ± 3.24	0.1	0.34

Table S5
Concentrations of antibiotics in surface water in February (ng L^{-1})

Site	ENX	OFX	NOR	CIP	EFX	OTC	TC	CTC	CTM	AZM	RTM	SDZ	STZ	SMA	SCP	SMX	SDX	SQX	TMP
P1	1.34	27.74	0.73	ND	ND	ND	ND	ND	8.03	6.98	48.68	2.52	0.75	ND	0.13	24.87	2.32	ND	2.57
P2	72.02	4.29	ND	ND	ND	ND	ND	ND	2.00	1.70	12.21	ND	ND	ND	0.15	23.08	0.15	ND	4.42
P3	1.06	14.75	ND	ND	ND	ND	ND	3.54	11.12	8.65	63.66	3.26	ND	ND	ND	17.72	12.52	ND	ND
P4	0.59	2.60	ND	ND	ND	ND	ND	141.80	2.70	2.66	12.21	0.08	0.37	ND	0.25	51.65	1.08	ND	0.78
P5	0.28	23.65	3.08	ND	0.90	ND	ND	ND	15.28	4.52	28.69	0.12	ND	ND	0.50	47.64	1.93	ND	5.12
P6	0.25	1.93	ND	ND	0.45	ND	ND	11.50	5.99	1.25	28.06	0.79	0.42	ND	0.50	25.25	0.62	ND	4.81
P7	0.58	73.70	ND	ND	ND	ND	ND	7.62	18.03	15.60	71.94	0.28	0.52	0.14	0.39	95.41	2.08	ND	18.94
P8	0.98	3.86	ND	ND	ND	ND	ND	ND	2.53	1.28	19.69	0.52	ND	0.56	0.21	18.25	13.01	0.71	4.81
P9	6.50	5.97	1.26	ND	ND	ND	ND	2.73	8.08	4.98	28.35	ND	0.43	ND	0.16	120.74	16.65	ND	5.48
P10	4.09	283.83	3.70	ND	0.76	ND	ND	ND	3.65	ND	11.16	ND	ND	ND	0.28	0.32	0.13	ND	1.45
P11	ND	5.25	0.46	1.12	1.13	ND	ND	ND	ND	0.31	13.55	1.82	ND	ND	ND	0.53	ND	ND	ND
P12	0.55	10.36	0.85	ND	ND	ND	ND	ND	16.13	12.92	49.60	0.16	ND	ND	0.34	ND	0.21	ND	23.68
P13	0.81	4.40	ND	ND	ND	ND	ND	ND	2.15	1.00	13.17	0.27	ND	ND	ND	0.37	ND	ND	6.52
P14	1.56	54.33	2.16	ND	ND	ND	ND	ND	0.65	0.47	8.22	0.96	ND	ND	ND	15.56	ND	ND	1.12
P15	1.03	95.25	1.56	ND	1.85	ND	ND	ND	7.59	2.93	14.28	0.31	ND	5.76	0.29	22.49	0.94	ND	5.32
P16	0.79	106.96	0.71	ND	1.16	ND	ND	ND	3.21	1.06	36.32	0.61	ND	ND	ND	12.29	ND	ND	12.25
P17	0.29	25.41	ND	ND	ND	ND	ND	ND	1.02	3.15	7.34	1.00	ND	ND	ND	8.99	ND	ND	25.26

ND: not detected

Table S5
In surface water in May (Continued)

Site	ENX	OFX	NOR	CIP	EFX	OTC	TC	CTC	CTM	AZM	RTM	SDZ	STZ	SMA	SCP	SMX	SDX	SQX	TMP
P1	0.31	5.67	ND	ND	ND	ND	ND	ND	16.70	3.16	18.91	9.19	0.55	0.99	0.78	3.26	2.02	0.92	1.20
P2	29.99	8.05	ND	ND	ND	ND	ND	ND	1.20	0.55	5.65	0.61	ND	ND	0.30	17.57	0.33	ND	5.28
P3	ND	7.50	ND	ND	ND	ND	ND	ND	8.18	4.92	26.21	1.96	ND	0.38	0.44	7.72	8.64	ND	ND
P4	ND	2.50	ND	ND	ND	ND	ND	41.80	4.69	2.73	9.39	0.85	ND	0.14	0.34	4.32	1.44	ND	ND
P5	ND	7.37	0.54	ND	0.79	ND	ND	ND	37.11	14.71	38.35	ND	ND	3.09	0.28	9.60	1.19	ND	2.79
P6	0.27	0.64	ND	ND	ND	ND	ND	7.98	4.83	1.74	8.98	0.15	ND	0.61	0.78	5.41	0.39	ND	1.71
P7	0.54	17.17	ND	ND	1.58	ND	ND	4.37	8.74	4.49	26.76	0.87	0.59	0.34	0.53	13.16	1.85	ND	15.11
P8	0.54	1.63	ND	ND	ND	ND	ND	ND	1.25	0.23	5.42	ND	ND	ND	ND	4.25	8.02	ND	1.12
P9	3.38	5.94	0.54	ND	ND	ND	ND	3.41	18.24	7.29	15.95	0.12	ND	0.41	0.10	43.96	12.52	ND	5.50
P10	1.70	118.54	1.15	ND	ND	ND	ND	ND	1.24	0.13	5.80	ND	ND	ND	ND	0.32	ND	ND	0.95
P11	ND	1.75	ND	ND	0.76	ND	ND	ND	ND	0.11	2.50	0.93	ND	0.32	0.82	0.53	0.31	ND	ND
P12	0.22	4.24	ND	ND	ND	ND	ND	ND	12.17	9.13	8.95	ND	ND	ND	ND	ND	ND	ND	6.25
P13	0.59	1.80	ND	ND	ND	ND	ND	ND	0.81	0.26	3.29	ND	ND	0.42	0.41	0.37	ND	ND	4.13
P14	0.68	5.50	1.28	ND	ND	ND	ND	ND	0.27	0.26	1.60	0.56	0.48	0.24	0.33	5.33	0.21	ND	ND
P15	ND	17.87	0.81	ND	0.96	ND	ND	2.38	5.32	1.95	11.63	0.41	ND	3.27	0.83	3.43	0.24	ND	1.67
P16	ND	27.25	ND	ND	ND	ND	ND	ND	4.96	1.48	10.37	0.20	ND	0.40	0.24	2.67	0.22	ND	5.31
P17	ND	7.81	ND	ND	ND	ND	ND	ND	0.18	1.46	4.78	0.78	ND	0.53	0.12	0.99	0.39	0.46	13.15

ND: not detected

Table S5
In surface water in August (Continued)

Site	ENX	OFX	NOR	CIP	EFX	OTC	TC	CTC	CTM	AZM	RTM	SDZ	STZ	SMA	SCP	SMX	SDX	SQX	TMP
P1	ND	2.58	ND	ND	ND	ND	ND	ND	4.50	0.70	11.08	ND	ND	ND	ND	ND	ND	ND	ND
P2	3.10	14.60	ND	ND	ND	ND	ND	ND	0.72	0.17	2.13	ND	ND	ND	ND	15.10	ND	ND	6.54
P3	ND	2.41	ND	ND	ND	ND	ND	ND	3.21	ND	8.39	ND	ND	ND	ND	5.25	5.21	ND	ND
P4	ND	8.41	ND	ND	ND	ND	ND	ND	0.70	0.27	10.90	ND	ND	ND	ND	1.16	ND	ND	ND
P5	ND	6.25	ND	ND	ND	ND	ND	ND	12.53	0.45	12.64	ND	ND	ND	ND	2.23	1.14	ND	ND
P6	ND	2.42	ND	ND	ND	ND	ND	ND	1.16	0.12	3.82	ND	ND	ND	ND	0.97	ND	ND	4.32
P7	ND	3.85	ND	ND	ND	ND	ND	ND	1.03	1.56	7.01	ND	ND	ND	ND	1.26	1.08	ND	3.13
P8	0.30	0.35	ND	ND	ND	ND	ND	ND	0.47	0.13	1.97	ND	ND	ND	ND	2.39	4.89	ND	0.79
P9	1.07	4.73	ND	ND	ND	ND	ND	ND	3.06	ND	1.39	ND	ND	ND	ND	ND	ND	ND	1.33
P10	0.67	41.61	ND	ND	ND	ND	ND	ND	1.86	ND	0.89	ND	ND	ND	ND	ND	ND	ND	0.65
P11	ND	0.92	ND	ND	ND	ND	ND	ND	ND	ND	2.80	ND	ND	ND	ND	ND	ND	ND	ND
P12	ND	1.30	ND	ND	ND	ND	ND	ND	7.17	1.29	2.66	ND	ND	ND	ND	ND	ND	ND	ND
P13	ND	0.78	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.64
P14	ND	3.10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.22	ND	ND	ND
P15	ND	6.14	ND	ND	ND	ND	ND	ND	0.96	ND	1.70	ND	ND	ND	ND	ND	ND	ND	ND
P16	ND	7.64	ND	ND	ND	ND	ND	ND	ND	ND	3.29	ND	ND	ND	ND	ND	ND	ND	2.69
P17	ND	2.81	ND	ND	ND	ND	ND	ND	ND	ND	0.67	ND	ND	ND	ND	ND	ND	ND	4.08

ND: not detected

Table S5
In sediment in August (Continued)

Site	ENX	OFX	NOR	CIP	EFX	OTC	TC	CTC	CTM	AZM	RTM	SDZ	STZ	SMA	SCP	SMX	SDX	SQX	TMP
P1	1.76	1827.18	79.07	24.85	1.44	20.67	4.19	ND	0.13	ND	1.84	0.53	ND	ND	0.23	1.97	0.24	ND	1.96
P2	ND	123.46	119.48	50.23	62.37	16.38	ND	ND	0.11	0.10	0.85	1.53	ND	ND	0.23	1.97	0.24	ND	ND
P3	ND	59.04	ND	8.24	2.53	8.33	ND	12.87	ND	ND	1.17	2.53	ND	ND	0.23	1.97	0.24	ND	0.18
P4	ND	8.63	ND	ND	ND	ND	ND	ND	0.10	ND	0.47	0.28	ND	ND	ND	ND	0.22	ND	ND
P5	ND	33.68	ND	ND	ND	ND	ND	ND	0.98	1.00	1.88	0.21	ND	ND	ND	ND	0.21	ND	0.36
P6	ND	10.65	ND	3.27	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.31	ND	0.38
P7	ND	87.28	ND	24.17	1.85	10.06	ND	ND	ND	ND	0.96	0.38	ND	ND	0.13	ND	0.33	0.23	0.13
P8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
P9	ND	79.21	ND	3.75	12.69	ND	ND	ND	0.10	ND	0.57	ND	ND	ND	ND	ND	0.32	ND	ND
P10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
P11	ND	4.26	ND	ND	ND	ND	ND	46.06	ND	ND	0.69	0.78	ND	ND	ND	ND	ND	ND	0.34
P12	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
P13	ND	4.05	ND	ND	ND	ND	ND	51.10	ND	ND	0.35	3.46	ND	ND	ND	ND	ND	ND	1.67
P14	ND	11.37	ND	1.83	ND	9.18	ND	ND	ND	ND	ND	ND	ND	ND	ND	4.48	0.39	ND	0.32
P15	ND	122.07	26.32	21.00	7.89	ND	ND	ND	ND	ND	0.43	ND	ND	ND	0.10	ND	0.39	ND	0.19
P16	ND	17.24	2.76	2.77	ND	ND	ND	ND	0.42	0.30	1.06	0.20	ND	ND	ND	ND	0.44	ND	0.11
P17	ND	10.61	ND	1.00	1.24	ND	ND	ND	ND	ND	0.35	0.21	ND	ND	ND	ND	0.38	ND	ND

ND: not detected